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Geneva, 18–22 October 2010

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Declarations of interest

Members and temporary advisers of the WHO Expert Committee on Specifications for Pharmaceutical Preparations reported the following:

Dr Nilka Guerrero Rivas: Her Institute at the University Octavio Méndez Pereira in Panama performs, as part of its public health mandate, as reference laboratory for quality control of pharmaceutical products, fixed-fee quality control services for local manufacturers, including Laboratorios Prieto, S.A./Panamá, LAFSA/Panamá, Medipán/Panamá and Laboratorios Rigar/Panamá.

Professor Henning Kristensen: His wife is a former employee of Novo Nordisk and holds approximately US$ 20,000 in stocks in this company. The WHO Expert Committee on Specifications for Pharmaceutical Preparations does not consider any of the products manufactured by Novo Nordisk.

Professor I. Addae-Mensah, Professor S. Bawazir, Mr E. Wondemagegnehu Biwota, Dr L. Cargill, Mr J.-M. Caudron, Mr A.C. da Costa Bezerra, Professor T.G. Dekker, Professor J. Hoogmartens, Dr T. Kawanishi, Dr K. Keller, Dr G.N. Mahlangu, Dr J.A. Molzon, Professor T.L. Paál, Dr L. Paleshnuik, Ms M.-L. Rabouhans, Dr J.-L. Robert, Dr S. Singh and Mr D. Smith reported no conflict of interest.

1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 18 to 22 October 2010. Dr Hans V. Hogerzeil, Director, Department of Essential Medicines and Pharmaceutical Policies, opened the meeting, and on behalf of the Director-General of the World Health Organization, welcomed all the participants to the forty-fifth meeting of the Expert Committee. He expressed his appreciation of the Expert Committee for its knowledge of and expertise in the work of WHO in the area of quality assurance of medicines and for its major contributions with technical expertise as well as with practical laboratory studies.

Dr Hogerzeil welcomed the members of the Committee and temporary advisers; representatives of the United Nations Children's Fund, the Global Fund to Fight AIDS, Tuberculosis and Malaria, United Nations Industrial Development Organization, World Intellectual Property Organization, the World Bank, World Customs Organization, World Trade Organization, European Union, Council of Europe/European Directorate for the Quality of Medicines and HealthCare, Commonwealth Pharmacists Association, European Chemical Industry Council/APIC, International Federation of Pharmaceutical Manufacturers Association, International Generic Pharmaceutical Alliance, International Pharmaceutical Federation and the World Self-Medication Industry; representatives of the Pharmacopoeias of Great Britain and of the United States of America; representatives from WHO Collaborating Centres in Hungary and South Africa; and observers from the Brazilian Health Surveillance Agency and from the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

Dr C.F. Etienne, Assistant Director-General for the Health Systems and Services Cluster, who was unable to attend the meeting, welcomed the Expert Committee with a written speech and acknowledged the elected Chairs, i.e. Professors I. Addae-Mensah (Chairperson) and S. Bawazir (Co-Chairperson), and the Co-Rapporteurs, Dr J.A. Molzon and Mr E. Wondemagegnehu Biwota.

She stated that the open session of the forty-fifth WHO Expert Committee on Specifications for Pharmaceutical Preparations had been organized in order to respond to the interest raised by Member States during the World Health Assembly held in May 2010 on the quality of medicines. The aim was to provide more information on this Expert Committee in an open and transparent manner. All the materials relating to the Expert Committee, both concerning the past and ongoing work, were to be found on their web sites. The Expert Committee members and the WHO Secretariat were here to explain the work related to the Committee and to respond to any questions.

Poor quality of medicines and "spurious/falsely-labelled/falsified/counterfeit medicines" are unfortunately a major threat to public health,

putting the health of numerous patients at risk and the trust of the patients in their health systems at stake; thus this was of critical importance for WHO.

WHO has been involved in medicines quality assurance and quality control since 1948. This Committee was created in the very first World Health Assembly. Its work had already begun in 1947, during the transition of health matters previously dealt with under the League of Nations. Thus it is one of WHO's oldest programmes.

Strong links exist with other WHO activities, such as support of national medicines regulatory authorities (NMRAs), the Prequalification of Medicines Programme, the Expert Committee on Biological Standardization, the Expert Committee on Selection and Use of Essential Medicines, Traditional Medicine and specific disease programmes.

The normative activities covered by this Expert Committee not only directly serve WHO Member States, but also, through implementation by programmes within WHO, international organizations as well, such as, UNICEF and The Global Fund to Fight AIDS, Tuberculosis and Malaria.

Most of these activities have in the past been funded from WHO's regular budget. Nowadays more than 80% of the finance is secured through extrabudgetary funding by donors, such as the European Union, UNITAID, and the Bill & Melinda Gates Foundation.

Dr Hogerzeil stated that the work of the Expert Committee within the Quality Assurance and Safety: Medicines team was becoming a focus of interest. The meetings of the Expert Committee used to be held every two years but had been held annually for the past four years in response to the increased need for normative work. The work of the Expert Committee is of the highest level of normative work existing at WHO and the outcome of each meeting is published in the WHO Technical Report Series, which is then presented to the WHO governing bodies at the Executive Board meeting, usually in May.

Members of the Expert Committee are invited in a personal capacity and do not represent their respective governments.

The work of *The International Pharmacopoeia* and the WHO Prequalification of Medicines Programme is based entirely on the work of the Expert Committee on Specifications for Pharmaceutical Preparations; all guidance documents are sent out worldwide for comments, revised and finally adopted by the Expert Committee.

While the normative work is unique, norms and standards is one of the key activities of the United Nations system. Dr Hogerzeil stated that WHO was supporting medicines related activities in nearly 100 countries.

In the medicines area, standard-setting work continues to be a pillar of WHO's activities and priorities.

Overall the Expert Committee structure has been and will continue to be the "backbone" of the Organization's standard-setting process.

The work of this Expert Committee is important for WHO Member States, United Nations agencies and international organizations, and in-house for all medicines-related programmes.

Work of this Expert Committee is closely linked to other organizations, for example, the European Medicines Agency (EMA), the European Directorate for the Quality of Medicines and HealthCare (EDQM), the Global Fund to Fight AIDS, Tuberculosis and Malaria, United Nations Children's Fund (UNICEF), World Intellectual Property Organization (WIPO), the World Bank, International Pharmaceutical Federation (FIP), International Federation of Pharmaceutical Manufacturers Associations (IFPMA), International Generic Pharmaceutical Alliance (IGPA), World Self-Medication Industry (WSMI), national and regional pharmacopoeias, and other clusters, institutions, bodies, authorities and other WHO Expert Committees.

Experts and WHO staff are committed to this important work, which enables quality medicines to reach the patients.

Quality for some essential medicines with a major health impact, e.g. for the treatment of tuberculosis and malaria, is still a problem worldwide. This is especially notable when looking at submission for prequalification dossiers and also in recent articles published by colleagues from Medécins sans Frontières (MSF) and related nongovernmental organizations. However, the international (donor) community is becoming increasingly aware about the problem of poor quality drugs, and countries with the above problem are more open to recognizing it. Nevertheless, there is still a long way to go before poor people will also gain access to good quality medicines.

Open session

The open session, held on Monday, 18 October 2010, was opened by Dr H.V. Hogerzeil, Director, Department of Essential Medicines and Pharmaceutical Policies on behalf of Dr C.F. Etienne, Assistant Director-General, Health Systems and Services. Dr Hogerzeil welcomed representation from a number of Permanent Representatives to the United Nations Offices, International Organizations based in Geneva, and Specialized Agencies in Switzerland; representatives from the WHO Regional Offices for Africa, the Americas (Pan American Health

Organization), the Eastern Mediterranean, Europe, South-East Asia and the Western Pacific.

The Secretary of the WHO Expert Committee on Specifications for Pharmaceutical Preparations gave an overview of the processes involved and the key areas covered. Time was allowed for any questions, comments and suggestions following the Secretary's presentation.

Recommendation. It was recommended that the key points of the Secretary's presentation be developed into a short article for wider dissemination to highlight the importance of the Expert Committee's work over the years and the need for normative standards and maintenance of quality guidelines.

The presentation would also be sent to interested parties and would be posted on the Medicines web site.

Questions were asked relating to WHO guidelines, namely concerning implementation, use of standards for procurement, and financing.

The Coordinator of the Quality Assurance and Safety: Medicines team, replied that the guidelines were all developed for use and implementation by Member States, and within WHO they were used inter alia within the Prequalification of Medicines Programme. Many partners and international organizations, such as the Global Fund, also make use of the guidance developed by this Expert Committee.

A question was posed relating to specifications for neglected diseases as some seemed to be missing and not included in the work plan, for example, Chagas' disease and leishmania. The secretary replied that the Quality Assurance and Safety: Medicines team would look into this matter further when reviewing the Expert Committee's work plan.

The Secretary said that a great deal of support was received by national authorities, quality control laboratories, and that experts contribute a lot without necessarily being paid for by WHO.

The Co-Chairperson stated that he had 25 years experience on the implementation of guidelines from WHO on raising the quality of NMRAs; otherwise the research for guidelines would be carried out to a large extent by developed countries, e.g. WHO good manufacturing practices (GMP) as adopted by the Expert Committee on Specifications for Pharmaceutical Preparations is used by many countries.

The focus of comments raised by the Expert Committee members was to emphasize that funding cuts were undermining normative functions which are supporting prequalification and assisting Member States' responsibilities and expectations.

The Expert Committee members were concerned about the serious problems regarding the funding of WHO's normative work in the area of quality assurance.

Update on spurious/falsely-labelled/falsified/counterfeit medicines

Discussion took place during the World Health Assembly in May 2010 regarding the *International Medical Products Anti-Counterfeiting Taskforce* (IMPACT) and issues regarding spurious/falsely-labelled/falsified/counterfeit medicines in general. The organization of an intergovernmental working group for Member States was currently ongoing based on a World Health Assembly decision. Concerns had been raised regarding WHO's role in this area. Two background papers had been prepared by the WHO Secretariat and submitted to the World Health Assembly. Several background papers were provided in the Expert Committee file regarding nomenclature and legal issues relating to substandard/spurious/falsely-labelled/falsified/counterfeit medicines. WHO has currently put on hold activities related to serving the Secretariat for IMPACT. The Director-General of WHO reconfirmed that spurious/falsely-labelled/falsified/counterfeit medicines are an important issue for the Organization.

The WHO Anti-Counterfeiting Programme is part of the Essential Medicines and Pharmaceutical Policies/Quality Assurance and Safety: Medicines work plan and team.

Major publications since October 2009

- The forty-fourth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 957) was ready for its presentation to the WHO Executive Board meeting held in May 2010. It is now available in printed and electronic form and published copies were distributed to the participants at the forty-fifth meeting of the Expert Committee.

In the pipeline

- The Second supplement to the fourth edition of *The International Pharmacopoeia* would soon be available on CD-ROM and online.
- A CD-ROM including all 60 current WHO quality assurance guidelines adopted by the Expert Committee on Specifications for Pharmaceutical Preparations would be available in a comprehensive and structured form by the end of 2010.

Expert Committee meeting topics

A variety of aspects relating to quality assurance were discussed, which involved more than 80 documents (including 30 quality assurance-related

working documents, 30 specifications and some 20 additional background documents).

A joint session with the WHO Expert Committee on Biological Standardization was held to discuss issues of common interest and an open session for interested Member States was held to provide an overview of the Expert Committee process, working style and work products over the past 45 meetings.

2. General policy

2.1 International collaboration

2.1.1 *Collaboration with international organizations and agencies*

European Directorate for the Quality of Medicines and HealthCare (Council of Europe)

A short update on the collaboration between the European Directorate for the Quality of Medicines and HealthCare (EDQM) and the WHO activities under this Expert Committee was given.

The Global Fund to fight AIDS, Tuberculosis and Malaria

The Global Fund to Fight AIDS, Tuberculosis and Malaria works in partnership with governments, civil society, the private sector and affected communities.

Of the approved Global Fund budget, 37% is used for medicines and health products. For instance, of US$ 19.4 billion approved by the Board, 62% was used for HIV/AIDS, 22% for malaria and 16% for tuberculosis. By region this amounts to: sub-Saharan Africa, 57%; East Asia and Pacific, 14%; Eastern Europe and Central Asia, 7%; South Asia, 9%; Middle East and North Africa, 6%. Overall the Global Fund has 600 active grants in 144 countries.

The Global Fund's quality policy for pharmaceuticals has been revised following advice from this Expert Committee and since 2009 the policy has been based on three criteria:

- *Clinical criteria* — medicines listed in WHO, national or institutional standard treatment guidelines (if not listed in one of the standard treatment guidelines, medicines require justification for selection from applicants or recipients).
- *Quality criteria* — authorization of a product in the recipient country is necessary for all products. In the case of antiretrovirals (ARVs) and medicines for treating TB and malaria, WHO prequalification or authorization by stringent regulatory authorities (SRAs) or recommendation by the Expert Review Panel (ERP) is applied.

- *Quality monitoring* — quality of products is monitored all along the supply chain recipients and the results are reported to The Global Fund.

The ERP hosted by WHO lessens potential use or benefits associated with the use of finished pharmaceutical products (FPPs) that are not WHO-prequalified or SRA-authorized. Eligibility criteria for dossier submission include products being manufactured at a GMP site and having already submitted a dossier to WHO for prequalification or SRA review. Recommendations by ERP are valid for 12 months.

Since 2009 the number of products permitted for use based on different approaches are 51 based on ERP advice, 18 prequalified by WHO and 7 approved by SRAs.

Challenges for The Global Fund include: an increased demand for malaria, tuberculosis and opportunistic infections (OI) medicines of assured quality; finding quality control laboratories with Global Fund requirements; and strengthening national regulatory capacity and regulatory networks for harmonization.

United Nations Children's Fund

The Expert Committee was briefed on the role of the Supply Division of the United Nations Children's Fund (UNICEF) which was established in 1946.

One of the main activities is the timely supply of quality medicines to countries and communities in need. The role of the Supply Division is to:

— oversee UNICEF's global procurement and logistic operations;
— procure supplies on behalf of UNICEF and procurement services partners; and
— ensure that high quality, good value supplies reach children and their families quickly.

Procurement of pharmaceuticals by UNICEF involves prequalification of supplies, which is based on assessment of suppliers by undertaking:

— a review of the documentation submitted and/or GMP inspection to ensure compliance with WHO GMP requirements; and
— assessment of products using the WHO Product Questionnaire in WHO Technical Report Series, No. 937.

Local authorities are invited to participate in GMP decisions based on:

— the regulatory environment in the country of origin and prior experience of UNICEF; and
— GMP inspection by UNICEF or a representative selected by UNICEF.

Contract manufacture is only accepted if the subcontractor is also approved by UNICEF.

Inspections are carried out primarily by UNICEF staff who check compliance with WHO GMP guidelines.

During 2006–2009, 89 GMP inspections were carried out and 27 companies failed (30%). In the case of GMP noncompliance (failure), a detailed GMP inspection report is forwarded to the company with a request to respond within one month.

UNICEF does GMP in collaboration with local authorities and also carries out joint inspection with WHO, ICRC and MSF. It is also a partner to PIC/S.

In the case of prequalification of vaccines, HIV/AIDS, malaria and tuberculosis products:

— products must be prequalified by WHO and listed on the WHO web site;
— the supplier has to confirm to UNICEF that its products are identical to those assessed by WHO; and
— UNICEF's purchase is "traced" in WHO/UNICEF GMP inspection.

2.1.2 *Pharmacopoeial Discussion Group*

A brief update was given by the representative from the Japanese Pharmacopoeia on the current activities of the Pharmacopoeial Discussion Group (PDG) which consists of the European Pharmacopoeia (PhEur), Japanese Pharmacopoeia (JP) and the United States Pharmacopeia (USP). At present, 27 of the 34 general chapters and 40 of the 63 excipient monographs of the current PDG work programme have been harmonized by these three pharmacopoeias. During the latest PDG meeting, a revision of the general chapter for Dissolution and corrections to Capillary electrophoresis were signed off. The sign-offs for excipients included revisions to previously harmonized excipient monographs. This exercise is aimed at achieving a higher level of harmonization of previously signed-off monographs. Harmonization has been achieved on nine of the 10 general chapters identified by the ICH Q6A Guideline. PDG's submission of Bulk and tapped density and bacterial endotoxins enabled the ICH Q4B to sign off the two texts at step 2. PDG re-emphasized the importance of consistent regulatory positions on harmonized text. At their joint meeting, PDG and ICH Q4B reflected on additional ways in which to accelerate declaration of regulatory interchangeability of pharmacopoeial texts.

The PDG parties agreed to provide their harmonized texts for the general methods in order to further enhance harmonization and to enable WHO to revise its text currently included in *The International Pharmacopoeia.*

2.1.3 *International Conference on Harmonisation*

The Expert Committee was informed about the International Conference on Harmonisation (ICH) meeting held in Tallinn, Estonia from 5 to 10 June 2010, with a focus on the area of quality of pharmaceuticals. It was reported that the highlight of this meeting was the progress made in the global implementation of ICH.

Guidelines Q8 (*Pharmaceutical development*), Q9 (*Quality risk management*) and Q10 (*Pharmaceutical quality system*) reflect the new paradigm in pharmaceutical quality towards more process–product understanding and process control rather than end-product testing. The ICH Quality Implementation Working Group (IWG) had held its first training workshop in Tallinn. The training consisted of a case-study representing the different phases of the life-cycle of a pharmaceutical product. The training was subsequently held in Washington, DC (USA) and in Tokyo (Japan).

Further progress was made on the harmonization of pharmacopoeial texts in the three ICH regions, with the aim of reducing testing requirements. Two annexes for the Q4B Guideline *Evaluation and recommendation of pharmacopoeial text for use in the ICH regions* (Annex 11 on *Capillary electrophoresis* and Annex 12 on *Analytical sieving*) reached Step 4, and another two annexes (Annex 13 on *Bulk and tapped density* and Annex 14 on *Bacterial endotoxin*) reached Step 2. These texts will also be considered for further harmonization within the context of *The International Pharmacopoeia*.

The Q3D Expert Working Group (EWG) began work on guidelines that will provide limits for *Metal impurities* in medicines, products and ingredients both qualitatively and quantitatively.

The ICH Steering Committee approved the establishment of an EWG for a new multidisciplinary topic (M7) on *Genotoxic impurities*. The guidelines will describe the evaluation, qualification and control of these impurities in medicines during development and after licensing.

2.1.4 *International Conference of Drug Regulatory Authorities*

The Committee was provided with an update on the 14th International Conference of Drug Regulatory Authorities (ICDRA) hosted by the Health Sciences Authority of Singapore (HSA) together with WHO from 30 November to 3 December 2010 in Singapore. In conjunction with the 14th ICDRA, a pre-conference, entitled "Effective collaboration: the future for medicines regulation," was to be held at the same location from 28 to 29 November 2010.

Globalization and rapid advances in information technology have brought about countless benefits and have improved living standards, but they

have also raised new challenges for public health and NMRAs. Increasing sophistication of health products, the development of cutting-edge technologies and extensive use of the Internet pose many challenges to the regulatory authorities of both developing and developed countries. ICDRA is a unique platform for NMRAs of WHO Member States to meet and discuss ways to strengthen collaboration and address issues of common concern. The organizing committee elaborated a programme that will provide opportunities for medicines regulators and interested stakeholders to share and discuss current and topical issues of global concern, for example, the H1N1 influenza situation, and access to high-quality medicines.

The pre-meeting would be open to other parties upon registration and would discuss collaboration and cooperation between NMRAs focusing on assessment and inspection.

2.2 Cross-cutting issues in pharmaceuticals — quality assurance issues

2.2.1 *Essential medicines*

An update on the activities of the Expert Committee on Selection and Use of Essential Medicines was given by its Secretary. Currently, the WHO Model List of Essential Medicines (EML) lists all medicines that are recommended for adults and children, including formulations. The 2nd WHO Model List of Essential Medicines for children (EMLc) includes children's medicines, together with age restrictions and medicines for neonates. However, at the moment there are certain discrepancies and difficulties between the two lists. For example, section 8.4 for palliative care does not list any medicines listed for adults and has a long list for children. It was explained that certain national contexts may not be evidence-based and made little use of the WHO Model List.

The Expert Committee was briefed on the project Better Medicines for Children, which provides intensive support to Ghana, two states in India and to the United Republic of Tanzania. Work is commencing with francophone African countries and there is ongoing support to other regions in aspects of implementation.

The eighteenth meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines will be held in Accra, Ghana from 21 to 25 March 2011. The agenda includes discussion on dosage forms, fixed-dose combinations, extemporaneous preparations, and ongoing application reviews.

The Committee recommended that the Expert Committee on Selection and Use of Essential Medicines consult with it on all issues relating to quality assurance of medicines.

2.2.2 *Herbal and complementary medicines*

The Traditional Medicine team, which used to be part of the Department of Essential Medicines and Pharmaceutical Policies is now under the Department of Health Policy, Development and Services. The resolution on traditional medicine adopted at the 62nd World Health Assembly in 2010 serves as the basis for its activities. The resolution requests WHO to strengthen cooperation with collaborating centres, research institutions and nongovernmental organizations in order to share evidence-based information and to support training programmes for national capacity building in the field of traditional medicines. It also requested WHO to continue providing technical guidance to support countries in ensuring the safety, efficacy and quality of traditional medicine, provide policy guidance to countries on how to integrate traditional medicine into health systems, and update the WHO traditional medicine strategy based on countries' progress and new challenges.

Strategic objectives and priority areas of the Programme include:

— capitalization on the potential contribution of traditional medicines to self-care and to people-centred primary care;
— modality of integration of traditional medicines into health systems;
— promoting agreement and consensus on criteria for endorsement, integration and evaluation of traditional medicine as a subsystem of national health systems; and
— strengthening research to promote the quality, safety and efficacy of traditional medicines and products.

An update on the activities undertaken in 2010 in the area of quality and safety of herbal medicines included the following:

- *Quality control methods for medicinal plant materials* — updated edition (currently in preparation for printing)
- *Key technical issues of quality impacting on the safety of homeopathic medicines* (printed in 2010)
- *Guidelines for selecting substances for quality control of herbal medicines* (in preparation)
- *Good processing practices for herbal materials* (in preparation)
- *Guidelines on safety management of toxic medicinal plants and monographs on selected commonly used toxic medicinal plants* (in preparation)

Important WHO documents on medicinal plants developed by the Programme include:

WHO monographs on selected medicinal plants — Volumes 1, 2, 3 and 4. These monographs provide scientific information on safety, efficacy and

quality control of widely used medicinal plants as well as providing models to assist countries in developing their own monographs or formularies.

WHO monographs on selected medicinal plants used in the Newly Independent States (2010). The publication is available in English and in Russian and includes monographs adopted from existing WHO monographs, and of which 14 are new.

Work is also being done to expand the evidence base on the quality, safety and efficacy of herbal medicines, including review and analysis of reports of clinical studies; technical documents on the safety of herbal medicines with reference to interaction with other medicines; and key technical issues of research methodologies.

Another ongoing activity is the 2nd WHO Global Survey on Material Policy and Regulation of Traditional Medicine. The objective of the survey is to assess the impact of implementation of the WHO Traditional Medicine Strategy: 2002–2005 and 2004–2007. The survey attempts to collect updated and more comprehensive information relating to practices and qualifications and to monitor progress in Member States. It also aims to identify new needs of each Member State and to update the WHO Traditional Medicine Strategy.

Basic training guidelines, benchmarks and manuals developed in 2010 include: osteopathy; Tuina; Nua Thai; therapies using herbal medicines — Chinese traditional medicines; ayurvedic medicine; Unani medicine; naturopathic medicine; and naturopathy.

2.2.3 *Regulatory support*

All WHO's normative work in the area of quality, safety and efficacy is intended to support NMRAs and is developed with them through the global consultative processes referred to above. The core functions of WHO's Medicines Regulatory Support Programme include the provision of direct support to countries and regions for strengthening medicines regulation; developing and continuously improving tools to assist regulatory work; facilitating communication; and promoting harmonization among NMRAs. Country support involves assessing medicines regulatory systems to identify needs, preparing institutional plans and providing technical support and capacity building, based on WHO's data collection tools and methodology.

The Programme Manager of the Medicines Regulatory Support Programme briefed the Expert Committee members on the current activities of this programme. To date 51 assessments have been made of 47 regulatory systems, with the involvement of regional offices, and in close collaboration with the capacity-building teams from the WHO Secretariat. Technical

assistance has also been given to regional harmonization initiatives and for supporting the participation of bodies such as the Southern African Development Community, the East African Community and the Caribbean Community.

In response to the need for continuous learning by the staff of NMRAs, WHO has delivered training courses on the assessment of quality, safety and efficacy in the marketing authorization process in all WHO regions, involving participants from more than 50 Member States. To support the work and decision-making processes of NMRAs, a model for medicines regulation — the WHO Medicines Regulatory Package — has been developed, field-tested and implemented in seven African countries as a tool for exchange of regulatory information and for building regulatory capacity.

The African Medicines Registration Harmonization Initiative has been established in response to the increased responsibilities placed on national regulatory systems. WHO is working with the Department for International Development of the United Kingdom of Great Britain and Northern Ireland, the World Bank, the Bill & Melinda Gates Foundation, the William J. Clinton Foundation and the New Partnership for Africa Development (NEPAD) to improve health in Africa by increasing the availability of medical products that meet standards for safety, efficacy and quality through regional regulatory harmonization. The issue was discussed at the Second African Medicines Regulatory Authorities Conference (held in Maputo, 16–18 November 2009) which brought together 54 heads and staff of NMRAs from 40 countries. A World Bank Trust Fund has been established to pool donors' contributions to the initiative.

WHO has continued to work closely with the NMRAs of Member States from all WHO regions in facilitating information exchange and knowledge transfer. Cooperation with regional networks — such as DRUGNET, which concerns the Newly Independent States — has enabled regulatory support to be provided to a large number of countries. Training has been offered to inspectors in conducting inspections of GMP, while quality control laboratories have received training in good practices for managing pharmaceutical laboratories in order to achieve a good level of quality assurance. Numerous capacity-building workshops have been organized with regulators, including workshops on new pharmaceutical legislation and on regulating medicines promotion.

3. Joint session with the Expert Committee on Biological Standardization

The joint session raised the following three topics that were of common interest:

— *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*;
— *Proposal to initiate a project to evaluate a candidate International Standard for Human Recombinant Insulin*; and
— *WHO GMP for blood establishments*.

Each of these topics was discussed jointly and again in each Committee's sessions; each Committee has taken appropriate action in a coordinated manner. Further details and recommendations are included under the specific sections of this report.

The Expert Committee appreciated the opportunity for joint discussion between the two Expert Committees of issues of mutual interest.

The conclusion and recommendation was that work should progress and the Expert Committees on Specifications for Pharmaceutical Preparations and on Biological Standardization should continue to collaborate on topics of common interest.

4. Quality control — specifications and tests

4.1 *The International Pharmacopoeia*

Second supplement

An update was presented on *The International Pharmacopoeia* (Ph.Int.) activities and work plan. The Expert Committee noted that the work on the compilation of the Second supplement to the fourth edition was progressing and that it would be published as a replacement CD-ROM and an online version.

This publication would comprise new and revised texts adopted by the Expert Committee since 2007.

As per the work process, the final version of the monographs adopted during the present meeting would be made available on the WHO Medicines web site once completed and would subsequently be compiled into a publication.

Collaboration with other pharmacopoeias

The Secretariat reported to the Expert Committee that an enhanced collaboration between *The International Pharmacopoeia* and *The British Pharmacopoeia* had commenced.

This collaboration between The Medicines and Healthcare products Regulatory Agency of the United Kingdom of Great Britain and Northern Ireland (MHRA), which hosts *The British Pharmacopoeia* and WHO, which hosts *The International Pharmacopoeia*, was aimed at developing

a closer cooperation and exchange in the field of quality specifications for medicines, which would be based on common priorities as identified by both pharmacopoeias in their respective work plans.

It was foreseen that by sharing their experience in the development of specifications for formulated products, this collaboration would be of mutual benefit for these pharmacopoeias, notably in making more specifications available to users.

The Secretariat informed the Expert Committee that, in the context of this cooperation, work had been rapidly initiated with a pilot phase comprising three monographs for anti-infectives (amoxicillin oral suspension, metronidazole oral suspension, sulfamethoxazole and trimethoprim tablets) that could be developed and discussed at the meeting of the Expert Committee.

Noting that this collaboration was to be formalized by an agreement between the two organizations hosting the pharmacopoeias, the Expert Committee welcomed this initiative and the outcome of this pilot phase in adopting the presented texts (see section 4.3.4 of this report on specifications for anti-infectives).

4.2 Current work plan and future work programme

Based on the 2010 work plan, the Expert Committee discussed and reviewed:

— the current development status of the monographs; and
— new proposals for developing specifications for active substances and dosage forms, including those for paediatric use.

New proposals were made, taking into account:

- substances remaining in the current work plan;
— substances initially listed in the previously adopted work programmes that were then prioritized, based on the importance of the products for the treatment of WHO priority diseases (including HIV/AIDS, tuberculosis, malaria, programmes and diseases with high prevalence in developing countries);
- new additions from the updated sixteenth WHO Model List of Essential Medicines (March 2010) and the updated second WHO Model List of Essential Medicines for Children (March 2010);
- new additions from the expressions of interest within the WHO Prequalification of Medicines Programme; and
- requests for medicines recommended in WHO's specific disease programmes.

Categories covered in the work programme included medicines used in the treatment of HIV/AIDS, malaria, tuberculosis, as well as anti-infectives (anthelmintics, antibacterial, antiprotozoal, antifungal, antiviral

and antimycobacterial agents), medicines used in oral rehydration therapy and those used for the treatment of various conditions grouped under the generic term "other medicines" (other antivirals, analgesics, antipyretics, agents used for palliative care, anti-epileptics, large-volume parenterals, reproductive health products, vitamins, cytotoxic agents and insulins).

The Expert Committee noted with satisfaction that good progress had been made in the development of specifications for essential medicines, notably for antiretrovirals (ARVs) where, with the exception of one substance, all the pharmaceutical substances recommended in the Model List of Essential Medicines for the treatment of HIV/AIDS were now covered in *The International Pharmacopoeia* in at least one single- or fixed-dose combination dosage form.

The Expert Committee members were informed that efforts were being made to make the work plan available on the web and through correspondence with manufacturers' associations. The aim was to enhance collaboration and to obtain samples, which was often not an easy undertaking.

The Expert Committee reviewed and approved the proposed new work programme in principle, and agreed that the list be reconfirmed with the WHO Prequalification of Medicines Programme and the respective disease programmes as well as partner organizations, to ensure that prioritization for development of specifications would reflect their needs.

4.3 Specifications for medicines, including children's medicines

4.3.1 *Medicines for HIV and related conditions*

New monographs for the following ARVs were presented to the Expert Committee for discussion:

dosage forms

- didanosine capsules
- efavirenz tablets
- emtricitabine capsules
- emtricitabine and tenofovir tablets
- emtricitabine, tenofovir and efavirenz tablets.

The monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the normal consultative process, i.e. in line with the steps followed in the development of new monographs, and based on comments made during discussion.

4.3.2 *Antimalarial medicines*

New monographs for the following antimalarials were presented to the Expert Committee for discussion:

dosage forms

- mefloquine tablets
- sulfadoxine and pyrimethamine tablets

The monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the normal consultative process, i.e. in line with the steps followed in the development of new monographs, and based on comments made during discussion.

While carrying out the work for the general revision on the artemisinin derivatives monographs (artemether, artemisinin, artemotil, artenimol, artesunate and their associated dosage forms), the opportunity was taken to develop in parallel a new specification for the parenteral preparation of artesunate, which is particularly recommended in the treatment of severe malaria.

The following monograph could, therefore, be presented to the Expert Committee for discussion:

dosage form

- artesunate for injection.

The monograph was adopted, subject to inclusion of the agreed changes, based on the comments received during the normal consultative process, i.e. in line with the steps followed in the development of new monographs, and based on comments made during discussion.

4.3.3 *Antituberculosis medicines*

New monographs for the following antituberculosis active substances and dosage forms were presented to the Expert Committee for discussion:

active pharmaceutical ingredients (APIs)

- capreomycin sulfate
- ofloxacin
- levofloxacin

dosage forms

- capreomycin injection
- ofloxacin tablets
- levofloxacin tablets

The monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the normal consultative process, i.e. in line with the steps followed in the development of new monographs, and based on comments made during discussion.

The following monograph was presented to the Expert Committee in October 2009 for addition to *The International Pharmacopoeia*:

dosage form

- kanamycin injection

Although the monograph was adopted, recirculation was recommended by the Expert Committee requesting comments on the shifting of the determination of the conversion factor from international units (IU) to micrograms.

To avoid the use of an arbitrary conversion factor, a revised version of the text was proposed for discussion during the consultation on specifications for medicines and quality control issues held in May 2010, where it was agreed that the replacement of the current microbiological assay by a high-performance liquid chromatography (HPLC) method would be preferable as this would allow direct expression of the quantities of kanamycin in terms of mass.

It was recognized, however, that the application of HPLC to this substance would be subject to detection difficulties owing to the poor absorbance properties of kanamycin in ultraviolet (UV). Possible HPLC methods and their suitability for inclusion in Ph.Int. were thus discussed and it was finally recommended that a UV detection method using derivatization be developed, rather than a method using more sophisticated detectors such as electrochemical ones that may not be widely available. While this HPLC method was still under investigation, it was agreed that, once ready, the revised monograph would be circulated for comment.

Meanwhile, and in order to make the monograph available to users, it was agreed that the text adopted in October 2009 be posted on the WHO Medicines web site with an appropriate *Note from the Secretariat* indicating that a forthcoming revision was envisaged for the assay.

The Expert Committee endorsed the recommendations made by the participants at the consultation.

4.3.4 *Anti-infectives*

New monographs for the active dosage forms of the following anti-infectives were presented to the Expert Committee for discussion:

- amoxicillin oral suspension[10]
- levamisole tablets
- metronidazole oral suspension[10]
- sulfamethoxazole and trimethoprim tablets[10]

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[10] These monographs were developed in the context of collaboration between *The International Pharmacopoeia and The British Pharmacopoeia*, on which these texts are based.

The monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the normal consultative process, i.e. in line with the steps followed in the development of new monographs, and based on comments made during discussion.

4.3.5 *Other medicines*

New monographs for the following dosage forms were presented to the Expert Committee for discussion:

- levonorgestrel tablets
- oseltamivir capsules
- sodium bicarbonate intravenous injection

The monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the normal consultative process, i.e. in line with the steps followed in the development of new monographs, and based on comments made during discussion.

4.4 *Revision of texts of* The International Pharmacopoeia

4.4.1 *Antimalarials: artemisinin derivatives*

Since 2008, extensive revision work had been initiated for the general revision of the artemisinin derivatives monographs of *The International Pharmacopoeia*.

Particular aspects that required revision were the method used for the Related substances test and the Assay; and the addition of potential impurities shown to be controlled by the requirements of the monographs.

Artesunate

Subsequent to the development of a new monograph for artesunate for injection, the monograph for artesunate, revised in 2009, needed further modification to add specific requirements for the API intended to be used for parenteral preparations. A newly revised text was thus presented to the Expert Committee for discussion. The monograph was adopted, subject to inclusion of the agreed changes, based on the comments received during the public inquiry and those made during the discussion.

Other artemisinin derivatives

This general revision of artemisinin derivatives involved about 15 texts. Monographs for artesunate and artesunate tablets had already been adopted in October 2009. Prioritization for revision had been proposed for the rest of this series in order to make the most useful monographs available to users in a timely manner.

In line with the WHO treatment guidelines for malaria, where the use of these antimalarials as a monotherapy was no longer prescribed, the Expert Committee agreed that while revising the monographs for the corresponding monocomponent dosage forms, priority would be assigned to the products that could be co-packaged.

The Expert Committee was pleased to note that work had progressed, notably for the API monographs on artenimol (dihydroartemisinin) and artemether. Further, it was acknowledged that the development of other specifications had been initiated for fixed-dose combination medicines used in the combination therapy, such as that for artesunate and amodiaquine tablets or artenimol and piperaquine phosphate tablets.

4.4.2 *Other medicines*

Oseltamivir phosphate

The monograph for oseltamivir phosphate was initially adopted in October 2008. A revision of this text was presented in October 2009 after receipt of several comments on the tests for Sulfated ash and Related substances, leading to the adoption of a revised text where only the correction proposed for the Related substances test was retained. To respond to the continuing difficulties encountered by users when carrying out the test for sulfated ash, a revised version of this monograph was considered.

The Expert Committee adopted the newly revised text, which now harmonized the Ph.Int. text to the specifications for oseltamivir phosphate, also available in other pharmacopoeias (Ph.Eur and USP).

Heparins

A brief update was presented on the revision of the Heparins monographs decided upon in 2009, in order to include an electrophoresis method capable of detecting potential glycosaminoglycan impurities of heparin (dermatan sulfate, chondroitin sulfate and oversulfated chondroitin sulfate). The Expert Committee noted that the revision work had been initiated.

Retinol

Vitamin A supplementation therapy was supported by several initiatives of WHO and partner organizations. UNICEF had expressed interest in pharmacopoeial specifications for oral dosage forms containing retinol concentrate, oily form, to fight vitamin A deficiency, xerophthalmia and nutritional blindness.

To satisfy these needs, draft versions of the monographs:

- retinol concentrate, oily form
- paediatric retinol capsules

- paediatric retinol oral solution

were prepared and preliminarily discussed during a tele-/videoconference on specifications for medicines and quality control laboratory issues in August 2010. The draft monographs were circulated and comments were collated. The revised monographs were presented at the 45th meeting of the Expert Committee.

The Committee adopted the monograph on retinol concentrate, oily form, subject to inclusion of the agreed changes, based on the comments received and those made during the discussion.

Paediatric vitamin A soft-gel capsules have a unique mode of delivery. They are furnished with a small nipple which can be cut off so that the liquid content can be easily squeezed into the mouth of a child. The Committee decided to subsume this dosage form under the monograph on vitamin A oral solution, considering the soft gelatin shell as a single-unit container and the liquid content as the actual dosage form. The Expert Committee recommended that the monograph on paediatric retinol oral solution be modified so that its specifications can also be applied to these single-dose units. The capsule monograph was then to be withdrawn.

Paracetamol

Draft versions of the monographs:

- paracetamol oral solution; and
- paracetamol oral suspension

were prepared and preliminarily discussed during a tele-/videoconference on specifications for medicines and quality control laboratory issues in August 2010. The draft monographs were circulated and comments were collated. The revised monographs were presented at the 45th meeting of the Expert Committee. The Committee adopted the monographs, subject to inclusion of the agreed changes, based on the comments received and those made during the discussion.

4.5 Review of published general monographs for dosage forms and associated method texts

4.5.1 *Pharmacopoeial Discussion Group: harmonized general texts*

The Expert Committee members were updated on the discussions and recommendations of the informal consultation held in May 2010. Ph.Int. general methods, as discussed during previous Expert Committee meetings, are suggested for revision, taking into account the texts harmonized by the PDG (*European Pharmacopoeia*, *Japanese Pharmacopoeia* and *United States Pharmacopeia*).

During their 42nd and 44th meetings, the Expert Committee endorsed the suggestion that "the relevant method texts of *The International Pharmacopoeia* should be reviewed alongside the finalized, harmonized PDG texts in order to identify any differences and to ascertain to what extent it might be appropriate to revise the texts of *The International Pharmacopoeia*. Any proposed changes would then be circulated in accordance with the usual WHO consultation process. Once the suggested actions had been identified and agreed by the Expert Committee, the WHO Secretariat would contact the PDG, as appropriate, with regard to its decisions on the use of PDG harmonized texts".

Following this recommendation, a formal request was formulated by the WHO Secretariat to the PDG, which resulted in authorization being given by all three pharmacopoeias of the PDG to use the sign-off text as a basis for publication in *The International Pharmacopoeia* and agreeing that the text needed to be converted into the style of *The International Pharmacopoeia*.

The Expert Committee agreed that individual PDG method texts might be included in the Ph.Int. as follows, either as:

- *methods supporting the text requirements of the Ph.Int. monographs*: included within the Methods of analysis section either in place of an existing method or as a new method.
  In the case of a method intended to replace an existing method, it might be possible to publish both for an interim period so that the "old" method can be used until the relevant monographs are revised; or
- *methods provided as guidance* with a specific reference made in the Ph.Int. monographs: included within the Supplementary information section; or
- *as general information* to which no reference is made within the Ph.Int. monographs: included within the Supplementary information section.

Revisions to existing Ph.Int. texts would be circulated in accordance with the usual WHO consultation process.

In the case of a new text to be included in the Method of analysis section of the Ph.Int., it was recommended to indicate the monographs (published and under elaboration) to which it was intended that the new texts should apply.

The PDG harmonized general methods reviewed and covered by this approach were the following:

- Residue on ignition/sulfated ash
- Test for extractable volume of parenteral preparations
- Test for particulate contamination: subvisible particles
- Microbial examination of non-sterile products: microbial enumeration tests
- Microbial examination of non-sterile products: tests for specified microorganisms

- Microbial examination of non-sterile products: acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use
- Disintegration test
- Uniformity of dosage units
- Dissolution test
- Sterility test
- Tablet friability

Harmonization of the tests was still under discussion at the PDG and would be considered at a later date.

The Expert Committee endorsed the proposals presented and the general approach outlined in the background paper. It advised that clear indications be added to the proposed revised texts when circulating them for comment to explain the approach followed for each harmonized method (e.g. revision, addition or for supplementary information).

The Expert Committee also recommended that once a harmonized PDG method was included in the Ph.Int. a mechanism would be needed to ensure that any further change implemented in the PDG texts be captured in the corresponding text published in Ph.Int.

4.5.2 *Uniformity of content for single-dose preparations*

The Expert Committee discussed the application of the test for uniformity of content as described in Method 5.1 of the Ph.Int. for fixed-dose combinations (FDCs) in view of the increasing importance of these products.

The Expert Committee recommended that, in deciding whether a requirement should be included in monographs for FDC tablets or capsules, where none of the APIs are present in less than 5 mg, each case would be judged on its merits. During development of the monograph, account would be taken of the WHO FDC guidelines. A test for uniformity of content of one or more of the active ingredients would be specified for application to the relevant tablet/capsule strength(s). Meanwhile, in accordance with the new approach adopted on the implementation of PDG harmonized texts in the Ph.Int., the general method text 5.1 would not be modified. It was noted that, in the absence of a requirement for uniformity of content in a specific, individual tablet/capsule monograph, compliance with the test for uniformity of mass (5.2) was usually required by means of the relevant general monograph.

The Expert Committee recommended that, when a requirement for uniformity was specified in a monograph:

— wherever possible, the analytical method would be described in the individual monograph; and

— where appropriate, the average of the 10 individual results obtained in the test would be used for the assay. This would avoid repeating the analysis on a mixed sample of the tablets or capsules.

4.6 General policy topics and general revision issues for *The International Pharmacopoeia*

4.6.1 *Update on dissolution tests*

Following the discussions held at several Expert Committee meetings and during consultations on the issue of the addition of dissolution tests in specific monographs, a document summarizing the previous discussions and recommendations was presented to the Expert Committee.

The main recommendations and priorities endorsed by the Expert Committee during previous discussions were as follows:

- a standardized dissolution test would be applied to tablets and capsules containing highly soluble APIs:
  - as an alternative to disintegration (using a defined format, that applied, for example, to the monograph of isoniazid and ethambutol hydrochloride tablets),
  - subject to amendment of the criteria; and
- the development of additional dissolution tests would be further reviewed.

In line with these recommendations, a dissolution test had recently been developed for a certain number of new or published monographs for products with highly soluble APIs (for example, during the process of the general revision on artemisinin derivatives). However, work still needed to be done on those monographs where a cross-reference to the general method was made.

In view of the amount of work that these revisions would require, it was proposed that priority for revision be given to those monographs where a statement clearly indicated that the test was under development or where a reference to the general method without requirements was made and to those monographs that were already assigned priority due to bioavailability or poor solubility problems (as identified in the 31st report of the Expert Committee and indicated with an asterisk* within the list below).

This represented *16 monographs,* extracted from the list of preparations presented in Annex 1 of document QSM/EC/07.21, amended to include affected monographs published since 2007:

- ampicillin capsules
- artemether capsules
- artemether tablets

- artemisinin capsules
- artemisinin tablets
- artenimol tablets
- carbamazepine tablets
- erythromycin ethylsuccinate tablets*
- erythromycin stearate tablets*
- griseofulvin tablets*
- ibuprofen tablets
- indometacin tablets
- phenytoin sodium tablets*
- rifampicin, isoniazid and ethambutol tablets
- rifampicin and isoniazid dispersible tablets
- rifampicin, isoniazid and pyrazinamide dispersible tablets

This priority list was discussed during the consultation held in May 2010, where it was recommended that priority should indeed be assigned to those monographs listed, with the exception, however, of the following monographs on artemisinin derivatives, the products of which were no longer marketed and, therefore, a revision was not required:

- artemether capsules
- artemether tablets
- artemisinin capsules
- artemisinin tablets

In order to be able to rapidly develop and include a dissolution test in the monographs that have been identified, the Expert Committee endorsed the recommendation that a pragmatic approach be followed, based on methods that are publicly available.

The Expert Committee further recommended that general guidance be developed for the dissolution test so that a clear general policy could be established on when to include this test in new monographs, preferably, if at all possible, at the early stages of their development.

4.6.2 *Dry powders*

With the development of the monograph on amoxicillin oral suspension in collaboration with *The British Pharmacopoeia (BP)*, the issue of how to deal in *The International Pharmacopoei*a with formulations that are intended to be modified by the patient before use was raised. It was noted that the two pharmacopoeias had different approaches for these formulations:

— BP was considering the final product (i.e. the reconstituted solution, suspension or injection) and reflecting this in the monograph titles (in this case Amoxicillin oral suspension); and

— Ph.Int. had so far been taking into consideration the product before reconstitution (i.e. the powders — several examples of powders for injections or oral powders can be found in the fourth edition).

When discussing the draft monograph on amoxicillin oral suspension during the consultation held in May 2010, it was recommended that a standardized policy be followed in *The International Pharmacopoeia* for monographs on oral solutions or suspensions that need to be reconstituted from powders.

It was recognized during the consultation that the particular case of powders for injections which are also formulations that should be reconstituted before use, was not affected by the policy to be defined for powders for oral use, because these reconstituted formulations were to be used immediately after reconstitution and, therefore, were not intended to be kept and eventually stored for analysis purposes, for reasons concerning stability and sterility.

The Expert Committee recommended distinguishing from now on in the titles of the Ph.Int. monographs between the injections that are manufactured as liquid preparations and those intended to be reconstituted before use from a powder, by adding the preposition "for" in the title of the monographs on reconstituted injections.

The titles of the following draft monographs presented to the Expert Committee illustrate this approach:

— Capreomycin *powder for injections* revised to Capreomycin *for* injection
— Artesunate *powder for injections* revised to Artesunate *for* injection

This revision has also been applied to the following texts, adopted in October 2009 and available on the WHO Medicines web site:

— Amikacin *powder for injections* revised to Amikacin *for* injection
— Kanamycin *powder for injections* revised to Kanamycin *for* injection

For the published monographs (listed below) on powders for injection, which now require revision, it was recommended that the same approach be followed. Any revision of the current titles could be made when the opportunity arose, either when the monographs in question were revised for technical reasons or on publication of a new edition:

— amphotericin B powder for injections
— ampicillin sodium powder for injections
— benzylpenicillin potassium powder for injections
— cloxacillin sodium powder for injections
— pentamidine isetionate powder for injections
— prednisolone sodium succinate powder for injections
— procaine benzylpenicillin powder for injections
— streptomycin sulfate powder for injections

As regards oral suspensions or solutions reconstituted from powders it was recommended to consider the final preparation throughout the monograph. This approach was reflected in the text for amoxicillin oral suspension presented for discussion and adopted at the present meeting, when considering the aspects of the monograph, as described hereafter.

Based on the above, the Expert Committee adopted the following new policy for such monographs.

Title of the monograph. Title and requirements of the monograph would correspond to the final preparation rather than the powder.

Definition. Any distinction, as to whether the oral suspension or solution needed to be reconstituted or was directly manufactured as a liquid, would be mentioned under Definition. Any necessary indication on the reconstitution of the final preparation would be given in this section as well.

Reference to general monographs. Compliance of the final product with the general monograph for "Liquid preparations for oral use" and that of the powder with the section of the monograph entitled "Powders for oral solutions, oral suspensions and oral drops" would be maintained, as it is currently mentioned in published monographs on powders for oral use.

Manufacture. When specific requirements referring to the powder needed to be included in the monograph, they would be mentioned by means of a statement or a test with or without specific limits, under this section (e.g. Test for water content).

It was also recognized that the quality of the reconstituted product during the in-use period as stated on the label should be considered. It was, therefore, proposed to cover this aspect by introducing, under the Manufacture section, a requirement with a minimum limit to be met at the end of the defined in-use period for content, with a statement as follows:

> "The product is formulated in such a way that when the suspension is constituted following manufacturer's instructions, stored at the temperature for the in-use period stated on the label and assayed using the method described below under Assay, it contains not less than 80.0% of the amount of amoxicillin ($C_{16}H_{19}N_3O_5S$) stated on the label."

Tests. Amounts to be taken for testing would be expressed in terms of quantities of the reconstituted solution or suspension and not the powder.

For example, "dilute an accurately weighed *quantity of the oral suspension* containing the equivalent of 60 mg of amoxicillin."

The published monographs on oral powders should be revised in accordance with this new policy. It was recommended to follow the same approach as above for the future revisions of monographs for powders for injections.

5. Quality control — international reference materials (International Chemical Reference Substances and International Infrared Reference Spectra)

5.1 Update on transfer of International Chemical Reference Substances

In April 2010 the European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe took over the responsibility for the establishment, preparation, storage and distribution of WHO International Chemical Reference Standards (ICRS) from Apoteket AB, the previous WHO Collaborating Centre for Chemical Reference Substances. Reference material that was held and distributed by Apoteket AB will from now on be distributed by EDQM.

Start-up meetings were held in June and September 2010 in Strasbourg, France. Essential agreements were made as follows:

1. For the analytical characterization of the reference substances, EDQM will follow the general *WHO Guidelines for the establishment, maintenance and distribution of chemical reference substances*, last revised and adopted during the 41st meeting of the Expert Committee on Specifications for Pharmaceutical Preparations.
2. In the first campaign EDQM will establish as a priority the following 10 ICRS (Table 1).

Table 1
Priority International Chemical Reference Substances for establishment by EDQM

No.	Substance
1	artemisinin
2	lumefantrine for system suitability
3	artenimol
4	artesunate
5	artemether
6	efavirenz impurity B
7	lopinavir
8	emtricitabine
9	tenofovir disoproxil fumarate
10	alpha-artemether

The Expert Committee members expressed their appreciation for these new developments in light of the technical expertise and experience of EDQM in establishing primary reference standards. This new collaboration was considered to enhance the availability of ICRS and thus foster the use of

The International Pharmacopoeia as a reference for specifications and analytical methods for medicines of major public health impact.

The Expert Committee took note of the report and endorsed the agreements made.

5.2 Proposal for an accelerated release of International Chemical References Standards

ICRS were in the past first provisionally adopted by the Expert Panel and then finally adopted by the Expert Committee during its annual meeting. The following process was followed:

> "Newly established International Chemical Reference Substances, proposed by the WHO Collaborating Centre for Chemical Reference Substances on the basis of adequate testing and characterization, are included in the Centre's annual report. The report is circulated, inter alia, to members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations, who are requested to consider the proposals carefully together with the attached analytical documentation, and to notify the Centre of any reservations or adverse comment within three months of the date of mailing. In these cases the Centre will proceed with any consultations or additional analyses necessary for the validation.
>
> If no adverse comments are received within the three-month period, the proposed new International Chemical Reference Substance may be considered provisionally adopted. It will be considered for final adoption during the subsequent meeting of the Expert Committee."[11]

EDQM will issue an individual analytical report after the establishment of a new reference substance, after the analysis of candidate material for stock replenishment and after monitoring the stability of material in stock.

The Secretariat made the proposal that these analytical case-reports be reviewed a priori by the Secretariat with assistance from the collaborating laboratory. If the testing is performed according to the above-mentioned adopted guidelines and if the candidate material is considered to be suitable to serve as a reference material the ICRS will be released provisionally. The Secretariat will contact the collaborating laboratory for assistance in the case that the analytical testing reveals information that requires further consideration. The distribution of the ICRS could start after the provisional release.

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[11] *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-second Report.* Geneva, World Health Organization, 1990 (WHO Technical Report Series, No 790, p. 15).

The analytical case-reports, together with a consolidated EDQM annual report describing all activities related to the establishment of ICRS, are then distributed first to the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations for comment, then again to the Expert Panel for adoption. The analytical case-reports are appended to the annual report as annexes.

The proposed simplification of the process will expedite the establishment of new reference substances and will enable WHO to react faster to the urgent demand for ICRS.

If additional explicit provisions for the release of reference substances are needed, they will also be presented to the Expert Committee for approval.

Support for the accelerated release procedure to speed up the availability of ICRS was given by the Committee.

The Expert Committee members approved this new procedure (Annex 1).

5.3 Proposed first International Standard for biosynthetic human insulin

In a joint session with the Expert Committee on Biological Standardization, the Committee discussed an initiative to evaluate a candidate International Standard for Human Recombinant Insulin.

The WHO Expert Committee on Biological Standardization establishes International Biological Reference preparations of complex composition that require the use of biological or immunological assays for appropriate characterization.

Reference standards (ICRS) for physicochemical assays are described in *The International Pharmacopoeia*. These are endorsed by the Expert Committee on Specifications for Pharmaceutical Preparations.

The Expert Committee on Biological Standardization agreed with a proposal to develop a reference preparation so that it continues to be possible to define the IU and also to investigate potential use of the reference preparations in the diagnostic area. The Expert Committee on Specifications for Pharmaceutical Preparations noted that diagnostics was outside its mandate. Both Expert Committees considered that further work was needed to make a decision on whether the proposed reference material would be of potential use in the therapeutic area. Both Committees requested WHO to publish a statement on the conversion factor between activity and mass units.

The Expert Committee on Specifications for Pharmaceutical Preparations recommended developing International Chemical Reference Standards on Insulin to be used as primary standards in physical and physicochemical

methods described in monographs on insulin and insulin dosage forms published in *The International Pharmacopoeia*. If the standards are intended to be used in assay tests the assay assignment should be in mass units of milligrams.

6. Quality control — national laboratories

6.1 External Quality Assurance Assessment Scheme

The External Quality Assurance Assessment Scheme (EQAAS) aims to give each participating laboratory the opportunity to measure its performance through a confidential system of testing of blind samples and to determine its ability to perform a given analytical procedure within a network of governmental control laboratories. The system should reinforce mutual confidence within the network.

Currently, WHO has been able to maintain this service and provides samples and testing protocols for Phase 5 of the EQAAS programme. Some 60 quality control laboratories from all six WHO regions have been invited to participate in this Scheme.

Phase 5 — Procedure 1: Assay by water-free titration

Participants were requested to determine the content of metronidazole in a common sample according to a method described in the monograph on metronidazole published in the fourth edition of *The International Pharmacopoeia*. Fifty-two participants submitted their results.

Twelve laboratories (23% of the participants) reported results that were either questionable or unsatisfactory. These laboratories were invited to share their investigations with WHO into the cause of the failure and their corrective and preventive actions. The laboratories concerned were informed by the Secretariat about the main approaches to dealing with questionable or unsatisfactory results.

Phase 5 — Procedure 2: Semi-microdetermination of water by Karl-Fischer

The study is currently taking place. The Committee was informed about the time lines.

Overview of planned proficiency tests in Phase 5

The planned proficiency tests were presented to the Committee and are listed in Table 2.

Table 2
Planned proficiency tests in Phase 5

Number	Test	Sample	Return of results by
5.3	Dissolution test	Artemether and lumefantrine tablets	1 April 2011
5.4	Density and pH measurement	Abacavir oral solution	15 September 2011
5.5	Assay by high-performance liquid chromatography	Amodiaquine and artesunate tablets	15 March 2012
5.6	Dissolution test	Rifampicin capsules	15 August 2012
5.7	Related substances by thin-layer chromatography	Artemether and lumefantrine oral suspension	15 December 2012

A discussion was held and questions were posed about the performance of laboratories and whether a change in personnel, e.g. laboratory staff, had an influence on performance. It was suggested that cross-checks be made to see whether in laboratories that had failures, these had been triggered by changes in personnel.

The Committee took note of the latest activities in this programme and fully supported the work carried out to assist quality control laboratories in their capacity-building efforts.

6.2 WHO good practices for pharmaceutical microbiology laboratories

Further to the revision of the WHO good practices for pharmaceutical control laboratories, during the inspections carried out when prequalifying laboratories, the inspectors had noticed that these guidelines might benefit from complementation with a specific text for pharmaceutical microbiology laboratories.

A draft document was presented to the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its 44th meeting and circulated for comments in accordance with the usual procedure. A revised draft was discussed during the informal consultation on quality assurance systems, medicines and risk analysis in May 2010 and mailed out for comments. These responses were currently under evaluation.

The guidelines were adopted subject to review by a group of selected specialists (constituted during the meeting) in light of the comments received. The Expert Committee members would receive the outcome of this

review for their reconfirmation and to confirm adoption of the guidelines (Annex 2).

7. Quality Assurance — good manufacturing practices

7.1 Update of WHO GMP main principles for pharmaceutical products

Proposals for updating the WHO GMP main principles were discussed at various informal consultations and received as feedback to the increased implementation of this text. Discussion during the consultation on WHO guidelines for medicines quality assurance, quality control laboratories and transfer of technology on 27–31 July 2009, revealed the need to incorporate a new section (1.6) on "Product quality review" under Chapter 1: "Quality assurance" in the *WHO good manufacturing practices (GMP): main principles for pharmaceutical products*.

In addition, several updates have been suggested to further enhance and include the concept of risk management (in paragraphs 1.2 and 1.4 and 1.5 (new) of the text), replacement of "drugs" by "medicines" and inclusion of the concept of a "quality unit" in the section on key personnel and related paragraphs in other parts of the text.

The Expert Committee agreed to update the guidelines accordingly and recommended publication of the entire guidelines as an Annex to its report in order to replace the one previously published as Annex 4, WHO Technical Report Series, No. 908 in 2003 (Annex 3).

7.2 WHO GMP for blood establishments

Based on recent discussions worldwide, including during the 63rd World Health Assembly, quality assurance for blood products has received increased attention. New concepts for blood establishments and blood collection are being discussed internationally as, currently, large amounts of blood samples have to be discarded. The World Health Assembly resolution was passed with the intention of strengthening the regulatory oversight for blood products. In response to these efforts, and in order to serve Member States, new good practices for blood establishments were drafted.

Relying on the expertise of the specialists in the Expert Committee on Biological Standardization — blood products track, the Expert Committee on Specifications for Pharmaceutical Preparations agreed to consider this new GMP text in order to provide Member States with the full set of WHO GMP texts in a comprehensive manner. The new GMP text describes the full series of steps to be covered by blood establishments. It was drafted by

a special taskforce, widely reviewed in-house and by WHO Regions, as well as by the blood regulatory network. Moreover, it was posted on the web for public comments.

The Expert Committee members considered this text to be more comprehensive than the texts for the rest of the pharmaceutical products. However, due to the special environment in which the new guidance will be used, it was found to be acceptable in this format to make it more user-friendly, as the users of this text are traditionally not used to working with the overall applied GMP principles.

The new good practices were adopted as amended by the specialists in the Expert Committee on Biological Standardization blood products track (Annex 4). It was recommended to add an explanatory note as to why it is more comprehensive than the guidelines for other pharmaceutical products.

7.3 Update of WHO GMP for heating, ventilation and air-conditioning for non-sterile pharmaceutical dosage forms

The supplementary guidelines on GMP for heating, ventilation and air-conditioning (HVAC) for non-sterile pharmaceutical dosage forms were published in 2006. This text was considered to be rather unique in the NMRA-related environment.

Feedback was received from inspectors and users suggesting that this text would benefit from an update in order to allow for inclusion of new trends in this area and to harmonize with other related new documents published, e.g. by the International Organization for Standardization (ISO). Comments received when circulating the proposal were discussed in an informal consultation on quality assurance systems, medicines and risk analysis on 4–6 May 2010. The Expert Committee members reviewed the proposed text and requested technical assistance from specialists in this area. A small subgroup was created which looked at the additional comments received prior to and during the Expert Committee meeting.

The guidelines were adopted subject to review by a group of selected specialists (constituted during the meeting) in light of the comments received. The Expert Committee members would receive the outcome of this review for their final adoption of the guidelines (Annex 5). The Committee further recommended publication of the entire guidelines as an annex to the report.

7.4 Update of WHO GMP: Water for pharmaceutical use

The *WHO good manufacturing practices: water for pharmaceutical use* was adopted by the Expert Committee on Specifications for Pharmaceutical Preparations in 2005 and published in its thirty-ninth report, WHO Technical

Report Series, No. 929 as Annex 3. During implementation a need for an update was identified and proposed by the WHO Prequalification Inspection team. This was reconfirmed and discussed during the informal consultation on quality assurance systems, medicines and risk analysis held in May 2010 in Geneva. The proposed changes were thereafter mailed out widely for comments.

The Expert Committee members recommended continuation of the consultation process.

7.5 Revision of WHO GMP: Sterile pharmaceutical products

During the 44th WHO Expert Committee on Specifications for Pharmaceutical Preparations in 2009 *GMP on sterile pharmaceutical products* were adopted in a revised version as Annex 4 to the Expert Committee report and published in the WHO Technical Report Series, No. 957, 2010. Since then a proposal for a maintenance process had been received and submitted to the Expert Committee members.

The Expert Committee reviewed all proposed changes in detail and found them to be of good editorial nature involving no change to the technical requirements. The Expert Committee members agreed to all modifications and recommended, in order to make the updated text easily available and to avoid confusion and misinterpretation, to republish the text in its entirety as Annex 6.

The Expert Committee members took this opportunity to recommend that the Secretariat should develop a general policy with regard to future maintenance processes and present it to the Expert Committee at its forty-sixth meeting.

8. Quality Assurance — new approaches

8.1 WHO guidelines on quality risk management

In response to the recommendations of the 44th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, the Secretariat had initiated the drafting of the *WHO guidelines on quality risk management*. The initial draft structure was reviewed at the informal consultation on quality assurance systems, medicines and risk analysis held in May 2010 and further elaborated thereafter. Upon circulation, numerous comments were received.

The Expert Committee members expressed their general support for this document which included more detail than other international guidance, e.g. the ICH Q9. It was recommended that a group of experts should continue to work on the document to bring it to a more mature level.

8.2 WHO guidelines on technology transfer

The Expert Committee members reviewed the feedback on the newly proposed *WHO guiding principles on transfer of technology in pharmaceutical manufacturing.* It was noted that a large number of comments were received. A small group was then constituted to discuss the feedback obtained both in the meeting and following circulation.

The Expert Committee subsequently reviewed the outcome of these discussions and adopted the revised text as Annex 7.

9. Quality assurance — distribution and trade of pharmaceuticals

9.1 Good pharmacy practice: standards for quality of pharmacy services

The Expert Committee members were briefed in detail about the steps undertaken towards a revision of the joint WHO/FIP good pharmacy practice (GPP) in order to accommodate new trends and developments.

The first text on good pharmacy practice had been submitted to the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1994. Following the recommendations of the WHO Expert Committee and the endorsement of the FIP Council in 1997, the FIP/WHO joint document on GPP was published in 1999 in the thirty-fifth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 885).

With the overall aim of improving standards and practice of distribution and use of medicines, using the FIP/WHO Guidelines for GPP as the framework, FIP took the initiative to explore the possibilities for providing technical assistance to its Member Organizations in Cambodia, Moldova, Mongolia, Paraguay, Thailand, Uruguay and Viet Nam, in developing national standards for GPP in a pilot study from 2005 to 2007. In 2007 the "Bangkok declaration on good pharmacy practice in the community pharmacy settings" in the South-East Asia Region was adopted by the FIP South-East Asia Pharmaceutical Forum and set out a strong commitment towards raising standards of pharmacy services and professional practice.

Since the adoption of the GPP guidelines in community and hospital settings, significant changes in practice, applied science and technology and pharmaceutical policy have occurred, including the relevance of more recent World Health Assembly resolutions: WHA54.11 (WHO Medicines Strategy), WHA54.13 (Strengthening health systems in developing

countries), WHA55.14 (Ensuring accessibility of essential medicines), WHA55.18 (Quality of care: patient safety), WHA57.16 (Health promotion) and WHA60.16 (Rational use of medicines).

Furthermore, in 2007 FIP established an initiative to investigate the need to update the guidelines on GPP to reflect contemporary standards of practice and thinking. An FIP working group on GPP first met on 15 October 2007 to identify key issues that needed to be considered in the revision of the guidelines.

In 2008 FIP organized an expert consultation in Basel, Switzerland during its 68th World Congress. Fifty participants attended the meeting, including the FIP Working Group (WG) on GPP, WHO staff from headquarters, representatives from the WHO Regional Office for the Eastern Mediterranean, country medicines advisers from Ghana, Nigeria and the United Republic of Tanzania, Presidents and Secretaries of the six FIP Regional Pharmaceutical Forums, FIP Member Organizations and several invited experts.

Following this consultation the FIP WG on GPP undertook an extensive review of the existing national standards on GPP in at least 37 countries and established a time frame that would allow sufficient consultation with all of FIP's 124 national Member Organizations, relevant experts and WHO. A proposal for this initiative was presented to the Committee on Specifications for Pharmaceutical Preparations at its forty-third meeting in October 2008 and an updated report was provided to the Expert Committee at its forty-fourth meeting in October 2009.

The revised GPP proposal was widely circulated for comments within the FIP and WHO consultation process. The outcome was presented to the FIP Member Organizations at their annual meeting in September 2010 and subsequent to additional discussions, it was adopted in principle with a view to presenting it to this Expert Committee.

This newly revised guidance is intended to serve as a standard forming a baseline to be adjusted to the needs in a specific country. The document is directed at civil society and Member States.

The Expert Committee members acknowledged the role of pharmacists in the supply chain. It was considered that it is up to each country itself to determine what can be done according to its regulatory framework. The Expert Committee also noted the shortage of pharmacists in numerous developing countries.

The Expert Committee welcomed the updated GPP, discussed several modifications to the text and adopted it in its revised form as new standards for quality of pharmacy services (Annex 8).

9.2 Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

The Expert Committee was briefed about the history and steps involved in the development of this new guidance in the joint session with the Expert Committee on Biological Standardization. After making suitable amendments, the Expert Committee on Biological Standardization and the Expert Committee on Specifications for Pharmaceutical Preparations recommended that the Guidelines be adopted and appended to their respective reports. In addition the Expert Committee on Biological Standardization recommended:

— that an addendum to the document be developed for labile blood products; and
— that WHO consider providing guidance to national regulatory authorities on how to define transport requirements for time- and temperature-sensitive pharmaceutical products (TTSPP).

During the joint session with the Expert Committee on Biological Standardization it was recommended to refer to "suspect" products in section 8.5 to allow for dealing with problems related to the quality of the product not covered in other sections of the document.

The Expert Committee adopted the text with the changes proposed (Annex 9).

9.3 WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce

9.3.1 *Update on current activities*

The Expert Committee was updated on the WHO Certification Scheme. The Committee was informed that a Circular Letter had been sent to Member States on 15 January 2010 asking them to comment on the report of the Expert Committee on Specifications for Pharmaceutical Preparations and to provide updated contact addresses of the respective competent authorities of Member States participating in the WHO Certification Scheme. The response received so far had been extremely low and comments received on the suggestions and recommendations made in previous Expert Committee meetings lacked uniformity. Countries made a number of requests to be covered by the Certification Scheme such as attachment of summary product characteristics (SPC), access to the WHO assessment report, creation of low-risk products, a separate certificate for low-risk products, and inclusion of a date of validity of the issued certificate, among others.

The Committee was also informed that Poland had joined the WHO pharmaceutical starting materials certification scheme (SMACS).

The Committee noted the update and recommended further encouragement to Member States to respond to the Circular Letter, e.g. during the forthcoming ICDRA meeting.

9.3.2 *Questions and answers*

Based on the Committee's recommendations, a question and answer paper was prepared on the function of the Scheme for posting on the WHO web site and for publication in *WHO Drug Information*, with the possibility for receiving comments and reviewing any question(s) and answers.

The Expert Committee noted the updated report from the Secretariat.

10. Prequalification of priority essential medicines

10.1 Update on the WHO Prequalification of Medicines Programme

The Manager of the WHO Prequalification of Medicines Programme briefed the Expert Committee on the existing procedure for prequalification of pharmaceutical products and activities undertaken so far. He said that the Programme provided services to United Nations and international agencies that procure and purchase medicines with donated funds. The work of the Programme includes dossier assessment and inspection of manufacturers, clinical trial sites and laboratories to ensure compliance with good practices. So far the Programme has prequalified 39 medicines of which three are manufactured in Africa (one in South Africa, one in Uganda and one in Zimbabwe). The Programme also has prequalified laboratories; for details see section 11.1.

Another activity of the Prequalification of Medicines Programme is to build NMRA capacity by conducting training seminars and providing technical assistance.

The Committee was informed that the Programme had also been active in quality surveys of antimalarials (QAMSA) in six African countries in 2008–2009. The activity involves collection of sample antimalarial drugs, using a standard protocol, from different levels of the supply chain, public and private as well as formal and informal outlets. The survey was conducted through WHO cooperation with the NMRAs from participating countries. Trained survey teams in each country were responsible for collecting samples according to national sampling plans from different distribution levels, including the informal market in at least three geographical regions of high malaria prevalence. In total 935 samples were collected from April to June 2008 and screened. Based on predefined criteria, 306 samples (from 64 manufacturers and 218 sampling sites) were selected for full quality control testing in the WHO-prequalified laboratory in South Africa and in the United States Pharmacopeia (USP) laboratory in the USA.

Testing was coordinated by WHO and specifications of *The International Pharmacopoeia* or USP were used.

During the survey, data were collected that made it possible to relate the results of quality testing to distribution levels, geographical regions, domestic production or import, registration status and prequalification status.

Of 306 samples selected for laboratory testing, 267 were fully tested and 28.5% of them failed to comply with specifications. Although noncompliance with pre-established criteria cannot be directly related to a risk for patients' health, such a high failure rate indicates a substantial problem with the quality of antimalarials present in distribution channels.

Comparison of results obtained during laboratory testing with the screening method indicated a substantially lower sensitivity of the latter to detect noncompliance in dissolution and in assay/related substances test (15% and 42% detected, respectively).

The difference between WHO-prequalified and non-WHO-prequalified products was striking. The failure rate of samples of non-prequalified co-packed samples was more than 10 times higher than that of samples of WHO-prequalified co-packed samples. In total three failures were identified. Two were not critical for patients' health and the third had a content of one API that was 8% below the acceptance limit. This demonstrates that medicines for which quality was confirmed by WHO prequalification have a much lower quality risk than do non-prequalified products.

Another quality survey of antituberculosis medicines was also carried out in 2009 in East European countries and Newly Independent States (NIS); 291 samples were collected and tested by independent laboratories. Among the samples collected and tested, a small percentage of samples (isoniazid, ofloxacin and rifampicin) failed to pass the test. None of the WHO-prequalified products failed to comply with specifications.

The Expert Committee reconfirmed that results obtained with screening tests should always be treated with caution and only be used for qualitative and semiquantitative testing. The results of this survey have again demonstrated that in situations requiring regulatory or forensic decisions, laboratory quality control testing should always be applied.

The Expert Committee acknowledged with satisfaction the work done by the Prequalification of Medicines Programme, in particular the WHO quality monitoring project, and advised the Programme to publish the results of the survey and use the publication to promote awareness among countries. It was noted that when the report was ready the Expert Committee members would be provided with copies. The Committee was pleased to note that

the detailed conclusions of the report would be published and put on the Prequalification of Medicines Programme web site. The Committee took note that the failure of prequalified products, in the above-reported studies on the antimalarial and tuberculosis medicines, was much less than for non-prequalified products, which is an important indicator for the work of the Prequalification of Medicines Programme.

10.2 Procedure for prequalification of pharmaceutical products

Following the update, the Manager of the Prequalification of Medicines Programme briefed the Expert Committee on the proposed modifications to the existing procedure for prequalification. Following discussion, the Committee adopted the document as recommended (Annex 10), provided no major comments were received during the remaining consultation period and with the understanding that WHO's Legal Counsel would be consulted during this update process.

10.3 Guide on submission of documentation for prequalification of innovator finished pharmaceutical products approved by stringent regulatory authorities

WHO recognizes the scientific evaluation of innovator finished pharmaceutical products (FPPs) by regulatory authorities, which apply similarly stringent standards for quality, safety and efficacy to those recommended by WHO. A proposal was, therefore, presented to facilitate the submission of documentation to the Prequalification of Medicines Programme for those products approved by such authorities. This proposal would be applicable where an applicant and a stringent regulatory authority (SRA) can agree to share information on an innovator FPP with WHO. WHO will then consider such an FPP for inclusion in the list of WHO-prequalified products, as and when information about such a product becomes available to WHO and when the applicant in question expresses his or her interest in the product being prequalified by WHO.

The guide summarizing this proposal was discussed. A definition of SRAs and stability conditions prevailing in hot and humid countries are specially included in this document. A comment was made regarding the possible expansion of NMRAs beyond SRA, i.e. ICH and associated members.

The Expert Committee adopted the guide as amended (Annex 11).

11. Prequalification of quality control laboratories

11.1 Update of activities

The Prequalification of Quality Control Laboratories Programme was established in 2004 for quality control laboratories in Africa. It is a voluntary

programme in which private or governmental laboratories participate. Priority in assessment is given to national laboratories providing services to the government as well as to quality control laboratories in areas where United Nations agencies identify the need for quality testing. The procedure involves invitation by WHO to participate and expressions of interest (EOIs) by interested laboratories.

In 2004 eight quality control laboratories expressed interest but none was prequalified. By October 2010 the number had increased to 46 out of which 17 are prequalified. Of the 46 laboratories 35 are national quality control laboratories. In the WHO Region for Africa alone there are six prequalified and 15 interested laboratories.

11.2 Procedure for prequalifying laboratories

The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted, in its thirty-eighth report in 2003, the *Procedure for assessing acceptability, in principle, of quality control laboratories for use by United Nations agencies* (WHO Technical Report Series, No. 917, 2003, Annex 4). In 2006, the WHO Expert Committee adopted, in its forty-first report, a revised version of this procedure entitled *Prequalification of quality control laboratories. Procedure for assessing acceptability, in principle, of quality control laboratories for use by United Nations agencies* (WHO Technical Report Series, No. 943, 2007, Annex 5).

During the last three years the interest of quality control laboratories in prequalification has grown, the procedure has expanded, and currently there are 17 prequalified laboratories and 28 other laboratories that have expressed an interest in being prequalified. The experience gained from implementation of the procedure and its extended use has revealed the need for clarification of some issues, such as:

— the possibility for WHO to rely on the inspection or audit of the laboratory by an authority applying standards at least equivalent to WHO-recommended quality standards for quality control laboratories;
— setting rules for priority assessment of interested quality control laboratories; and
— monitoring of performance of prequalified laboratories.

These amendments were also recommended for inclusion by the WHO Expert Committee on Specifications for Pharmaceutical Preparations during informal consultations on specifications for medicines and quality control laboratory issues held on 17–19 June 2007.

The recent revisions of the WHO guidelines on *Good practices for pharmaceutical quality control laboratories* and the *Procedure for prequalification of*

pharmaceutical products also led to the need for some amendments of the procedure for prequalification of quality control laboratories.

The first draft revision of the procedure was mailed out for comments in March 2010 and discussed during the informal consultation held on 10–12 May 2010. Based on this discussion the second draft was prepared and submitted to the WHO Legal Counsel for comments. The comments of the WHO Legal Counsel were implemented in this third draft revision.

On the basis of the above, the revised text is proposed to replace the previously published procedure.

The discussion focused on the cooperation with other authorities doing audits. The proposal includes rules for prioritization of laboratories applying for prequalification and rules for monitoring of laboratories after prequalification.

It was suggested to include United Nations agencies in the appropriate paragraphs of the revised procedure.

The new procedure was adopted including the changes proposed and discussed (Annex 12).

11.3 Update on the WHO guidelines for preparing a laboratory information file

The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted in its thirty-eighth report in 2003 the *Guidelines for preparing a laboratory information file* (WHO Technical Report Series, No. 917, 2003, Annex 5).

The content of these guidelines is closely related to the *WHO guidelines on good practices for pharmaceutical quality control laboratories*, which have been recently revised (the revised version was adopted by the WHO Expert Committee at its forty-fourth meeting in 2009).

The WHO Expert Committee on Specifications for Pharmaceutical Preparations discussed the need for a revision of both guidelines at its forty-third meeting in 2008 and recommended that if the WHO guidelines on *Good practices for national pharmaceutical control laboratories* were revised, the *Guidelines for preparing a laboratory information file* should be revised accordingly.

On the basis of the above the revised text is proposed to replace the previously published guidelines. It was presented in track-change mode in order to show the changes that had been made.

The Expert Committee adopted the revised guidelines as proposed (Annex 13).

12. Prequalification of active pharmaceutical ingredients

The Manager of the WHO Prequalification of Medicines Programme provided an update on the Programme and the prequalification of active pharmaceutical ingredients (APIs).

The Programme facilitates access to quality medicines through assessment of products and inspection of manufacturing sites. Since good-quality APIs are vital to the production of good-quality medicines, and in response to requests from Member States, the Programme has started a pilot project to prequalify APIs. Details of the pilot project are posted on the Prequalification of Medicines Programme web site.

The API prequalification procedure, which will guide this process, was adopted by the Expert Committee in 2008 and is published as Annex 4 in the WHO Technical Report Series, No. 953, Annex 4.

Prequalification of APIs consists of a comprehensive evaluation procedure that has two components: assessment of the API master file (APIMF) to verify compliance with WHO norms and standards and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements. Prequalification of an API is done with specific reference to the manufacturing details and quality controls described in the APIMF submitted for assessment.

WHO-prequalified APIs are listed on the WHO List of prequalified active pharmaceutical ingredients. The list provides United Nations agencies, NMRAs and others with information on APIs that have been found to meet WHO-recommended quality standards. It is believed that identification of sources of good-quality APIs will facilitate the manufacture of good-quality FPPs needed for procurement by United Nations agencies and disease treatment programmes.

The Expert Committee noted with appreciation these new developments.

13. Regulatory guidance

13.1 WHO guidelines for preparing a site master file

The Committee was informed about the current style used in the WHO Prequalification of Medicines Programme for the submission of a site master file (SMF) and its intent to review it through the Expert Committee and the related consultation process. The SMF has been in place for a number of years within the context of the inspections carried out in the Prequalification of Medicines Programme. When the document including the SMF was circulated globally, numerous comments were received.

Based on the new developments and the comments received, the proposal was made to align the current WHO format with the new PIC/S format which was being finalized. This would address the majority of the comments received and be in line with the intent to harmonize internationally.

The Expert Committee recommended that the current WHO format used in prequalification be harmonized with the new PIC/S format and adopted the site master file (Annex 14).

13.2 Guidelines on submission of documentation for a multisource (generic) finished product: general format: preparation of product dossiers in common technical document format

The document was presented to the Expert Committee together with the guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part. It was proposed to create a short document explaining how the two documents fitted together to assist NMRAs and companies in implementing the documents.

The Expert Committee adopted these guidelines with a view to enhancing exchange of information between NMRAs and also the Prequalification of Medicines Programme (Annex 15).

13.3 Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part

The newly proposed *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part* was adapted from the one used in the WHO Prequalification of Medicines Programme with the intent to serve NMRAs wishing to update their generic medicine registration process. It was meant to be used together with the *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): preparation of product dossiers (PDS) in common technical document (CTD) format* (see section 13.2).

The guidelines were developed with the intent to update and not to increase the requirements. It was considered to be helpful to developing countries wishing to update requirements for generics and would also assist in switching to a CTD format.

Numerous comments were received, reviewed and discussed at the meeting. The ICH Q11 Manufacturing development of drug substances: treatment of starting materials, is expected to reach the deadline for public comment in the near future and should also be considered when further developing this document.

The Committee noted that the guidelines were more advanced than the present ones used by a number of Member States.

The Expert Committee recommended that the document be provisionally adopted and that it should be issued in a pilot phase after consolidation of comments within the Prequalification of Medicines Programme.

13.4 Pharmaceutical development for multisource (generic) pharmaceutical products

The Expert Committee was briefed on the progress regarding the new guidance on pharmaceutical development for multisource (generic) pharmaceutical products. The draft guidance was widely circulated for comments and underwent a major revision during the informal consultation in April 2010; thereafter numerous comments were received. The Expert Committee reviewed the feedback and considered that the comments received would need to be revisited by a group of experts. It was also suggested that the document be reorganized to follow the CTD format in order to bring it in line with the other approaches recommended by the Committee during the present meeting.

The Expert Committee recommended following the normal procedure, organizing an informal consultation and providing feedback to the next Expert Committee meeting.

13.5 Classification of orally administered drugs on the WHO Model List of Essential Medicines according to the Biopharmaceutics Classification System

The WHO Collaborating Centre for Research on Bioequivalence Testing of Medicines in Frankfurt, Germany, provided a report with a proposal to update the *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms* published in 2006, with a view to including the new medicines selected for inclusion in the Model list of Essential Medicines (EML) since 2006.

The Expert Committee members:

— endorsed the follow-up and continuation of this update;
— endorsed the efforts to update the list by adding the new EML entries through publication of those that are unambiguously classified in the report;
— advised that WHO collaborating centres should be contacted and that laboratories collaborating in the development of new monographs for *The International Pharmacopoeia* should collaborate by possibly either undertaking the solubility studies or by providing APIs to the WHO Collaborating Centre in Frankfurt;

— stated that the published list should be reviewed with a view to further consolidating the proposed classifications and possibly confirming some of the previously tentative classifications; and
— stated that the outcomes as listed above should be presented to the forty-sixth meeting of the Expert Committee on Specifications for Pharmaceutical Preparations.

13.6 Development of paediatric medicines: pharmaceutical development

The document summarizing the *Points to consider in the development of paediatric medicines: pharmaceutical development* was discussed at the informal WHO consultation on pharmaceutical development of paediatric medicines and pharmaceutical development for multisource (generic) pharmaceutical products, which was held in Geneva on 29–30 April 2010.

The Expert Committee was provided with a short history of the document, including previous comments and proposed further revision. It reviewed the main comments in detail.

The Expert Committee recommended that taste-masking and palatability should be addressed in more detail in the text provided, with special reference to other WHO documents, including, e.g. the one on zinc tablets.

The Expert Committee recommended that the revised version of this document should again be circulated widely for comments, including to the paediatric regulatory network. Progress would be reported to the next Expert Committee meeting.

The Committee noted that the guidelines currently under development did not include any details on extemporaneous preparations. The Expert Committee recommended that the paediatric regulatory network, and especially the group dealing with extemporaneous preparations, take advantage of the expertise provided by this Expert Committee.

13.7 Quality requirements for artemisinin as a starting material in the production of antimalarial active pharmaceutical ingredients

The Secretariat briefed the Expert Committee on the history and purpose of the document which was prepared in response to the need expressed by major donor organizations.

It was discussed that on various occasions the quality control specifications applicable to active substances are used not only per se but also as starting materials for the production of other active substances. An illustrative

example is artemisinin which is an important API itself and also serves as a starting material for the production of artemisinin-derived antimalarials.

The main challenge identified is that some national authorities require the same quality standard for an API and for a starting material. However, it was considered sufficient that a starting material has a quality that guarantees that the final product meets a relevant pharmacopoeial standard. Demanding a quality for a starting material that is too exacting will increase the price and in consequence reduce the availability of the API.

Working document QAS/10.349/Rev.1 has been prepared to clarify the need for different quality levels. It includes a specification for artemisinin used as a starting material for the synthesis of artemisinin derivatives.

The original paper was circulated for comments in March–April 2010. Comments were consolidated and the revised draft, based on an additional review by a subgroup of experts in August 2010, was presented to the Expert Committee.

The assignment of possible impurities to signals in the chromatographic assay for related substances is based on literature data and regarded as tentative until further experimental validation has been obtained.

Finalization of the impurity profile was required and would determine when the document could be discussed. The manufacturer was contacted to submit the starting material needed to carry out the analyses at the laboratory level.

It was noted that a WHO botanical "monograph" was available which detailed the cultivation and collection of the starting material.

The Expert Committee recognized the need to finalize the impurity profile before the document could be completed. It further recommended that the document be revised by a subgroup of experts in light of the comments received.

14. Nomenclature, terminology and databases

14.1 New definition for "substandard medicines"

In connection with the discussions during the meetings of the WHO governing bodies, the terminology for "substandard medicines" was raised during the forty-fourth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

Within the context of the work of this Expert Committee no officially adopted definition currently existed for "substandard medicines". As this question was frequently raised a "Question and Answer" section had been introduced on the WHO web site. On the basis of this the Expert Committee proposed during its 44th meeting to circulate a slightly modified proposal for the elaboration of a new definition.

The comments received upon circulation were reviewed during the following two WHO consultations which took place in Geneva: Quality assurance systems, medicines and risk analysis (4–6 May 2010); and Specifications for medicines and quality control laboratory issues (10–12 May 2010). An extensive discussion took place on the feedback received and additional input was provided by all experts who participated in the consultations. On the basis of this outcome a new revised definition was suggested and reviewed by the Expert Committee.

The Chair noted that it was not feasible to write a definition for every country in the world, but there was a need to provide sufficient background so that countries could interpret the underlying concepts. The Expert Committee recommended that the definition be reviewed by a legal expert to ensure that the text covers both standards and specifications in an appropriate manner.

The following new proposal was discussed based on the comments received and adopted by the Expert Committee:

> "Substandard medicines are pharmaceutical products that fail to meet either their quality standards or their specifications, or both.[12]
>
> Each pharmaceutical product that a manufacturer produces has to comply with quality assurance standards and specifications, at release and throughout its shelf-life, according to the requirements of the territory of use. Normally, these standards and specifications are reviewed, assessed and approved by the applicable national or regional medicines regulatory authority before the product is authorized for marketing."

14.2 "Spurious/falsely-labelled/falsified/counterfeit medicines"

In connection with the discussions during the WHO governing bodies' meetings, the terminology for "counterfeit medicines" has been raised since 2008. During the 63rd World Health Assembly the proposal was made that, until consensus could be reached, the following term should be used: "substandard/ spurious/falsely-labelled/falsified/counterfeit medical products".

Within the context of the work of this Expert Committee, definitions for "counterfeit medicines" were included in the glossary of the various WHO guidelines, e.g. in the *WHO Good distribution practices for pharmaceutical products* (40th report, 2006), the *WHO Guidelines for inspection of drug distribution channels* (35th report, 1999); and the *WHO Guidelines on import procedures for pharmaceutical products* (34th report, 1996).[13]

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[12] Modified after review by the WHO Legal Counsel.

[13] WHO Database on Quality Assurance (http://www.who.int/medicines/services/expertcommittees/pharmprep/TermListcategory.pdf).

Within the context of the work of the IMPACT Annual Meeting held in December 2008 (Hammamet, Tunisia) and based on the work carried out in the IMPACT Working Group on Legislative and Regulatory Infrastructure, a new definition was developed.[14] This definition is included in the document entitled *Draft principles and elements for national legislation against counterfeit medical products* which was sent out for comments.

Triggered by the governing bodies' discussion, a Circular Letter was mailed inviting Member States to share the terms and details of what national legislations regarded as "counterfeit medicines". The feedback was summarized by specialists and posted as a preliminary report on the WHO web site to allow for additional feedback. The responses of Member States to the Circular Letter of the Director-General of WHO were presented to the Expert Committee. They related to:

- definitions of "counterfeit medicines" in the Member States;
- Member States' national legislation; and
- definition included in the above-cited IMPACT document.

It was explained that different types of legislation address the problem in the various Member States, which led to the diversity of responses. Also, English is not necessarily the language used in the national or regional legislations, which adds to the complexity. Many Member States are, however, in line with the current WHO definition. The Expert Committee took note that, although the majority of Member States supported the IMPACT definition and document, a considerable number of Member States did not, for various reasons.

The Expert Committee members fully recognized that spurious/falsely-labelled/falsified/counterfeit medical products presented a major public health problem. Several political and technical issues were raised. There was discussion whether or not APIs and excipients should be included in the definition and whether it was better to address "medicines" only rather than the broader category of "medical products".

The Expert Committee took note that there was neither agreement among the Member States' definitions nor the terms used in the various legal contexts. However, several participants indicated that whatever the decision was on the future terminology within the WHO context, the word "counterfeit" was already widely used by the public.

During the 63rd World Health Assembly all Member States adopted by consensus the decision to have a working group on "Substandard/spurious/falsely-labelled/falsified/counterfeit medical products" and had requested

[14] http://www.who.int/impact/resources/IMPACTthirdgeneralmeeting_%20report.pdf.

the Director-General of WHO to convene a meeting to discuss this issue. It was, therefore, agreed that in light of the Member States' decision, a specially constituted working group would be the most appropriate forum to discuss this issue and that the Expert Committee on Specifications for Pharmaceutical Preparations should, therefore, not take the discussion further for the time being.

In summary, further to the discussions, the Expert Committee recommended that:

- the working group of the Member States considers the WHO and the IMPACT definitions in order to develop an appropriate definition and include an explanation that will avoid confusion;
- in so doing WHO should address the issue and its public health consequences instead of concentrating on the terminologies; and
- as the first step, the work of this Committee should concentrate on medicines.

14.3 International Nonproprietary Names (INN) for pharmaceutical substances

Various background materials including the cumulative list of International Nonproprietary Names (INN) were presented by the Manager of the INN Programme, including the use of stems and radicals in the selection of INN for pharmaceutical substances.

INN online application architecture was described. It was scheduled for implementation with the USA being used as beta tester. A training programme for industry would be held in January–February 2011. An instruction manual was available and two systems would be used at the beginning: online and also paper submissions.

During 2009–2010, WHO published 299 Proposed INNs and 252 Recommended INNs in lists 101-104 of proposed and lists 61-64 of recommended INNs, respectively. Discussion was based around the number of new INNs, objections to proposed INNs and a recent request for substitution of a recommended INN due to possible confusion between two INNs.

The Expert Committee noted the report.

15. Summary and recommendations

The Expert Committee on Specifications for Pharmaceutical Preparations provides recommendations and tools to assure the quality of medicines from their development phase to their final distribution to the patients. It advises the Director-General of WHO in the area of quality assurance of medicines.

The Expert Committee on Specifications for Pharmaceutical Preparations is looking back on a history of more than 60 years! The first meeting of the Expert Committee, named "Unification on Pharmacopoeias" at that time, was held in 1947. Since the inception of this WHO Expert Committee, its members have worked towards making available clear, independent and practical recommendations, written and physical standards, as well as international guidelines for quality medicines. Standards in the area of quality assurance for medicines are developed by the Committee through a wide international consensus building process. Detailed recommendations can be found under each relevant section in the report.

The activities discussed during this Expert Committee meeting have broad inter- and intracluster relationships and links. There are joint activities, specifically with the WHO Expert Committees on Biological Standardization, and on the Selection and Use of Essential Medicines and its Subcommittee on Medicines for Children. In addition, the Committee serves to develop specific additional guidance and specifications as needed for the various medicines recommended by WHO Programmes.

This Committee also serves the United Nations Prequalification of Medicines Programme managed and operated by WHO, as the Programme could not function without the guidelines, standards and specifications adopted by this Committee after passage through its rigorous, international and wide consultative process. The advantage for the Committee is that, as a result of implementing these guidelines and specifications, practical suggestions for potential revision or on the need for additional guidance are communicated in return to the Expert Committee.

Regarding implementation from a wider perspective the international guidelines, specifications and nomenclature developed under the aegis of this Committee serve all Member States, international organizations, United Nations agencies, regional and interregional harmonization efforts, and underpin important initiatives, including the prequalification of medicines, the Roll Back Malaria Programme, Stop TB, essential medicines and medicines for children. The advice and recommendations provided by this Expert Committee are intended to help national and regional authorities and procurement agencies, as well as major international bodies and institutions, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, and international organizations such as UNICEF to combat circulation of substandard medicines and to work towards access to good-quality medicines.

In conclusion, the Expert Committee on Specifications for Pharmaceutical Preparations gives recommendations and provides independent international standards and guidelines in the area of quality assurance for implementation by WHO Member States, international organizations, United Nations

agencies, regional and interregional harmonization efforts, as well as WHO's medicines' related programmes and initiatives. Making resources available for these activities is, therefore, very cost-effective.

The following new guidelines were adopted and recommended for use:

- Release procedure of International Chemical Reference Substances (Annex 1)
- WHO good practices for pharmaceutical microbiology laboratories (Annex 2)
- WHO good manufacturing practices: main principles for pharmaceutical products (Annex 3)
- WHO good manufacturing practices for blood establishments (jointly with the Expert Committee on Biological Standardization) (Annex 4)
- WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms (Annex 5)
- WHO good manufacturing practices for sterile pharmaceutical products (Annex 6)
- WHO guidelines on transfer of technology in pharmaceutical manufacturing. (Annex 7)
- Good pharmacy practice: standards for quality of pharmacy services (joint FIP/WHO) (Annex 8)
- Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (jointly with the Expert Committee on Biological Standardization) (Annex 9)
- Procedure for prequalification of pharmaceutical products (Annex 10)
- Guide on submission of documentation for prequalification of innovator finished pharmaceutical products approved by stringent regulatory authorities (Annex 11)
- Prequalification of quality control laboratories. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies (Annex 12)
- WHO guidelines for preparing a laboratory information file (Annex 13)
- WHO guidelines for drafting a site master file (Annex 14)
- Guidelines on submission of documentation for a multisource (generic) finished product: general format: preparation of product dossiers in common technical document format (Annex 15)

For inclusion in *The International Pharmacopoeia*

The following monographs were adopted:

- *For antiretroviral medicines*

efavirenz tablets
didanosine capsules

emtricitabine capsules
emtricitabine and tenofovir tablets
efavirenz, emtricitabine and tenofovir tablets

- *For antimalarial medicines*

artesunate
artesunate for injection
mefloquine tablets
sulfadoxine and pyrimethamine tablets

- *For antituberculosis medicines*

capreomycin sulfate
capreomycin for injection
ofloxacin
ofloxacin tablets
levofloxacin
levofloxacin tablets

- *For anti-infectives*

amoxicillin oral suspension
levamisole tablets
metronidazole oral suspension
sulfamethoxazole and trimethoprim tablets

- *For other medicines*

oseltamivir phosphate
oseltamivir capsules
sodium bicarbonate intravenous infusion
paracetamol oral solution
paracetamol oral suspension
levonorgestrel tablets
retinol concentrate

General policy topics and general revision issues for:

- uniformity of content for single-dose preparations
- oral suspension/solutions reconstituted from powder
- dissolution testing

Harmonization with PDG general texts for the following:

- Residue on ignition/sulfated ash
- Test for extractable volume of parenteral preparations
- Test for particulate contamination: subvisible particles
- Microbial examination of non-sterile products: microbial enumeration tests
- Microbial examination of non-sterile products: tests for specified microorganisms

- Microbial examination of non-sterile products: acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use
- Disintegration test
- Uniformity of dosage units
- Dissolution test
- Sterility test
- Tablet friability

International reference standards:
- New procedure for the release of International Chemical Reference Substances (see also Annex 1)
- General policy regarding international standards for human recombinant insulin

The following recommendations were made in the various quality assurance-related areas. Progress on the suggested actions should be reported to the Expert Committee at its next meeting.

The underlying principle is that the development of specifications and guidelines will be carried out using the established international consultative process.

Overall policy

- To prepare overviews on the key activities and on the history and working process of this Expert Committee for wide dissemination and information.
- To prepare a general policy paper for future maintenance, revision and update of WHO guidelines adopted by this Expert Committee.

The International Pharmacopoeia

- Continue development of specifications for medicines, general methods and texts and general supplementary information in accordance with the work plan and as decided at this meeting.
- Continue the efforts of international collaboration in relation to the revision and inclusion of general methods.
- Continue the preparatory work on the Second supplement to *The International Pharmacopoeia*, fourth edition and towards the fifth edition, especially in electronic form (CD-ROM and online).

International Chemical Reference Substances (ICRS)

- Continue promoting the use of ICRS through various activities, including a promotional offer to national authorities and improvements to the ICRS web site.
- Continue the efforts to further enhance the development of new ICRS.

External Quality Assurance Assessment Scheme (EQAAS)

- Continue the External Quality Assurance Assessment Scheme (EQAAS) for pharmaceutical quality control laboratories, Phase 5, test series 3 onwards.

Good manufacturing practices (GMP) and manufacture

- Follow up on the revision process for GMP for biologicals undertaken under the aegis of the Expert Committee on Biological Standardization.
- Continue the consultation process with regard to a revision of GMP: water for pharmaceutical use.
- Continue the consultation process on Quality risk management principles with a view to updating the WHO guidelines on hazard analysis and critical control points (HACCP) to cover new trends.
- Finalize the special guidance for artemisinin as a starting material for production of antimalarials based on the confirmation of the impurity profile through additional laboratory analysis.

WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce

- Continue the steps to be taken regarding the *WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce* in consultation with WHO Member States and the WHO Legal Counsel.

Regulatory guidance

- Continue the consultation process and advancement of the *Development of paediatric medicines: pharmaceutical development. Points to consider*.
- Continue the development of the *Pharmaceutical development for multisource (generic) pharmaceutical products*.
- Continue the update of the *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms* published in 2006, with a view to including the new medicines selected for the WHO Model List of Essential Medicines (EML).
- Report back to the next Expert Committee meeting on the pilot project undertaken by the Prequalification of Medicines Programme regarding the implementation of the provisionally adopted *Guidelines on submission of documentation for multisource (generic) finished pharmaceutical product: quality part.*

Quality assurance terminology

- Make the updated database on quality assurance terminology widely available.

- Provide feedback from the Working Group of Member States regarding the terminology for "spurious/falsely-labelled/falsified/counterfeit medical products", with a view to further discussion of the outcome during the next meeting of the Expert Committee.

Pharmacopoeia references

- Post an update of the references and contact details for national, regional and international pharmacopoeias on the Medicines Quality Assurance web site.

WHO databases

- Maintain the consolidated database on nomenclature used in WHO quality assurance.
- Maintain the INN database and continue to make it available on the web site.

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Anti-Counterfeiting Medicines Programme, WHO, Geneva, Switzerland; Blood Products and Related Biologicals Programme, WHO, Geneva, Switzerland; Global Malaria Programme, WHO, Geneva, Switzerland; HIV/AIDS Programme, WHO, Geneva, Switzerland; International Medical Products Anti-Counterfeiting Taskforce (IMPACT), WHO, Geneva, Switzerland; Medicine Access and Rational Use Team, WHO, Geneva, Switzerland; Medicines Regulatory Support Programme, WHO, Geneva, Switzerland; Prequalification of Medicines Programme, WHO, Geneva, Switzerland; Quality and Safety: Medicines Team, WHO, Geneva, Switzerland; Quality, Safety and Standards Team, WHO, Geneva, Switzerland; Traditional Medicine Team, WHO, Geneva, Switzerland; WHO Regional Office for Africa, Brazzaville, Congo; WHO Regional Office for the Americas/Pan American Health Organization, Washington, DC, USA; WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt; WHO Regional Office for Europe, Copenhagen, Denmark; WHO Regional Office for South-East Asia, New Delhi, India; WHO Regional Office for the Western Pacific, Manila, Philippines.

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Annex 1

Release procedure of International Chemical Reference Substances

International Chemical Reference Substances (ICRS) were in the past first provisionally adopted by the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and then finally adopted by the Expert Committee on Specifications for Pharmaceutical Preparations during its annual meeting.

Since April 2010 the European Directorate for the Quality of Medicines & HealthCare (EDQM) has been responsible for the establishment, preparation, storage and distribution of WHO ICRS. For the analytical characterization of ICRS, EDQM follows the *General guidelines for the establishment, maintenance and distribution of chemical reference substances*.

EDQM will issue an individual analytical report after:

— the establishment of a new reference substance;
— analysis of candidate material for stock replenishment; and
— monitoring the stability of material in stock.

The Expert Committee members newly adopted the following procedure:

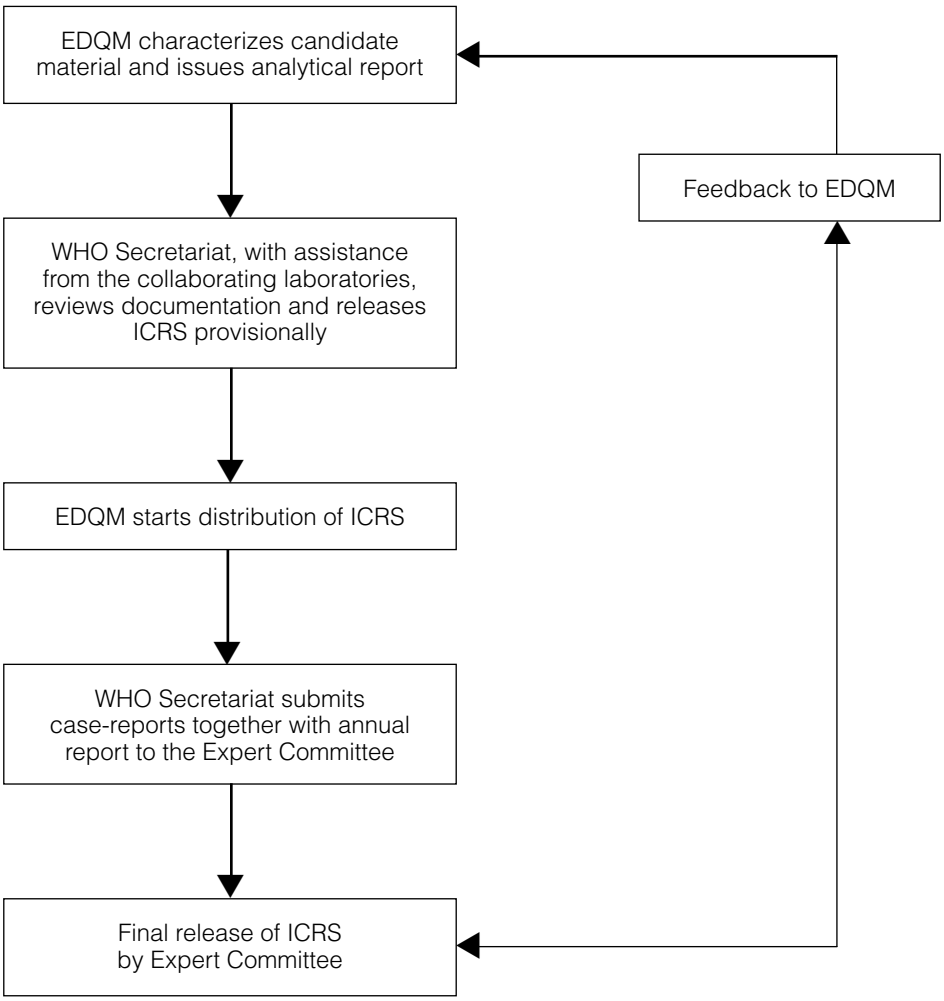
Analytical case-reports to be reviewed *a priori* by the Secretariat with assistance from the collaborating laboratories. If the testing has been performed according to the above-mentioned adopted guidelines *(1)* and the candidate material has been proven to be suitable, the Secretariat with assistance from the collaborating laboratories, will then in future provisionally release the ICRS. The distribution of the ICRS will start after the provisional release.

The analytical case-reports together with a consolidated EDQM annual report describing all activities related to the establishment of ICRS will then be distributed to the WHO Expert Committee on Specifications for Pharmaceutical Preparations for adoption. The analytical case-reports will be appended to the annual report as annexes.

The new process will expedite the establishment of new reference substances and will enable WHO to react faster to the urgent demand for ICRS. The new procedure is illustrated in Figure 1.

If additional explicit provisions for the release of reference substances are needed, they will also be presented to the Expert Committee for approval.

Figure 1
New procedure



EDQM, European Directorate for the Quality of Medicines & HealthCare; ICRS, International Chemical Reference Substances.

Reference

1. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second Report.* Geneva, World Health Organization, 1990 (WHO Technical Report Series, No 790), p. 15.

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Annex 2

WHO good practices for pharmaceutical microbiology laboratories

Background

The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted in 2009 a revised version of the *Good practices for pharmaceutical quality control laboratories* (*1*).

During the inspections carried out when prequalifying laboratories, the inspectors had noticed that some of the texts of these guidelines might benefit from additional guidance, with a special focus on microbiology.

In light of the above, the Expert Committee recommended that the WHO Secretariat initiate the process of developing a new text on good practices for pharmaceutical microbiology laboratories.

The following text is proposed to cover this specific type of laboratory.

Introduction and scope of document

Glossary

1. Personnel

2. Environment
   - 2.1 Premises
   - 2.2 Environmental monitoring in the laboratory
   - 2.3 Cleaning, disinfection and hygiene
   - 2.4 Sterility test facilities

3. Validation of test methods

4. Equipment
   - 4.1 Maintenance of equipment
   - 4.2 Qualification
   - 4.3 Calibration, performance verification and monitoring of use

5. Reagents and culture media
   - 5.1 Reagents
   - 5.2 Media
   - 5.3 Labelling
   - 5.4 Organism resuscitation

Introduction and scope of document

Pharmaceutical microbiology laboratories may be involved in:

— sterility testing;
— detection, isolation, enumeration and identification of microorganisms (bacteria, yeast and moulds) and testing for bacterial endotoxins in different materials (e.g. starting materials, water), products, surfaces, garments and the environment; and
— assay using microorganisms as part of the test system.

These guidelines relate to all microbiology laboratories involved in the above-mentioned testing activities, whether they are independent or a department or unit of a pharmaceutical manufacturing facility.

These guidelines are based on and supplement the requirements described in *Good practices for pharmaceutical quality control laboratories* (*1*); *General guidelines for the establishment, maintenance and distribution of chemical reference substances. Revision* (*2*); *The International Pharmacopoeia*, Fourth Edition (*3*); First Supplement to *The International Pharmacopoeia*, Fourth Edition (*4*); and ISO/IEC 17025 (*5*).

Glossary

calibration

The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

certified reference material

Reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty and a statement of metrological traceability.

limit of detection

The lowest number of microorganisms that can be detected, but in numbers that cannot be estimated accurately.

precision

The degree of agreement among individual results.

quantitation limit (limit of quantitation)

Applied to quantitative microbiological tests. The lowest number of microorganisms within a defined variability that may be counted under the experimental conditions of the method under evaluation.

reference cultures

Collective term for reference strain and reference stocks.

reference material

Material sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process.

reference method

A method which has been validated as being fit for purpose, with which an alternative method may be compared.

reference stocks

A set of separate identical cultures obtained by a single subculture from the reference strain *(6)*.

reference strains

Microorganisms defined at least to the genus and species level, catalogued and described according to its characteristics and preferably stating its origin *(6)*. Normally obtained from a recognized national or international collection.

repeatability

Closeness of the agreement between the results of successive measurements of the same measure and under the same conditions of measurement (adapted from ISO).

reproducibility

Reproducibility expresses precision between laboratories.

robustness (or ruggedness)

The ability of the procedure to provide analytical results of acceptable accuracy and precision under a variety of conditions.

sensitivity

The fraction of the total number of positive cultures or colonies correctly assigned in the presumptive inspection *(7)*.

specificity (selectivity)

The ability of the method to detect the required range of microorganisms that might be present in the test sample.

validation

Action of proving, in accordance with the principles of good practice quality guidelines and regulations (GxP), that any procedure, process, equipment (including the software or hardware used), material, activity or system actually and consistently leads to the expected results.

verification

The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with GxP principles.

working culture

A primary subculture from a reference stock *(6)*.

1. Personnel

1.1 Microbiological testing should be performed and supervised by an experienced person, qualified in microbiology or equivalent. Staff should have basic training in microbiology and relevant practical experience before being allowed to perform work covered by the scope of testing.

1.2 Current job descriptions for all personnel involved in tests and/or calibrations, validations and verifications should be maintained. The laboratory should also maintain records of all technical personnel, describing their qualifications, training and experience.

1.3 If the laboratory includes opinions and interpretations of test results in reports, this should be done by authorized personnel with suitable experience and relevant knowledge of the specific application including, for example, regulatory and technological requirements and acceptability criteria.

1.4 The laboratory management should ensure that all personnel have received adequate training for the competent performance of tests and operation of equipment. This should include training in basic techniques, e.g. plate pouring, counting of colonies, aseptic technique, media preparation, serial dilutions, and basic techniques in identification, with acceptability determined using objective criteria where relevant. Personnel may only perform tests on samples if they are either recognized as competent to do so, or if they do so under adequate supervision. Competence should be monitored continuously with provision for retraining where necessary. Where a method or technique is not in regular use, the competency of the personnel to perform the test should be verified before testing is undertaken. In some cases it is acceptable to relate competence to a general technique or instrument being used rather than to particular methods.

1.5 Personnel should be trained in necessary procedures for containment of microorganisms within the laboratory facility.

1.6 Personnel should be trained in safe handling of microorganisms.

2. Environment

2.1 Premises

2.1.1 Microbiology laboratories and certain support equipment (e.g. autoclaves and glassware) should be dedicated and separated from other areas, especially from production areas.

2.1.2 Microbiology laboratories should be designed to suit the operations to be carried out in them. There should be sufficient space for all activities to avoid mix ups, contamination and cross-contamination. There should be adequate suitable space for samples, reference organisms, media (if necessary, with cooling), testing and records. Due to the nature of some materials (e.g. sterile media versus reference organisms or incubated cultures), separate storage locations may be necessary.

2.1.3 Laboratories should be appropriately designed and should take into account the suitability of construction materials to enable appropriate cleaning, disinfection and minimize the risks of contamination.

2.1.4 There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions, including temperature and humidity controls where required, should be in place for microbiological laboratories. The air supplied to the laboratory should be of appropriate quality and should not be a source of contamination.

2.1.5 Access to the microbiological laboratory should be restricted to authorized personnel. Personnel should be made aware of:

— the appropriate entry and exit procedures including gowning;
— the intended use of a particular area;
— the restrictions imposed on working within such areas;
— the reasons for imposing such restrictions; and
— the appropriate containment levels.

2.1.6 Laboratory activities, such as sample preparation, media and equipment preparation and enumeration of microorganisms, should be segregated by space or at least in time, so as to minimize risks of cross-contamination, false-positive results and false-negative results. Where non-dedicated areas are used, risk management principles should be applied. Sterility testing should always be performed in a dedicated area.

2.1.7 Consideration should be given to designing appropriate classified areas for the operations to be performed within the microbiology laboratory. The classification should be based on the criticality of the product and the

operation being carried out in the area. Sterility testing should be performed under the same class as used for sterile/aseptic manufacturing operations. Appendix 1 shows recommendations for zone classifications.

2.1.8 In general, laboratory equipment should not routinely be moved between areas of different cleanliness class, to avoid accidental cross-contamination. Laboratory equipment used in the microbiology laboratory should not be used outside the microbiology area, unless there are specific precautions in place to prevent cross-contamination.

2.2 Environmental monitoring in the laboratory

2.2.1 Where necessary and appropriate (e.g. in areas for sterility testing) an environmental monitoring programme should be in place which covers, for example, use of active air monitoring, air settling or contact plates, temperature and pressure differentials. Alert and action limits should be defined. Trending of environmental monitoring results should be carried out.

2.3 Cleaning, disinfection and hygiene

2.3.1 There should be a documented cleaning and disinfection programme. Results of environmental monitoring should be considered where relevant.

2.3.2 There should be a procedure for dealing with spillages.

2.3.3 Adequate hand-washing and hand-disinfection facilities should be available.

2.4 Sterility test facilities

2.4.1 Sterility test facilities have specific environmental requirements to ensure the integrity of tests carried out. *WHO good manufacturing practices (GMP) for sterile pharmaceutical products* (*8*) requires that sterility testing should be carried out and specifies requirements for sterility testing. This section details the clean-room requirements for a sterility test facility.

2.4.2 Sterility testing should be performed under aseptic conditions, which should be equivalent to air quality standards required for the aseptic manufacture of pharmaceutical products. The premises, services and equipment should be subject to the appropriate qualification process.

2.4.3 The sterility testing should be carried out within a Grade A unidirectional airflow protected zone or a biosafety cabinet (if warranted), which should be located within a clean room with a Grade B background. Alternatively, the testing can be carried out within a barrier isolator. Care should be taken with the design of the facility layout and room airflow patterns, to ensure that the unidirectional airflow patterns are not disrupted.

2.4.4 The clean-room classification and air-handling equipment of the sterility test facilities should be requalified at least annually by a competent person or contractor. The environment should comply with the non-viable and viable limits, and verification of high efficiency particulate air (HEPA) filter integrity and room airflows should be performed. However, an alternative frequency of the monitoring may be justified based on quality risk management (QRM). Mapping locations for sample points for routine monitoring should be documented, as well as exposure duration, and frequency of all types of microbiological environmental monitoring should be specified in written procedures.

2.4.5 Air supplied to Grade A and B zones should be via terminal HEPA filters.

2.4.6 Appropriate airflow alarms and pressure differentials and indication instruments should be provided (*GMP: Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* (*8*); and *GMP for sterile pharmaceutical products* (*8*).

2.4.7 Room pressure readings should be taken and recorded from externally mounted gauges unless a validated continuous monitoring system is installed. As a minimum, readings should be taken prior to entry of the operator to the test suite. Pressure gauges should be labelled to indicate the area served and the acceptable specification.

2.4.8 Entry to the clean room should be via a system of airlocks and a change room where operators are required to don suitable clean-room garments. The final change room should be under "at rest" conditions of the same grade as the room it serves. Change rooms should be of adequate size for ease of changing. There should be clear demarcation of the different zones.

2.4.9 Garments for the sterility test operator should comply with the principles of section 10 of *WHO GMP for sterile pharmaceutical products* (*8*). Operators should be trained and certified in gowning procedures with training records maintained.

2.4.10 The fittings and finishes of the premises should comply with section 11 of *WHO GMP for sterile pharmaceutical products* (*8*).

2.4.11 Environmental microbiological monitoring should reflect the facility used (room or isolator) and include a combination of air and surface sampling methods appropriate to the facility, such as:

— active air sampling;
— settle (exposure) plates;
— surface contact — replicate organism detection and counting (RODAC) plates, swabs or flexible films;
— operators' glove prints.

Microbial environmental monitoring of the sterility test zone should be performed during every work session under operational (dynamic) conditions.

There should be written specifications, including appropriate alert and action limits for microbial contamination. Limits for microbiological environmental monitoring are given in the *WHO GMP for sterile pharmaceutical products* (*8*).

3. Validation of test methods

3.1 Standard (pharmacopoeial) test methods are considered to be validated. However, the specific test method to be used by a specific laboratory for testing of a specific product needs to be shown to be suitable for use in recovering bacteria, yeast and mould in the presence of the specific product. The laboratory should demonstrate that the performance criteria of the standard test method can be met by the laboratory before introducing the test for routine purposes (method verification) and that the specific test method for the specific product is suitable (test method suitability including positive and negative controls).

3.2 Test methods not based on compendial or other recognized references should be validated before use. The validation should comprise, where appropriate, determining accuracy, precision, specificity, limit of detection, limit of quantitation, linearity and robustness. Potentially inhibitory effects from the sample should be taken into account when testing different types of sample. The results should be evaluated with appropriate statistical methods, e.g. as described in the national, regional or international pharmacopoeias.

4. Equipment

Each item of equipment, instrument or other device used for testing, verification and calibration should be uniquely identified.

As part of its quality system, a laboratory should have a documented programme for the qualification, calibration, performance verification, maintenance and a system for monitoring the use of its equipment.

4.1 Maintenance of equipment

4.1.1 Maintenance of essential equipment should be carried out at predetermined intervals in accordance with a documented procedure. Detailed records should be kept. (For examples of maintenance of equipment and intervals see Appendix 2.)

4.2 Qualification

4.2.1 For qualification of equipment see sections 8 and 12 in *Good practices for pharmaceutical quality control laboratories* (*1*).

4.3 Calibration, performance verification and monitoring of use

4.3.1 The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.

4.3.2 The frequency of calibration and performance verification will be determined by documented experience and will be based on need, type and previous performance of the equipment. Intervals between calibration and verification should be shorter than the time the equipment has been found to take to drift outside acceptable limits. (For examples of calibration checks and intervals for different laboratory equipment, see Appendix 3; and for equipment qualification and monitoring, see Appendix 4.) The performance of the equipment should conform to predefined acceptance criteria.

4.3.3 *Temperature measurement devices*

4.3.3.1 Where temperature has a direct effect on the result of an analysis or is critical for the correct performance of equipment, temperature measuring devices should be of appropriate quality to achieve the accuracy required (e.g. liquid-in-glass thermometers, thermocouples and platinum resistance thermometers (PRTs) used in incubators and autoclaves).

4.3.3.2 Calibration of devices should be traceable to national or international standards for temperature.

4.3.4 *Incubators, water-baths and ovens*

The stability of temperature, uniformity of temperature distribution and time required to achieve equilibrium conditions in incubators, water-baths, ovens and temperature-controlled rooms should be established initially and documented, in particular with respect to typical uses (for example, position, space between, and height of, stacks of Petri dishes). The constancy of the characteristics recorded during initial validation of the equipment should be checked and recorded after each significant repair or modification. The operating temperature of this type of equipment should be monitored and records retained. The use of the equipment should be considered when determining what temperature controls are required.

4.3.5 *Autoclaves, including media preparators*

4.3.5.1 Autoclaves should be capable of meeting specified time and temperature tolerances; monitoring pressure alone is not acceptable. Sensors

used for controlling or monitoring operating cycles require calibration and the performance of timers should be verified.

4.3.5.2 Initial validation should include performance studies (spatial temperature distribution surveys) for each operating cycle and each load configuration used in practice. This process must be repeated after any significant repair or modification (e.g. replacement of thermoregulator probe or programmer, change to loading arrangements or operating cycle) or where indicated by the results of quality control checks on media or risk assessment. Sufficient temperature sensors should be positioned within the load (e.g. in containers filled with liquid/medium) to enable location differences to be demonstrated. In the case of media preparators, where uniform heating cannot be demonstrated by other means, the use of two sensors, one adjacent to the control probe and one remote from it, would generally be considered appropriate. Validation and revalidation should consider the suitability of come-up and come-down times as well as time at sterilization temperature.

4.3.5.3 Clear operating instructions should be provided based on the heating profiles determined for typical uses during validation/revalidation. Acceptance/rejection criteria should be established and records of autoclave operations, including temperature and time, maintained for every cycle.

4.3.5.4 Monitoring may be achieved by one of the following:

— using a thermocouple and recorder to produce a chart or printout;
— direct observation and recording of maximum temperature achieved and time at that temperature.

In addition to directly monitoring the temperature of an autoclave, the effectiveness of its operation during each cycle may be checked by the use of chemical or biological indicators for sterilization or decontamination purposes. Autoclave tape or indicator strips should be used only to show that a load has been processed, not to demonstrate completion of an acceptable cycle.

Laboratories should have a separate autoclave for decontamination. However, in exceptional cases one autoclave may be acceptable provided that extensive precautions are taken to separate decontamination and sterilization loads, and a documented cleaning programme is in place to address both the internal and external environment of the autoclave.

4.3.6 *Weights and balances*

Weights and balances shall be calibrated traceably at regular intervals (according to their intended use) using appropriate standard weights traceable to certified standard weights.

4.3.7 *Volumetric equipment*

4.3.7.1 Microbiology laboratories should carry out initial verification of volumetric equipment (automatic dispensers, dispenser/diluters, mechanical hand pipettes and disposable pipettes) and then make regular checks, as appropriate, to ensure that the equipment is performing within the required specification. Initial verification should not be necessary for glassware which has been certified to a specific tolerance. Equipment should be checked for the accuracy of the delivered volume against the set volume (for several different settings in the case of variable volume instruments) and the precision of the repeat deliveries should be measured.

4.3.7.2 For "single-use" disposable volumetric equipment, laboratories should obtain supplies from companies with a recognized and relevant quality system. After initial validation of the suitability of the equipment, it is recommended that random checks on accuracy are carried out. If the supplier does not have a recognized quality system, laboratories should check each batch of equipment for suitability.

4.3.8 *Other equipment*

Conductivity meters, oxygen meters, pH meters and other similar instruments should be verified regularly or before each use. The buffers used for verification purposes should be stored in appropriate conditions and should be marked with an expiry date.

Where humidity is important to the outcome of the test, hygrometers should be calibrated, the calibration being traceable to national or international standards.

Timers, including the autoclave timer, should be verified using a calibrated timer or national time signal.

When centrifuges are used in test procedures, an assessment of the rotations per minute (RPM) should be made. Where it is critical, the centrifuge should be calibrated.

5. Reagents and culture media

Laboratories should ensure that the quality of reagents and media used is appropriate for the test concerned.

5.1 Reagents

5.1.1 Laboratories should verify the suitability of each batch of reagents critical for the test, initially and during its shelf-life.

5.2 Media

5.2.1 Media may be prepared in-house or purchased either partially or fully prepared. Vendors of purchased media should be approved and qualified. The qualified vendor may certify some of the quality parameters listed subsequently. Growth promotion and, if appropriate, other suitable performance tests (see section 5.2.2) should be done on all media on every batch and on every shipment. Where the supplier of fully prepared media is qualified and provides growth promotion certification per batch of media and transportation conditions have been qualified, the user may rely on the manufacturer's certificate with periodic verification of his or her results.

5.2.2 The suitable performance of culture media, diluents and other suspension fluids should be checked, where relevant, with regard to:

— recovery or survival maintenance of target organisms. Recovery of 50–200% (after inoculation of not more than 100 colony-forming units (CFU or cfu) should be demonstrated;
— inhibition or suppression of non-target organisms;
— biochemical (differential and diagnostic) properties; and
— other appropriate properties (e.g. pH, volume and sterility).

Quantitative procedures for evaluation of recovery or survival are preferred.

5.2.3 Raw materials (both commercial dehydrated formulations and individual constituents) and media should be stored under appropriate conditions recommended by the manufacturer, e.g. cool, dry and dark. All containers, especially those for dehydrated media, should be sealed tightly. Dehydrated media that are caked or cracked or show a colour change should not be used.

5.2.4 Water of a suitable microbiological quality and which is free from bactericidal, inhibitory or interfering substances, should be used for preparation unless the test method specifies otherwise.

5.2.5 Media containing antimetabolites or inhibitors should be prepared using dedicated glassware, as carry-over of these agents into other media could inhibit the growth and detection of microorganisms present in the sample under test. If dedicated glassware is not used, washing procedures for glassware should be validated.

5.2.6 Repartition of media after sterilization should be performed under unidirectional airflow (UDAF) to minimize potential for environmental contamination. This should be considered a minimum requirement for media to be used in relation to sterile product testing. This includes the cooling of media, as container lids will need to be removed during cooling to prevent build-up of condensation.

5.2.7 Plated media which is to be irradiated may require the addition of an antioxidant and free radical scavenger to provide protection from the effects of the irradiation process. The irradiated media should be validated by performing quantitative growth promotion testing on both irradiated and non-irradiated media.

5.2.8 Shelf-life of prepared media under defined storage conditions shall be determined and verified.

5.2.9 Batches of media should be identifiable and their conformance with quality specifications documented. For purchased media the user laboratory should ensure that it will be notified by the manufacturer of any changes to the quality specification.

5.2.10 Media should be prepared in accordance with any manufacturer's instructions, taking into careful account specifications such as time and temperature for sterilization.

5.2.11 Microwave devices should not be used for the melting of media due to the inconsistent distribution of the heating process.

5.3 Labelling

5.3.1 Laboratories should ensure that all reagents (including stock solutions), media, diluents and other suspending fluids are adequately labelled to indicate, as appropriate, identity, concentration, storage conditions, preparation date, validated expiry date and/or recommended storage periods. The person responsible for preparation should be identifiable from records.

5.4 Organism resuscitation

5.4.1 Organism resuscitation is required where test methodologies may produce sublethally injured cells. For example, exposure to:

— injurious effects of processing, e.g. heat;
— antimicrobial agents;
— preservatives;
— extremes of osmotic pressure; and
— extremes of pH.

5.4.2 Organism resuscitation may be achieved by:

— exposure to a liquid media like a simple salt solution at room temperature for 2 hours;
— exposure to a solid repair medium for 4–6 hours.

6. Reference materials and reference cultures

6.1 International standards and pharmacopoeial reference substances

6.1.1 Reference materials and certified reference materials are generally used in a microbiological laboratory to qualify, verify and calibrate equipment.

Whenever possible these reference materials should be used in appropriate matrices.

International standards and pharmacopoeial reference substances are employed, for example, to:

— determine potency or content;
— validate methods;
— enable comparison of methods;
— perform positive controls; and
— perform growth promotion tests.

If possible reference materials should be used in appropriate matrices.

6.2 Reference cultures

6.2.1 Reference cultures are required for establishing acceptable performance of media (including test kits), for validating methods, for verifying the suitability of test methods and for assessing or evaluating ongoing performance. Traceability is necessary, for example, when establishing media performance for test kit and method validations. To demonstrate traceability, laboratories must use reference strains of microorganisms obtained directly from a recognized national or international collection, where these exist. Alternatively, commercial derivatives for which all relevant properties have been shown by the laboratory to be equivalent at the point of use may be used.

6.2.2 Reference strains may be subcultured once to provide reference stocks. Purity and biochemical checks should be made in parallel as appropriate. It is recommended to store reference stocks in aliquots either deep-frozen or lyophilized. Working cultures for routine use should be primary subcultures from the reference stock (see Appendix 5 on general use of reference cultures). If reference stocks have been thawed, they must not be refrozen and reused.

6.2.3 Working stocks should not normally be subcultured. Usually not more than five generations (or passages) from the original reference strain can be subcultured if defined by a standard method or laboratories can

provide documentary evidence that there has been no change in any relevant property. Commercial derivatives of reference strains may only be used as working cultures.

7. Sampling

For general principles reference is made to *Good practices for pharmaceutical quality control laboratories* (*1*).

7.1 Where testing laboratories are responsible for primary sampling to obtain test items, it is strongly recommended that this sampling be covered by a quality assurance system and it should be subject to regular audits.

7.2 Any disinfection processes used in obtaining the sample (e.g. disinfection of sample points) should not compromise the microbial level within the sample.

7.3 Transport and storage of samples should be under conditions that maintain the integrity of the sample (e.g. chilled or frozen where appropriate). Testing of the samples should be performed as soon as possible after sampling. For samples where a growth in the microbial population during transport and storage is possible it should be demonstrated that the storage conditions, time and temperature, will not affect the accuracy of the testing result. The storage conditions should be monitored and records kept. The responsibility for transport, storage between sampling and arrival at the testing laboratory should be clearly documented.

7.4 Sampling should only be performed by trained personnel. It should be carried out aseptically using sterile equipment. Appropriate precautions should be taken to ensure that sample integrity is maintained through the use of sterile sealed containers for the collection of samples where appropriate. It may be necessary to monitor environmental conditions, for example, air contamination and temperature, at the sampling site. Time of sampling should be recorded, if appropriate.

8. Sample handling and identification

8.1 The laboratory should have procedures that cover the delivery and receipt of samples and sample identification. If there is insufficient sample or the sample is in poor condition due to physical deterioration, incorrect temperature, torn packaging or deficient labelling, the laboratory should consult with the client before deciding whether to test or refuse the sample.

8.2 The laboratory should record all relevant information, e.g.

— date and, where relevant, the time of receipt;
— condition of the sample on receipt and, when necessary, temperature; and

— characteristics of the sampling operation (including sampling date and sampling conditions).

8.3 Samples awaiting testing should be stored under suitable conditions to minimize changes to any microbial population present. Storage conditions should be validated, defined and recorded.

8.4 The packaging and labels of samples may be highly contaminated and should be handled and stored with care so as to avoid any spread of contamination. Disinfection processes applied to the outer container should not affect the integrity of the sample. It should be noted that alcohol is not sporicidal.

8.5 Subsampling by the laboratory immediately prior to testing may be required as part of the test method. It may be appropriate that it is performed according to national or international standards, where they exist, or by validated in-house methods. Subsampling procedures should be designed to collect a representative sample.

8.6 There should be a written procedure for the retention and disposal of samples. If sample integrity can be maintained it may be appropriate that samples are stored until the test results are obtained, or longer if required. Laboratory sample portions that are known to be contaminated should be decontaminated prior to being discarded (see section 11.1).

9. Disposal of contaminated waste

9.1 The procedures for the disposal of contaminated materials should be designed to minimize the possibility of contaminating the test environment or materials. It is a matter of good laboratory management and should conform to national/international environmental or health and safety regulations.

10. Quality assurance of results and quality control of performance

10.1 Internal quality control

10.1.1 The laboratory should have a system of internal quality assurance or quality control (e.g. handling deviations, use of spiked samples, replicate testing and participation in proficiency testing, where appropriate) to ensure the consistency of results from day to day and their conformity with defined criteria.

11. Testing procedures

11.1 Testing should normally be performed according to procedures described in the national, regional and international pharmacopoeias.

11.2 Alternative testing procedures may be used if they are appropriately validated and equivalence to official methods has been demonstrated.

12. Test reports

12.1 If the result of the enumeration is negative, it should be reported as "not detected for a defined unit" or "less than the detection limit for a defined unit". The result should not be given as "zero for a defined unit" unless it is a regulatory requirement. Qualitative test results should be reported as "detected/not detected in a defined quantity or volume". They may also be expressed as "less than a specified number of organisms for a defined unit" where the specified number of organisms exceeds the detection limit of the method and this has been agreed with the client. In the raw data the result should not be given as zero for a defined unit unless it is a regulatory requirement. A reported value of "0" may be used for data entry and calculations or trend analysis in electronic databases

12.2 Where an estimate of the uncertainty of the test result is expressed on the test report, any limitations (particularly if the estimate does not include the component contributed by the distribution of microorganisms within the sample) have to be made clear to the client.

References

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3. *The International Pharmacopoeia*, Fourth Edition. Geneva, World Health Organization, 2006. Also available on CD-ROM.
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8. WHO good manufacturing practices: main principles for pharmaceutical products. In: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, 2nd updated edition. Good manufacturing practices (GMP) and inspection.* Geneva, World Health Organization, 2007, and subsequent updates, including WHO GMP for sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report*. Geneva, World Health Organization. WHO Technical Report Series, No. 961, Annex 6, 2011; and GMP: Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report*. Geneva, World Health Organization. WHO Technical Report Series, No. 961, 2011, Annex 5.

Further reading

ISO 7218 (2007) *Microbiology of food and animal feeding stuffs — General requirements and guidance for microbiological examinations*.

ISO 6887-1 (1999) *Microbiology of food and animal feeding stuffs — Preparation of test samples, initial suspension and decimal dilutions for microbiological examination — Part 1: General rules for the preparation of the initial suspension and decimal dilutions*.

ISO Guide 30 (1992) *Terms and definitions used in connection with reference materials*.

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Draft ISO/DIS 16140. (1999) *Food microbiology. Protocol for the validation of alternative methods*.

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EN 12741 (1999). *Biotechnology — Laboratories for research, development and analysis — Guidance for biotechnology laboratory operations*.

Appendix 1

Examples of zones in which operations could be carried out

The zones are designed as the following grades, during the installation and monitoring can be carried out, e.g. through appropriate air supply.

Zone	Installation grade	Proposed
Sample receipt	Unclassified	Unclassified
Media preparation	Unclassified	Unclassified
Autoclave loading	Unclassified	Unclassified
Autoclave unloading, inside the sterility testing area	Grade B	ISO 5 (turbulent) and <10 cfu/m^3
Sterility testing — UDAF	Grade A	ISO 5 (UDAF) and <1 cfu/m^3
Sterility testing — background to UDAF	Grade B	ISO 5 (turbulent) and <10 cfu/m^3
Sterility testing — isolator	Grade A (NVP and microbiology only)	ISO 5 (UDAF) and <1 cfu/m^3
Sterility testing — background to isolator	Unclassified	Unclassified
Incubator	Unclassified	Unclassified
Enumeration	Unclassified[a]	Unclassified[a]
Decontamination	Unclassified	Unclassified

cfu, colony-forming unit.

[a] Critical steps should be done under laminar flow.

Appendix 2

Examples of maintenance of equipment

This information is provided as an example and the frequency will be based on the need, type and previous performance of the equipment and on the recommendations in suppliers' manuals.

Type of equipment	Requirement	Suggested frequency
— Incubators — Fridges — Freezers, ovens	Clean and disinfect internal surfaces	— Monthly — When required (e.g. every 3 months) — When required (e.g. annually)
Water-baths	Empty, clean, disinfect and refill	— Monthly, or every 6 months if biocide used
Centrifuges	— Service — Clean and disinfect	— Annually — Each use
Autoclaves	— Make visual checks of gasket, clean/drain chamber — Full service — Safety check of pressure vessel	— Regularly, as recommended by manufacturer — Annually or as recommended by manufacturer — Annually
Safety cabinets unidirectional cabinets	Full service and mechanical check	Annually or as recommended by manufacturer
Microscopes	Full maintenance service	Annually
pH meters	Clean electrode	Each use
Balances, gravimetric diluters	— Clean — Service	— Each use — Annually
Stills	Clean and descale	As required (e.g. every 3 months)
De-ionizers, reverse osmosis units	Replace cartridge/ membrane	As recommended by manufacturer
Anaerobic jars	Clean/disinfect	After each use
Media dispensers, volumetric equipment, pipettes and general service equipment	Decontaminate, clean and sterilize as appropriate	Each use
Spiral platers	— Service — Decontaminate, clean and sterilize	— Annually — Each use
Laboratory	— Clean and disinfect working surfaces — Clean floors, disinfect sinks and basins — Clean and disinfect other surfaces	— Daily and during use — Daily — Every 3 months

Appendix 3

Examples of calibration checks and intervals for different laboratory equipment

This information is provided as an example and the frequency will be based on the need, type, previous performance and criticality of the equipment.

Type of equipment	Requirement	Suggested frequency
Reference thermometers (liquid-in-glass)	Full traceable recalibration Single point (e.g. ice-point check)	Every 3 years Annually
Reference thermocouples	Full traceable recalibration Check against reference thermometer	Every 3 years Annually
Working thermometers and working thermocouples	Check against reference thermometer at ice-point and/or working temperature range	Annually
Balances	Full traceable calibration	Annually
Calibration weights	Full traceable calibration	Annually
Check weight(s)	Check against calibrated weight or check on balance immediately following traceable calibration	Annually
Volumetric glassware	Gravimetric calibration to required tolerance	Annually
Microscopes	Traceable calibration of stage micrometer (where appropriate)	Initially
Hygrometers	Traceable calibration	Annually
Centrifuges	Traceable calibration or check against an independent tachometer, as appropriate	Annually

Appendix 4

Examples of equipment qualification and monitoring

This information is provided as an example and the frequency will be based on the need, type, previous performance and criticality of the equipment.

Type of equipment	Requirement	Suggested frequency
Temperature-controlled equipment (incubators, baths, fridges, freezers)	— Establish stability and uniformity of temperature — Monitor temperature	— Initially, every 2 years and after repair/modification — Daily/each use
Sterilizing ovens	— Establish stability and uniformity of temperature — Monitor temperature	— Initially, every 2 years and after repair/modification — Each use
Autoclaves	— Establish characteristics for loads/cycles — Monitor temperature/ pressure/time	— Initially, every 2 years and after repair/modification — Each use
Grade A areas used for sterility testing: • safety unidirectional cabinets • isolators	— Establish performance — Microbiological monitoring — Airflow monitoring — Test for integrity of HEPA filters	— Initially, every year and after repair/modification — Each use — 6-monthly — 6-monthly
Unidirectional cabinets	— Establish performance — Microbiological monitoring — Airflow monitoring — Test for integrity of HEPA filters	— Initially, and after repair/ modification — Weekly — 6-monthly — 6-monthly
Timers	Check against national time signal	Annually
Microscopes	Check alignment	Daily/each use
pH meters	Adjust using at least two buffers of suitable quality	Daily/each use
Balances	Check zero, and reading against check weight	Daily/each use
De-ionizers and reverse osmosis units	— Check conductivity — Check for microbial contamination	— Weekly — Monthly
Gravimetric diluters	— Check weight of volume dispensed — Check dilution ratio	— Daily — Daily
Media dispensers	Check volume dispensed	Each adjustment or replacement
Pipettors/pipettes	Check accuracy and precision of volume dispensed	Regularly (to be defined by taking account of the frequency and nature of use)

Appendix 4

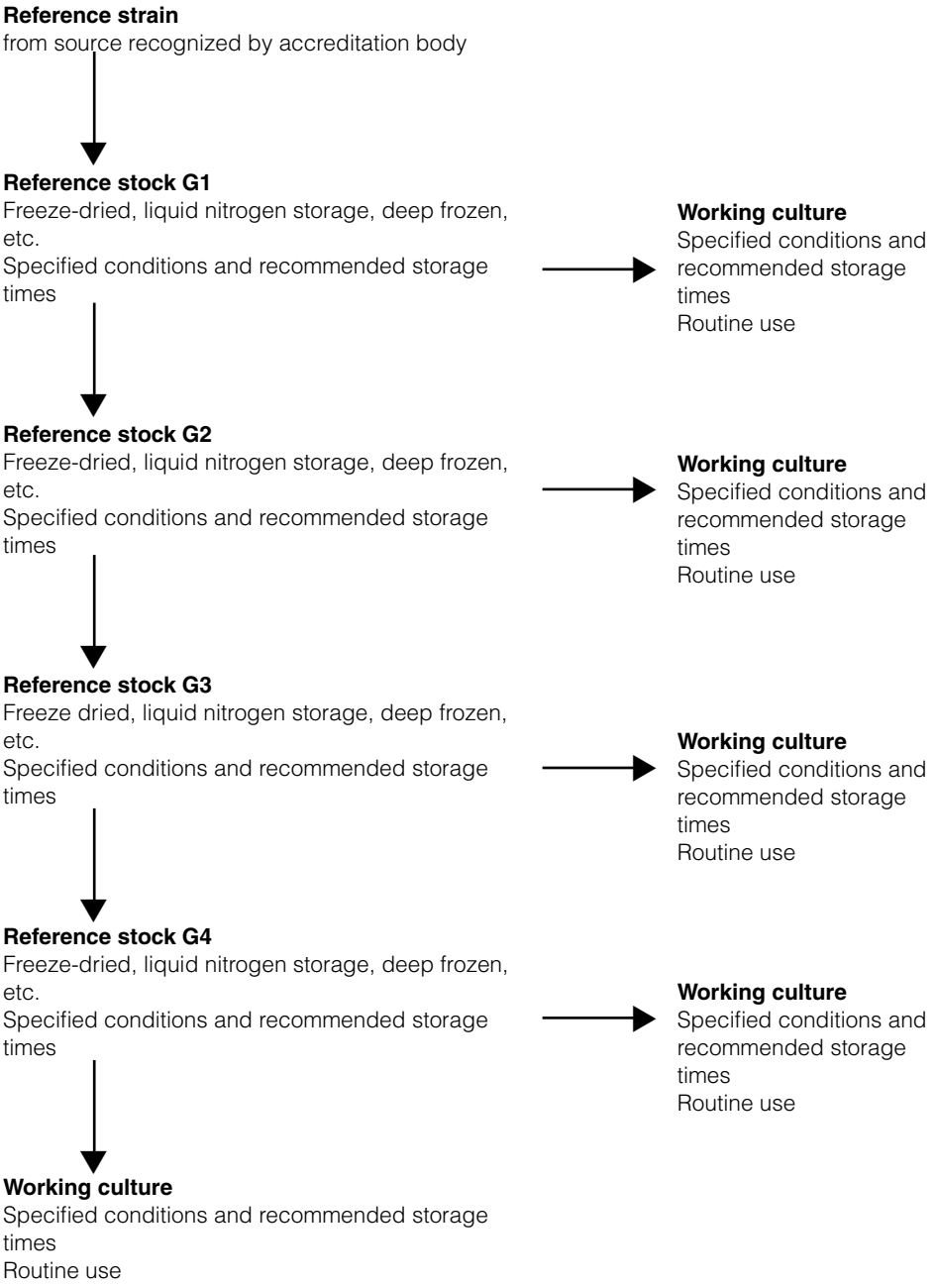
Examples of equipment qualification and monitoring (continued)

Type of equipment	Requirement	Suggested frequency
Spiral platers	— Establish performance against conventional method — Check stylus condition and the art start and end-points — Check volume dispensed	— Initially and annually — Daily/each use — Monthly
Colony counters	Check against number counted manually	Annually
Centrifuges	Check speed against a calibrated and independent tachometer	Annually
Anaerobic jars/ incubators	Check with anaerobic indicator	Each use
Laboratory environment	Monitor for airborne and surface microbial contamination using, e.g. air samplers, settle plates, contact plates or swabs	Based on risk assessment, an appropriate environmental monitoring programme should be established

HEPA, high-efficiency particulate air.

Appendix 5

General use of reference cultures



All parts of the process should be fully documented and detailed records of all stages must be maintained. Purity checks and biochemical tests should be made as appropriate.

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Annex 3

WHO good manufacturing practices for pharmaceutical products: main principles

Introduction

The first WHO draft text on good manufacturing practices (GMP) was prepared in 1967 by a group of consultants at the request of the Twentieth World Health Assembly (resolution WHA20.34). It was subsequently submitted to the Twenty-first World Health Assembly under the title "Draft requirements for good manufacturing practice in the manufacture and quality control of medicines and pharmaceutical specialities" and was accepted.

The revised text was discussed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1968 and published as an annex to its twenty-second report. The text was then reproduced (with some revisions) in 1971 in the Supplement to the second edition of *The International Pharmacopoeia*.

In 1969, when the World Health Assembly recommended the first version of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce in resolution WHA22.50, it accepted at the same time the GMP text as an integral part of the Scheme. Revised versions of both the Certification Scheme and the GMP text were adopted in 1975 by resolution WHA28.65. Since then, the Certification Scheme has been extended to include the certification of:

— veterinary products administered to food-producing animals;
— starting materials for use in dosage forms, when they are subject to control by legislation in both the exporting Member State and the importing Member State;
— information on safety and efficacy (resolution WHA41.18, 1988).

In 1992, the revised draft requirements for GMP were presented in three parts, of which only Parts One and Two are reproduced in this document (*1*).

"Quality management in the medicines industry: philosophy and essential elements", outlines the general concepts of quality assurance (QA) as well as the principal components or subsystems of GMP, which are joint responsibilities of top management and of production and quality control management. These include hygiene, validation, self-inspection, personnel, premises, equipment, materials and documentation.

"Good practices in production and quality control", provides guidance on actions to be taken separately by production and by quality control personnel for the implementation of the general principles of QA.

These two parts were subsequently supplemented by further guidelines which are integral parts of these GMP for pharmaceutical products. All these texts are available on the Medicines web page (http.www.who.int/

medicines/organization/qsm/activities/qualityassurance/gmp/gmpcover.html).

Considerable developments in GMP have taken place in the intervening years, and important national and international documents, including new revisions, have appeared (*2*,*3*,*4*,*5*). Thus the necessity to revise the main principles and incorporate the concept of validation.

Among other feedback which was discussed during the consultation on WHO guidelines for medicines quality assurance, quality control (QC) laboratories and transfer of technology on 27–31 July 2009, the need was identified to incorporate a new section (1.6) on "Product quality review" under Chapter 1: "Quality assurance".

In addition, several updates were suggested to further enhance the guidelines and include the concept of risk management, replacing "drugs" by the term "medicines" and newly introduce the concept of a "quality unit".

General considerations

Licensed pharmaceutical products (marketing authorization) should be manufactured only by licensed manufacturers (holders of a manufacturing authorization) whose activities are regularly inspected by competent national authorities. This guide to GMP shall be used as a standard to justify GMP status, which constitutes one of the elements of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce, through the assessment of applications for manufacturing authorizations and as a basis for the inspection of manufacturing facilities. It may also be used as training material for government medicines inspectors, as well as for production, QC and QA personnel in the industry.

The guide is applicable to operations for the manufacture of medicines in their finished dosage forms, including large-scale processes in hospitals and the preparation of supplies for use in clinical trials.

The good practices outlined below are to be considered general guides[1], and they may be adapted to meet individual needs. The equivalence of alternative approaches to QA, however, should be validated. The guide as a whole does not cover safety aspects for the personnel engaged in manufacture or environmental protection: these are normally governed by national legislation. A new concept of hazard analysis related to the risks in production and personnel safety is also newly recommended (Annex 7). The manufacturer should assure the safety of workers and take the necessary measures to prevent pollution of the external environment.

[1] The word "should" in the text means a strong recommendation.

International Nonproprietary Names (INN) for pharmaceutical substances designated by WHO should be used when available, together with other designated names.

Glossary

The definitions given below apply to the terms used in this guide.

They may have different meanings in other contexts.

active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

airlock

An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for use either by people or for goods and/or equipment.

authorized person

The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with the laws and regulations in force in that country.

batch (or lot)

A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

batch number (or lot number)

A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

batch records

All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

bulk product

Any product that has completed all processing stages up to, but not including, final packaging.

calibration

The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

clean area

An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

consignment (or delivery)

The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

critical operation

An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

finished product

A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling.

in-process control

Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

intermediate product

Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

large-volume parenterals

Sterile solutions intended for parenteral application with a volume of 100 ml or more in one container of the finished dosage form.

manufacture

All operations of purchase of materials and products, production, quality control (QC), release, storage and distribution of pharmaceutical products, and the related controls.

manufacturer

A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

marketing authorization (product licence, registration certificate)

A legal document issued by the competent medicines regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.

master formula

A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

master record

A document or set of documents that serve as a basis for the batch documentation (blank batch record).

packaging

All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

packaging material

Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

pharmaceutical product

Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

production

All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

qualification

Action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. The meaning of the word "validation" is sometimes extended to incorporate the concept of qualification.

quality assurance

See Part One (*6*).

quality control

See Part One (*6*).

quality unit(s)

An organizational unit independent of production which fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

quarantine

The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

reconciliation

A comparison between the theoretical quantity and the actual quantity.

recovery

The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined

stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

reprocessing

Subjecting all or part of a batch or lot of an in-process medicine, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological medicines and, in such cases, are validated and pre-approved as part of the marketing authorization.

reworking

Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization.

self-contained area

Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well established procedures, controls and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

specification

A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

starting material

Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

validation

Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

Quality management in the medicines industry: philosophy and essential elements[6]

In the medicines industry at large, quality management is usually defined as the aspect of management function that determines and implements the "quality policy", i.e. the overall intention and direction of an organization regarding quality, as formally expressed and authorized by top management.

The basic elements of quality management are:

— an appropriate infrastructure or "quality system", encompassing the organizational structure, procedures, processes and resources; and
— systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality.

The totality of these actions is termed "quality assurance" (QA). Within an organization, QA serves as a management tool. In contractual situations, QA also serves to generate confidence in the supplier.

The concepts of QA, GMP, QC and quality risk management (QRM) are interrelated aspects of quality management and should be the responsibility of all personnel. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

1. Quality assurance

1.1 *Principle.* QA is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. QA, therefore, incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

1.2 The system of QA appropriate to the manufacture of pharmaceutical products should ensure that:

(a) pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such

[6] Good manufacturing practices for pharmaceutical products, Part One. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823); and in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, Second updated edition. Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007; and in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials*. Geneva, World Health Organization, 2010 (CD-ROM).

as those of good laboratory practice (GLP)[7] and good clinical practice (GCP);

(b) production and control operations are clearly specified in a written form and GMP requirements are adopted;
(c) managerial responsibilities are clearly specified in job descriptions;
(d) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
(e) all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out;
(f) the finished product is correctly processed and checked, according to the defined procedures;
(g) pharmaceutical products are not sold or supplied before the authorized persons (see also sections 9.11 & 9.12) have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products;
(h) satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf-life;
(i) here is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the QA system;
(j) deviations are reported, investigated and recorded;
(k) there is a system for approving changes that may have an impact on product quality;
(l) regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement; and
(m) there is a system for QRM.

1.3 The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in many different departments and at all levels within the company, the company's

[7] This is a code governing the testing of chemicals to obtain data on their properties and ensuring safety with respect to human health and the environment. It is different from that described in "Good laboratory practices in governmental drug control laboratories" in the Thirtieth report of the *WHO Expert Committee on Specifications for Pharmaceutical Preparations* (WHO Technical Report Series, No. 748, 1987, Annex 1).

suppliers, and the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of QA incorporating GMP and QC. It should be fully documented and its effectiveness monitored. All parts of the QA system should be adequately staffed with competent personnel, and should have suitable and sufficient premises, equipment and facilities.

1.4 QRM is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

1.5 QRM should ensure that:

— the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient; and
— the level of effort, formality and documentation of the QRM process is commensurate with the level of risk.

Product quality review

1.6 Regular, periodic or rolling quality reviews of all medicinal products, including export-only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

(i) a review of starting materials and packaging materials used for the product, especially those from new sources;
(ii) a review of critical in-process controls and finished product results;
(iii) a review of all batches that failed to meet established specification(s) and their investigation;
(iv) a review of all significant deviations or non-conformances, the related investigations and the effectiveness of resultant corrective and preventive actions taken;
(v) a review of all changes made to the processes or analytical methods;
(vi) a review of dossier variations submitted, granted or refused;
(vii) a review of the results of the stability monitoring programme and any adverse trends;
(viii) a review of all quality-related returns, complaints and recalls and the investigations performed at the time;
(ix) a review of adequacy of any other previous corrective actions on product process or equipment;

(x) for new dossiers and variations to the dossiers, a review of post-marketing commitments;
(xi) the qualification status of relevant equipment and utilities, e.g. heating, ventilation and air-conditioning (HVAC), water, or compressed gases; and
(xii) a review of technical agreements to ensure that they are up to date.

The manufacturer and marketing authorization holder, where different, should evaluate the results of this review and an assessment should be made whether corrective and preventive action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventive actions should be completed in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures should be verified during self-inspection.

Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, or sterile products, where scientifically justified.

Where the marketing authorization holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The authorized person responsible for final batch certification, together with the marketing authorization holder, should ensure that the quality review is performed in a timely manner and is accurate.

2. Good manufacturing practices for pharmaceutical products

2.1 GMP is that part of QA which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMP are aimed primarily at diminishing the risks inherent in any pharmaceutical production.

Such risks are essentially of two types: cross-contamination (in particular of unexpected contaminants) and mix ups (confusion) caused by, for example, false labels being put on containers. Under GMP:

(a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;
(b) qualification and validation are performed;
(c) all necessary resources are provided, including:
    (i) appropriately qualified and trained personnel;

(ii) adequate premises and space;
(iii) suitable equipment and services;
(iv) appropriate materials, containers and labels;
(v) approved procedures and instructions;
(vi) suitable storage and transport;
(vii) adequate personnel, laboratories and equipment for in-process controls;

(d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;
(e) operators are trained to carry out procedures correctly;
(f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated;
(g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
(h) the proper storage and distribution of the products minimizes any risk to their quality;
(i) a system is available to recall any batch of product from sale or supply;
(j) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.

3. Sanitation and hygiene

3.1 A high level of sanitation and hygiene should be practised in every aspect of the manufacture of medicines products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene. (For *Personal hygiene* see section 11, and for *sanitation* see section 12, "Premises".)

4. Qualification and validation

4.1 In accordance with GMP, each pharmaceutical company should identify what qualification and validation work is required to prove that the critical aspects of their particular operation are controlled.

4.2 The key elements of a qualification and validation programme of a company should be clearly defined and documented in a validation master plan.

4.3 Qualification and validation should establish and provide documentary evidence that:

(a) the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP (design qualification or DQ);
(b) the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications (installation qualification or IQ);
(c) the premises, supporting utilities and equipment operate in accordance with their design specifications (operational qualification or OQ);
(d) a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process validation or PV, also called performance qualification or PQ).

4.4 Any aspect of operation, including significant changes to the premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, should be qualified and validated.

4.5 Qualification and validation should not be considered as one-off exercises. An ongoing programme should follow their first implementation and should be based on an annual review.

4.6 The commitment to maintain continued validation status should be stated in the relevant company documentation, such as the quality manual or validation master plan.

4.7 The responsibility of performing validation should be clearly defined.

4.8 Validation studies are an essential part of GMP and should be conducted in accordance with predefined and approved protocols.

4.9 A written report summarizing the results recorded and the conclusions reached should be prepared and stored.

4.10 Processes and procedures should be established on the basis of the results of the validation performed.

4.11 Particular attention should be paid to the validation of analytical test methods, automated systems and cleaning procedures.

5. Complaints

5.1 *Principle*. All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken.

5.2 A person responsible for handling the complaints and deciding the measures to be taken should be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter should be made aware of any complaint, investigation or recall.

5.3 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

5.4 Special attention should be given to establishing whether a complaint was caused because of a suspect product.

5.5 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for QC should normally be involved in the review of such investigations.

5.6 If a product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular, other batches that may contain reprocessed product from the defective batch should be investigated.

5.7 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.

5.8 All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

5.9 Complaints records should be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.

5.10 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, a suspect product or any other serious quality problems with a product.

6. Product recalls

6.1 *Principle*. There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.

6.2 The authorized person should be responsible for the execution and coordination of recalls. He/she should have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.

6.3 There should be established written procedures, which are regularly reviewed and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly down to the required level in the distribution chain.

6.4 An instruction should be included in the written procedures to store recalled products in a secure segregated area while their fate is decided.

6.5 All competent authorities of all countries to which a given product has been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.

6.6 The distribution records should be readily available to the authorized person, and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.

6.7 The progress of the recall process should be monitored and recorded. Records should include the disposition of the product. A final report should be issued, including a reconciliation between the delivered and recovered quantities of the products.

6.8 The effectiveness of the arrangements for recalls should be tested and evaluated from time to time.

7. Contract production and analysis

7.1 *Principle*. Contract production and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality.

General

7.2 All arrangements for contract production and analysis, including any proposed changes in technical or other arrangements, should be in accordance with the marketing authorization for the product concerned.

7.3 The contract should permit the contract giver to audit the facilities of the contract acceptor.

7.4 In the case of contract analysis, the final approval for release must be given by the authorized person.

The contract giver

7.5 The contract giver is responsible for assessing the competence of the contract acceptor in successfully carrying out the work or tests required, for

approval for contract activities, and for ensuring by means of the contract that the principles of GMP described in this guide are followed.

7.6 The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The contract giver should ensure that the contract acceptor is fully aware of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products.

7.7 The contract giver should ensure that all processed products and materials delivered by the contract acceptor comply with their specifications or that the product has been released by the authorized person.

The contract acceptor

7.8 The contract acceptor must have adequate premises, equipment, knowledge, and experience and competent personnel to carry out satisfactorily the work ordered by the contract giver. Contract manufacture may be undertaken only by a manufacturer who holds a manufacturing authorization.

7.9 The contract acceptor should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract acceptor and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract acceptor.

7.10 The contract acceptor should refrain from any activity that may adversely affect the quality of the product manufactured and/or analysed for the contract giver.

The contract

7.11 There must be a written contract between the contract giver and the contract acceptor which clearly establishes the responsibilities of each party.

7.12 The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.

7.13 Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and GMP.

7.14 All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

7.15 The contract should describe clearly who is responsible for purchasing, testing and releasing materials and for undertaking production and QC, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the contract acceptor should take samples at the premises of the manufacturer.

7.16 Manufacturing, analytical, distribution records and reference samples should be kept by, or be available to, the contract giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the contract giver.

7.17 The contract should describe the handling of starting materials, intermediate and bulk products and finished products if they are rejected. It should also describe the procedure to be followed if the contract analysis shows that the tested product must be rejected.

8. Self-inspection, quality audits and supplier's audits and approval

8.1 *Principle.* The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and QC. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

Items for self-inspection

8.2 Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:

(a) personnel;

(b) premises including personnel facilities;
(c) maintenance of buildings and equipment;
(d) storage of starting materials and finished products;
(e) equipment;
(f) production and in-process controls;
(g) QC;
(h) documentation;
(i) sanitation and hygiene;
(j) validation and revalidation programmes;
(k) calibration of instruments or measurement systems;
(l) recall procedures;
(m) complaints management;
(n) labels control;
(o) results of previous self-inspections and any corrective steps taken.

Self-inspection team

8.3 Management should appoint a self-inspection team consisting of experts in their respective fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of self-inspection

8.4 The frequency at which self-inspections are conducted may depend on company requirements but should preferably be at least once a year. The frequency should be stated in the procedure.

Self-inspection report

8.5 A report should be made at the completion of a self-inspection. The report should include:

(a) self-inspection results;
(b) evaluation and conclusions; and
(c) recommended corrective actions.

Follow-up action

8.6 There should be an effective follow-up programme. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality audit

8.7 It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part

of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (see section 7, "Contract production and analysis").

Suppliers' audits and approval

8.8 The person responsible for QC should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

8.9 Before suppliers are approved and included in the approved supplier's list or specifications, they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier's ability to conform with GMP standards.

9. Personnel

9.1 *Principle.* The establishment and maintenance of a satisfactory system of QA and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

General

9.2 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive so as to present any risk to quality.

9.3 Responsible staff should have its specific duties recorded in written descriptions and adequate authority to carry out its responsibilities.

Its duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP. The manufacturer should have an organization chart.

9.4 All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high quality standards.

9.5 Steps should be taken to prevent unauthorized people from entering production, storage and QC areas. Personnel who do not work in these areas should not use them as a passageway.

Key personnel

9.6 Key personnel include the heads of production, the head(s) of quality unit(s) and the authorized person. The quality unit(s) typically comprise the quality assurance and quality control functions. In some cases, these could be combined in one department. The authorized person may also be responsible for one or more of these quality unit(s). Normally, key posts should be occupied by full-time personnel. The heads of production and quality unit(s) should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.

9.7 Key personnel responsible for supervising the production and quality unit(s) for pharmaceutical products should possess the qualifications of a scientific education and practical experience required by national legislation. Their education should include the study of an appropriate combination of:

(a) chemistry (analytical or organic) or biochemistry;
(b) chemical engineering;
(c) microbiology;
(d) pharmaceutical sciences and technology;
(e) pharmacology and toxicology;
(f) physiology; and
(g) other related sciences.

They should also have adequate practical experience in the manufacture and QA of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such as to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and QC of pharmaceutical products.

9.8 The heads of the production and the quality unit(s) generally have some shared, or jointly exercised, responsibilities relating to quality.

These may include, depending on national regulations:

(a) authorization of written procedures and other documents, including amendments;
(b) monitoring and control of the manufacturing environment;
(c) plant hygiene;

(d) process validation and calibration of analytical apparatus;
(e) training, including the application and principles of QA;
(f) approval and monitoring of suppliers of materials;
(g) approval and monitoring of contract manufacturers;
(h) designation and monitoring of storage conditions for materials and products;
(i) performance and evaluation of in-process controls;
(j) retention of records;
(k) monitoring of compliance with GMP requirements; and
(l) inspection, investigation and taking of samples in order to monitor factors that may affect product quality.

9.9 The head of the production generally has the following responsibilities:

(a) to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
(b) to approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation;
(c) to ensure that the production records are evaluated and signed by a designated person;
(d) to check the maintenance of the department, premises and equipment;
(e) to ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available;
(f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

9.10 The head(s) of the quality unit(s) generally have the following responsibilities:

(a) to approve or reject starting materials, packaging materials, and intermediate, bulk and finished products in relation with their specifications;
(b) to evaluate batch records;
(c) to ensure that all necessary testing is carried out;
(d) to approve sampling instructions, specifications, test methods and other QC procedures;
(e) to approve and monitor analyses carried out under contract;
(f) to check the maintenance of the department, premises and equipment;
(g) to ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are carried out;
(h) to ensure that the required initial and continuing training of quality unit personnel is carried out and adapted according to need.
(i) establishment, implementation and maintenance of the quality system;
(j) supervision of the regular internal audits or self-inspections;

(k) participation in external audit (vendor audit);
(l) participation in validation programmes.

Other duties of QC are summarized in sections 17.3 and 17.4.

9.11 The authorized person is responsible for compliance with technical or regulatory requirements related to the quality of finished products and the approval of the release of the finished product for sale or supply.

9.12 Assessment of finished products should embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack.

9.13 No batch of product is to be released for sale or supply prior to certification by the authorized person(s). In certain countries, by law, the batch release is a task of the authorized person from production together with the authorized person from QC.

9.14 The authorized person responsible for approving a batch for release should always ensure that the following requirements have been met:

(a) the marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned;
(b) the principles and guidelines of GMP, as laid down in the guidelines published by WHO, have been followed;
(c) the principal manufacturing and testing processes have been validated, if different;
(d) all the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records;
(e) any planned changes or deviations in manufacturing or quality control have been notified in accordance with a well defined reporting system before any product is released. Such changes may need notification to, and approval by, the medicines regulatory authority;
(f) any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations;
(g) all necessary production and QC documentation has been completed and endorsed by supervisors trained in appropriate disciplines;
(h) appropriate audits, self-inspections and spot-checks are carried out by experienced and trained staff;
(i) approval has been given by the head of QC; and
(j) all relevant factors have been considered, including any not specifically associated with the output batch directly under review (e.g. subdivision of output batches from a common input, factors associated with continuous production runs).

9.15 The function of the approval of the release of a finished batch or a product can be delegated to a designated person with appropriate qualifications and experience who will release the product in accordance with an approved procedure. This is normally done by QA by means of batch review.

10. Training

10.1 The manufacturer should provide training in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required.

10.2 Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness periodically assessed. Approved training programmes should be available. Training records should be kept.

10.3 Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.

10.4 The concept of QA and all the measures which aid its understanding and implementation should be fully discussed during the training sessions.

10.5 Visitors or untrained personnel should preferably not be taken into the production and QC areas. If this is unavoidable, they should be given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing. They should be closely supervised.

10.6 Consultant and contract staff should be qualified for the services they provide. Evidence of this should be included in the training records.

11. Personal hygiene

11.1 All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.

11.2 All personnel should be trained in the practices of personal hygiene. A high level of personal hygiene should be observed by all those concerned with manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions observed.

11.3 Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials or medicines products until the condition is no longer judged to be a risk.

11.4 All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment or personnel) that they consider may adversely affect the products.

11.5 Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product.

11.6 To ensure protection of the product from contamination, personnel should wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, should be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.

11.7 Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines should not be permitted in production, laboratory and storage areas, or in any other areas where they might adversely influence product quality.

11.8 Personal hygiene procedures including the use of protective clothing should apply to all persons entering production areas, whether they are temporary or full-time employees or nonemployees, e.g. contractors' employees, visitors, senior managers and inspectors.

12. Premises

12.1 *Principle*. Premises must be located, designed, constructed, adapted and maintained to suit the operations to be carried out.

General

12.2 The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and in general, any adverse effect on the quality of products.

12.3 Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning.

12.4 Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

12.5 Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.

12.6 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.

12.7 Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.

12.8 Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

12.9 Premises should be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals. There should be a procedure for rodent and pest control.

12.10 Premises should be designed to ensure the logical flow of materials and personnel.

Ancillary areas

12.11 Rest and refreshment rooms should be separate from manufacturing and control areas.

12.12 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not communicate directly with production or storage areas.

12.13 Maintenance workshops should if possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

12.14 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

Storage areas

12.15 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.

12.16 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean, dry, sufficiently lit and

maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, controlled, monitored and recorded where appropriate.

12.17 Receiving and dispatch bays should be separated and protect materials and products from the weather. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

12.18 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.

12.19 Segregation should be provided for the storage of rejected, recalled, or returned materials or products.

12.20 Highly active and radioactive materials, narcotics, other dangerous medicines, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.

12.21 Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling and special attention should be paid to sampling and the safe and secure storage of these materials.

12.22 There should normally be a separate sampling area for starting materials. (If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.)

Weighing areas

12.23 The weighing of starting materials and the estimation of yield by weighing should be carried out in separate weighing areas designed for that use, for example, with provisions for dust control. Such areas may be part of either storage or production areas.

Production areas

12.24 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g. penicillins) or biological preparations (e.g. live microorganisms). The production of certain other highly active products, such as some antibiotics, hormones, cytotoxic substances and certain non-pharmaceutical products, should not be conducted in the same facilities. In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken

and the necessary validations (including cleaning validation) are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products.

12.25 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

12.26 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

12.27 Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth and free from cracks and open joints, should not shed particulate matter, and should permit easy and effective cleaning and, if necessary, disinfection.

12.28 Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

12.29 Drains should be of adequate size and designed and equipped to prevent back-flow. Open channels should be avoided where possible, but if they are necessary they should be shallow to facilitate cleaning and disinfection.

12.30 Production areas should be effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas should be regularly monitored during both production and non-production periods to ensure compliance with their design specifications.

12.31 Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix ups, contamination or cross-contamination.

12.32 Production areas should be well lit, particularly where visual online controls are carried out.

Quality control areas

12.33 QC laboratories should be separated from production areas. Areas where biological, microbiological or radioisotope test methods are employed should be separated from each other.

12.34 QC laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix ups and cross-contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents and records.

12.35 The design of the laboratories should take into account the suitability of construction materials, prevention of fumes and ventilation. There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, microbiological and radioisotope laboratories.

12.36 A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors, or where it is necessary to isolate the instruments.

13. Equipment

13.1 Equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

13.2 Equipment should be installed in such a way as to minimize any risk of error or of contamination.

13.3 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

13.4 All service pipings and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.

13.5 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated on a scheduled basis.

13.6 Production equipment should be thoroughly cleaned on a scheduled basis.

13.7 Laboratory equipment and instruments should be suited to the testing procedures undertaken.

13.8 Washing, cleaning and drying equipment should be chosen and used so as not to be a source of contamination.

13.9 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.

13.10 Defective equipment should be removed from production and QC areas. If this is not possible, it should be clearly labelled as defective to prevent use.

13.11 Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is opened, precautions should be taken to minimize contamination.

13.12 Non-dedicated equipment should be cleaned according to validated cleaning procedures between production of different pharmaceutical products to prevent cross-contamination.

13.13 Current drawings of critical equipment and support systems should be maintained.

14. Materials

14.1 *Principle.* The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging).

14.2 Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labelling materials.

General

14.3 No materials used for operations such as cleaning, lubrication of equipment and pest control, should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks.

14.4 All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.

14.5 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation by a first-expire, first-out rule.

14.6 Water used in the manufacture of pharmaceutical products should be suitable for its intended use.

Starting materials

14.7 The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.

14.8 Starting materials should be purchased only from approved suppliers and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all critical aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements as well as complaints and rejection procedures, are contractually agreed between the manufacturer and the supplier.

14.9 For each consignment, the containers should be checked for at least integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.

14.10 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.

14.11 Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the QC department and investigated.

14.12 If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release.

14.13 Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

(a) the designated name of the product and the internal code reference where applicable;
(b) the batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;
(c) the status of the contents (e.g. on quarantine, on test, released, rejected, returned, recalled);
(d) where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully validated computerized storage systems are used, not all of the above information need be in a legible form on the label.

14.14 There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material.

Bulk containers from which samples have been drawn should be identified.

14.15 Only starting materials released by the QC department and within their shelf-life should be used.

14.16 Starting materials should be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

14.17 Each dispensed material and its weight or volume should be independently checked and the check recorded.

14.18 Materials dispensed for each batch of the final product should be kept together and conspicuously labelled as such.

Packaging materials

14.19 The purchase, handling and control of primary and printed packaging materials should be as for starting materials.

14.20 Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized access. Roll feed labels should be used wherever possible. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.

14.21 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

14.22 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and its disposal recorded.

14.23 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

Intermediate and bulk products

14.24 Intermediate and bulk products should be kept under appropriate conditions.

14.25 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

Finished products

14.26 Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.

14.27 The evaluation of finished products and the documentation necessary for release of a product for sale are described in section 17, "Good practices in quality control".

Rejected, recovered, reprocessed and reworked materials

14.28 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a timely manner. Whatever action is taken should be approved by authorized personnel and recorded.

14.29 The reworking or recovery of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept of the reworking or recovery. A reworked batch should be given a new batch number.

14.30 The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery should be recorded.

14.31 The need for additional testing of any finished product that has been reprocessed, reworked or into which a recovered product has been incorporated, should be considered by the QC department.

Recalled products

14.32 Recalled products should be identified and stored separately in a secure area until a decision is taken on their fate. The decision should be made as soon as possible.

Returned goods

14.33 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabelling, or alternative action taken only after they have been critically assessed by the QC function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse.

Any action taken should be appropriately recorded.

Reagents and culture media

14.34 There should be records for the receipt and preparation of reagents and culture media.

14.35 Reagents made up in the laboratory should be prepared according to written procedures and appropriately labelled. The label should indicate the concentration, standardization factor, shelf-life, the date when restandardization is due, and the storage conditions. The label should be signed and dated by the person preparing the reagent.

14.36 Both positive and negative controls should be applied to verify the suitability of culture media each time they are prepared and used. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

Reference standards

14.37 Whenever official reference standards exist, these should preferably be used.

14.38 Official reference standards should be used only for the purpose described in the appropriate monograph.

14.39 Reference standards prepared by the producer should be tested, released and stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.

14.40 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization.

14.41 Reference standards should be properly labelled with at least the following information:

(a) name of the material;
(b) batch or lot number and control number;
(c) date of preparation;
(d) shelf-life;
(e) potency;
(f) storage conditions.

14.42 All in-house reference standards should be standardized against an official reference standard, when available, initially and at regular intervals thereafter.

14.43 All reference standards should be stored and used in a manner that will not adversely affect their quality.

Waste materials

14.44 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

14.45 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

Miscellaneous

14.46 Rodenticides, insecticides, fumigating agents and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products.

15. Documentation

15.1 *Principle*. Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a medicine for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases some or all of the documents described below may be brought together, but they will usually be separate.

General

15.2 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.

15.3 Documents should be approved, signed and dated by the appropriate responsible persons. No document should be changed without authorization and approval.

15.4 Documents should have unambiguous contents: the title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

15.5 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.

15.6 Where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.

15.7 Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

15.8 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records should be retained for at least one year after the expiry date of the finished product.

15.9 Data (and records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures (SOPs) relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked. Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs or other means. It is particularly important that, during the period of retention, the data are readily available.

Documents required

Labels

15.10 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (e.g. quarantined, accepted, rejected, clean).

15.11 All finished medicines products should be identified by labelling, as required by the national legislation, bearing at least the following information:

(a) the name of the medicines product;
(b) a list of the active ingredients (if applicable, with the INNs), showing the amount of each present and a statement of the net contents (e.g. number of dosage units, weight, volume);
(c) the batch number assigned by the manufacturer;
(d) the expiry date in an uncoded form;
(e) any special storage conditions or handling precautions that may be necessary;
(f) directions for use, and warnings and precautions that may be necessary;
(g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

15.12 For reference standards, the label and/or accompanying document should indicate potency or concentration, date of manufacture, expiry date, date the closure is first opened, storage conditions and control number, as appropriate.

Specifications and testing procedures

15.13 Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routine testing.

15.14 There should be appropriately authorized and dated specifications, including tests on identity, content, purity and quality, for starting and packaging materials and for finished products; where appropriate, they should also be available for intermediate or bulk products. Specifications for water, solvents and reagents (e.g. acids and bases) used in production should be included.

15.15 Each specification should be approved, signed and dated, and maintained by the QC, QA units or documentation centre. Specifications for starting materials, intermediates, and bulk, finished products and packaging materials are referred to in sections 15.18–15.21.

15.16 Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.

15.17 Pharmacopoeias, reference standards, reference spectra and other reference materials should be available in the QC laboratory.

Specifications for starting and packaging materials

15.18 Specifications for starting, primary and printed packaging materials should provide, if applicable, a description of the materials, including:

(a) the designated name (if applicable, the INN) and internal code reference;
(b) the reference, if any, to a pharmacopoeial monograph;
(c) qualitative and quantitative requirements with acceptance limits.

Depending on the company's practice other data may be added to the specification, such as:

(a) the supplier and the original producer of the materials;
(b) a specimen of printed materials;
(c) directions for sampling and testing, or a reference to procedures;
(d) storage conditions and precautions;
(e) the maximum period of storage before re-examination.

Packaging material should conform to specifications, and should be compatible with the material and/or with the medicines product it contains.

The material should be examined for compliance with the specification, and for defects as well as for the correctness of identity markings.

15.19 Documents describing testing procedures should state the required frequency for re-assaying each starting material, as determined by its stability.

Specifications for intermediate and bulk products

15.20 Specifications for intermediate and bulk products should be available. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

15.21 Specifications for finished products should include:

(a) the designated name of the product and the code reference, where applicable;
(b) the designated name(s) of the active ingredient(s) (if applicable, with the INN(s));
(c) the formula or a reference to the formula;
(d) a description of the dosage form and package details;
(e) directions for sampling and testing or a reference to procedures;
(f) the qualitative and quantitative requirements, with acceptance limits;
(g) the storage conditions and precautions, where applicable;
(h) the shelf-life.

Master formulae

15.22 A formally authorized master formula should exist for each product and batch size to be manufactured.

15.23 The master formula should include:

(a) the name of the product, with a product reference code relating to its specification;
(b) a description of the dosage form, strength of the product and batch size;
(c) a list of all starting materials to be used (if applicable, with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);
(d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
(e) a statement of the processing location and the principal equipment to be used;
(f) the methods, or reference to the methods, to be used for preparing and operating the critical equipment, e.g. cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;
(g) detailed step-wise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
(h) the instructions for any in-process controls with their limits;
(i) where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions;
(j) any special precautions to be observed.

Packaging instructions

15.24 Formally authorized packaging instructions should exist for each product, pack size and type. These should normally include, or make reference to:

(a) the name of the product;
(b) a description of its pharmaceutical form, strength and, where applicable, method of application;
(c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
(d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging material;
(e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;

(f) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;
(g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
(h) details of in-process controls with instructions for sampling and acceptance limits.

Batch processing records

15.25 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)

15.26 Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.

15.27 During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations:

(a) the name of the product;
(b) the number of the batch being manufactured;
(c) dates and times of commencement, of significant intermediate stages, and of completion of production;
(d) the name of the person responsible for each stage of production;
(e) the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g. weighing);
(f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
(g) any relevant processing operation or event and the major equipment used;
(h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
(i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;
(j) notes on special problems including details, with signed authorization for any deviation from the master formula.

Batch packaging records

15.28 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)

15.29 Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.

15.30 The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:

(a) the name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;
(b) the date(s) and time(s) of the packaging operations;
(c) the name of the responsible person carrying out the packaging operation;
(d) the initials of the operators of the different significant steps;
(e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
(f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;
(g) whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;
(h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
(i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

Standard operating procedures and records

15.31 SOPs and associated records of actions taken or, where appropriate, conclusions reached should be available for:

(a) equipment assembly and validation;
(b) analytical apparatus and calibration;
(c) maintenance, cleaning and sanitization;
(d) personnel matters including qualification, training, clothing and hygiene;
(e) environmental monitoring;
(f) pest control;
(g) complaints;
(h) recalls;
(i) returns.

15.32 There should be SOPs and records for the receipt of each delivery of starting material and primary and printed packaging material.

15.33 The records of the receipts should include:

(a) the name of the material on the delivery note and the containers;
(b) the "in-house" name and/or code of material if different from (a);
(c) the date of receipt;
(d) the supplier's name and, if possible, manufacturer's name;
(e) the manufacturer's batch or reference number;
(f) the total quantity, and number of containers received;
(g) the batch number assigned after receipt;
(h) any relevant comment (e.g. state of the containers).

15.34 There should be SOPs for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

15.35 SOPs should be available for each instrument and piece of equipment (e.g. use, calibration, cleaning, maintenance) and placed in close proximity to the equipment.

15.36 There should be SOPs for sampling, which specify the person(s) authorized to take samples.

15.37 The sampling instructions should include:

(a) the method of sampling and the sampling plan;
(b) the equipment to be used;
(c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
(d) the amount(s) of sample(s) to be taken;
(e) instructions for any required subdivision of the sample;
(f) the type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling, and labelling;
(g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

15.38 There should be an SOP describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.

15.39 The SOPs for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

15.40 The SOP for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.

15.41 Batch-number allocation should be immediately recorded, e.g. in a logbook. The record should include at least the date of allocation, product identity and size of batch.

15.42 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

15.43 Analysis records should include at least the following data:

(a) the name of the material or product and, where applicable, dosage form;
(b) the batch number and, where appropriate, the manufacturer and/or supplier;
(c) references to the relevant specifications and testing procedures;
(d) test results, including observations and calculations, and reference to any specifications (limits);
(e) date(s) and reference number(s) of testing;
(f) the initials of the persons who performed the testing;
(g) the date and initials of the persons who verified the testing and the calculations, where appropriate;
(h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

15.44 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.

15.45 Records should be maintained of the distribution of each batch of a product in order, e.g. to facilitate the recall of the batch if necessary.

15.46 Records should be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.

15.47 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.

15.48 There should be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned. Such written procedures should be followed.

16. Good practices in production

16.1 *Principle*. Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

General

16.2 All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

16.3 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be done in accordance with an approved procedure. The authorization of the deviation should be approved in writing by a designated person, with the involvement of the QC department, when appropriate.

16.4 Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

16.5 Operations on different products should not be carried out simultaneously or consecutively in the same room or area unless there is no risk of mix up or cross-contamination.

16.6 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate, the rooms and packaging lines being used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and the batch number. Where applicable, this indication should also mention the stage of production. In some cases it may be useful to also record the name of the previous product that has been processed.

16.7 Access to production premises should be restricted to authorized personnel.

16.8 Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.

16.9 In-process controls are usually performed within the production area. The performance of such in-process controls should not have any

negative effect on the quality of the product or another product (e.g. cross-contamination or mix up).

Prevention of cross-contamination and bacterial contamination during production

16.10 When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g. supply and extraction of air of suitable quality).

16.11 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, particles, vapours, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated.

Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials.

Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.

16.12 Cross-contamination should be avoided by taking appropriate technical or organizational measures, for example:

(a) carrying out production in dedicated and self-contained areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations and certain other biologicals);
(b) conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;
(c) providing appropriately designed airlocks, pressure differentials, and air supply and extraction systems;
(d) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
(e) wearing protective clothing where products or materials are handled;
(f) using cleaning and decontamination procedures of known effectiveness;
(g) using a "closed system" in production;
(h) testing for residues;
(i) using cleanliness status labels on equipment.

16.13 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to SOPs.

16.14 Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological monitoring and particulate matter where appropriate).

Processing operations

16.15 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation.

16.16 Any necessary in-process controls and environmental controls should be carried out and recorded.

16.17 Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

16.18 Time limits for storage of equipment after cleaning and before use should be stated and based on data.

16.19 Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

16.20 Any significant deviation from the expected yield should be recorded and investigated.

16.21 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

16.22 Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

16.23 Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.

16.24 Repair and maintenance operations should not present any hazard to the quality of the products.

Packaging operations

16.25 When the programme for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or an alternative system that will provide equal assurance.

16.26 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents used previously and which are not required for the current operation. The line clearance should be performed according to an appropriate procedure and checklist, and recorded.

16.27 The name and batch number of the product being handled should be displayed at each packaging station or line.

16.28 Normally, filling and sealing should be followed as quickly as possible by labelling. If labelling is delayed, appropriate procedures should be applied to ensure that no mix ups or mislabelling can occur.

16.29 The correct performance of any printing (e.g. of code numbers or expiry dates) done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand, which should be rechecked at regular intervals.

16.30 Special care should be taken when cut labels are used and when overprinting is carried out off-line, and in hand-packaging operations. Roll feed labels are normally preferable to cut labels in helping to avoid mix ups. Online verification of all labels by automated electronic means can be helpful in preventing mix ups, but checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly. When labels are attached manually, in-process control checks should be performed more frequently.

16.31 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

16.32 Regular online control of the product during packaging should include at least checks on:

(a) the general appearance of the packages;
(b) whether the packages are complete;
(c) whether the correct products and packaging materials are used;
(d) whether any overprinting is correct;
(e) the correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

16.33 Products that have been involved in an unusual event during packaging should be reintroduced into the process only after special inspection, investigation and approval by authorized personnel. A detailed record should be kept of this operation.

16.34 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated, satisfactorily accounted for, and recorded before release.

16.35 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure requiring checks to be performed before returning unused materials should be followed if uncoded printed materials are returned to stock.

16.36 Production records should be reviewed as part of the approval process of batch release before transfer to the authorized person. Any divergence or failure of a batch to meet production specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

17. Good practices in quality control

17.1 QC is the part of GMP concerned with sampling, specifications and testing, and with the organization and documentation which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. QC is not confined to laboratory operations, but may be involved in many decisions concerning the quality of the product.

17.2 The independence of QC from production is considered fundamental.

17.3 Each manufacturer should have a QC function. The QC function should be independent of other departments and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his or her disposal. Adequate resources must be available to ensure that all the QC arrangements are effectively and reliably carried out. The basic requirements for QC are as follows:

(a) adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing starting materials,

packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;

(b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the QC department;

(c) qualification and validation;

(d) records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated;

(e) the finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container and correctly labelled;

(f) records must be made of the results of inspecting and testing the materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;

(g) sufficient samples of starting materials and products must be retained to permit future examination of the product if necessary; the retained product must be kept in its final pack unless the pack is exceptionally large.

17.4 QC as a whole will also have other duties, such as to establish, validate and implement all QC procedures, to evaluate, maintain, and store the reference standards for substances, to ensure the correct labelling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients (APIs) and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

17.5 QC personnel must have access to production areas for sampling and investigation as appropriate.

Control of starting materials and intermediate, bulk and finished products

17.6 All tests should follow the instructions given in the relevant written test procedure for each material or product. The result should be checked by the supervisor before the material or product is released or rejected.

17.7 Samples should be representative of the batches of material from which they are taken in accordance with the approved written procedure.

17.8 Sampling should be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled should be marked accordingly and carefully resealed after sampling.

17.9 Care should be taken during sampling to guard against contamination or mix up of, or by, the material being sampled. All sampling equipment that comes into contact with the material should be clean. Some particularly hazardous or potent materials may require special precautions.

17.10 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.

17.11 Each sample container should bear a label indicating:

(a) the name of the sampled material;
(b) the batch or lot number;
(c) the number of the container from which the sample has been taken;
(d) the number of the sample;
(e) the signature of the person who has taken the sample;
(f) the date of sampling.

17.12 Out-of-specification results obtained during testing of materials or products should be investigated in accordance with an approved procedure. Records should be maintained.

Test requirements

Starting and packaging materials

17.13 Before releasing a starting or packaging material for use, the QC manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters.

17.14 An identity test should be conducted on a sample from each container of starting material (see also section 14.14).

It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labelled.

This validation should take account of at least the following aspects:

— the nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements;
— the QA system of the manufacturer of the starting material;

— the manufacturing conditions under which the starting material is produced and controlled; and
— the nature of the starting material and the medicinal products in which it will be used.

Under such a system it is possible that a validated procedure for exemption from the requirement for identity testing of each incoming container of starting material could be accepted for the following:

— starting materials coming from a single product manufacturer or plant; or
— starting materials coming directly from a manufacturer, or in the manufacturer's sealed container where there is a history of reliability, and regular audits of the manufacturer's QA system are conducted by the purchaser (the manufacturer of the medicinal product) or by an officially accredited body.

It is improbable that such a procedure could be satisfactorily validated for either:

— starting materials supplied by intermediaries, such as brokers, where the source of manufacture is unknown or not audited; or
— starting materials for use in parenteral products.

17.15 Each batch (lot) of printed packaging materials must be examined following receipt.

17.16 In lieu of full testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results (see sections 8.8 and 8.9) and through on-site audits of the supplier's capabilities. (This does not affect section 17.15.) Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain at least the following information (*7*):

(a) identification (name and address) of the issuing supplier;
(b) signature of the competent official, and statement of his or her qualifications;
(c) the name of the material tested;
(d) the batch number of the material tested;
(e) the specifications and methods used;
(f) the test results obtained;
(g) the date of testing.

In-process control

17.17 In-process control records should be maintained and form a part of the batch records (see section 15.25).

Finished products

17.18 For each batch of medicines product, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

17.19 Products failing to meet the established specifications or any other relevant quality criteria should be rejected.

Batch record review

17.20 QC records should be reviewed as part of the approval process of batch release before transfer to the authorized person. Any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

17.21 Retention samples from each batch of finished product should be kept for at least one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials should be retained for at least one year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases and water) should be retained for a minimum of two years if their stability allows. Retention samples of materials and products should be of a size sufficient to permit at least two full re-examinations.

Stability studies

17.22 QC should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.

17.23 QC should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

17.24 A written programme for ongoing stability determination should be developed and implemented to include elements such as:

(a) a complete description of the medicine involved in the study;
(b) the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
(c) provision for the inclusion of a sufficient number of batches;

(d) the testing schedule for each medicine;
(e) provision for special storage conditions;
(f) provision for adequate sample retention;
(g) a summary of all the data generated, including the evaluation and the conclusions of the study.

17.25 Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.

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Annex 4

WHO guidelines on good manufacturing practices for blood establishments

1. Introduction

The World Health Organization (WHO) requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (*1*) define a quality assurance system based on (i) the existence of a national structure that is independent of manufacturers, (ii) compliance with the process of quality assurance for biological products — i.e. control of starting material(s), production processes and final product(s) — and (iii) strict adherence to the principles of good manufacturing practice (GMP). Since the last revision of these requirements in 1992, two relevant items have been reviewed and new recommendations adopted, namely on virus inactivation and removal of plasma derivatives (2004) (*2*) and human plasma for fractionation (2007) (*3*). However, a number of issues, such as the requirement for a quality assurance system in blood establishments, have not yet been addressed. The WHO Expert Committee on Biological Standardization (ECBS), therefore, considered that the development of WHO guidelines on GMP for blood establishments is of highest priority in assisting Member States to meet their needs in this area, as requested by the International Conference of Drug Regulatory Authorities in 2008 (*4*).

The importance of establishing reliable quality assurance systems for the whole chain of blood collection, processing and distribution of blood components in blood establishments was also emphasized by the Sixty-third World Health Assembly in resolution WHA63.12 on the availability, safety and quality of blood products (*5*). In that resolution, quality assurance was seen as a necessary measure that would contribute to increased global availability of plasma that meets internationally recognized standards.

Resolution WHA63.12 recognized that a special effort is needed to strengthen globally the technical capacity of national regulatory authorities (NRAs) to assure the appropriate control of blood products. The resolution recalls earlier related resolutions which urged Member States to promote the full implementation of well organized, nationally coordinated and sustainable blood programmes stressing the role of voluntary, non-remunerated blood donations from low-risk populations.

In recent years, safety and quality in the transfusion chain has become an important topic in many countries and regions (*6*). Blood establishments should establish and maintain quality systems, based on GMP principles, involving all activities that determine quality policy objectives and responsibilities, and should implement them by such means as quality planning, quality control, quality assurance and quality improvement. A GMP approach to manufacturing safe blood components that consistently meet predefined specifications and customers' expectations provides a model that allows for a documented system of incorporating quality into

the entire process. When collecting and processing blood and plasma from human donors, GMP considerations should be addressed in a biological context due to the specific characteristics of materials of human origin.

The guidelines in this document include:

— general GMP topics such as quality management, personnel, documentation, premises and equipment, qualification and validation, materials management, contract manufacturing, and complaints and recalls;
— GMP concepts such as quality risk management and product quality reviews;
— topics specific to the manufacturing of blood components from donor selection to distribution of the final product.

They address current and widely accepted GMP principles that are relevant to the consistent production of safe and assured quality blood components in blood establishments, including related donor safety concerns. The document is intended to serve as guidance for both blood establishments and NRAs when implementing and enforcing these principles. It does not address the practice of transfusion medicine or management of emergencies or crises where specific policies defined by the NRA apply. Aspects of personnel and environmental protection are also not within the scope of this document.

Complementary guidance, especially with respect to the production of plasma for fractionation, is available in the *WHO recommendations for the production, control and regulation of human plasma for fractionation* (*3*).

2. Glossary and abbreviations

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

apheresis

The process by which one or more blood components are selectively obtained from a donor by withdrawing whole blood, separating it by centrifugation and/or filtration into its components, and returning those not required to the donor.

blood collection

The procedure whereby a single donation of blood is collected in an anticoagulant and/or stabilizing solution, under conditions designed to minimize microbial contamination, cellular damage and/or coagulation activation of the resulting blood donation.

blood component

A constituent of blood (erythrocytes, leukocytes, platelets, cryoprecipitate and plasma) that can be prepared by various separation methods and under such conditions that it can be used either directly for therapeutic purposes or for further processing/manufacturing.

blood establishment

Any structure, facility or body that is responsible for any aspect of the collection, testing, processing, storage, release and/or distribution of human blood or blood components when intended for transfusion or further industrial manufacturing.

blood products

Any therapeutic substances derived from human blood, including whole blood, blood components and plasma-derived medicinal products.

calibration

The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

CJD/vCJD

Creutzfeld-Jakob-Disease/variant Creutzfeld-Jakob-Disease.

closed system

A system developed for aseptic collection and separation of blood and blood components, manufactured under clean conditions, sealed to the external environment and sterilized by a validated and approved method.

computerized system

A system including the input of data, electronic processing and the output of information to be used either for reporting or for automatic control.

contract acceptor

An establishment or institution that performs particular work or services under a contract for a different institution.

contract giver

An establishment or institution that is subcontracting particular work or services to a different institution and sets up a contract defining the duties and responsibilities of each side.

donor

A person in defined good health conditions who voluntarily donates blood or blood components, including plasma for fractionation.

distribution

The act of delivery of blood and blood components to other blood establishments, hospital blood banks or manufacturers of blood- and plasma-derived medicinal products. It does not include the issuing of blood or blood components for transfusion.

first-time (tested) donor

A donor whose blood or plasma is tested for the first time for infectious disease markers in a blood establishment.

good manufacturing practice (GMP)

All elements in the established practice that will collectively lead to final products or services that consistently meet appropriate specifications and compliance with defined regulations.

HAV, hepatitis A virus

A non-enveloped single-stranded RNA virus that is the causative agent of hepatitis A.

HBsAg, hepatitis B surface antigen

The antigen on the periphery of the hepatitis B virus.

HBV, hepatitis B virus

An enveloped double-stranded DNA virus that is the causative agent of hepatitis B.

HCV, hepatitis C virus

An enveloped single-stranded, RNA virus that is the causative agent of hepatitis C.

HIV, human immunodeficiency virus

An enveloped, single-stranded RNA virus that is the causative agent of the acquired immunodeficiency syndrome (AIDS).

HTLV 1 and 2, human T-cell lymphotropic virus, types 1 and 2

Enveloped, single stranded RNA viruses that are typically cell-associated.

manufacture

All operational processes or steps — including purchase or selection of materials and products, production, quality control, release, storage and distribution of products and the related controls — used to produce a blood product. This includes also the donation process.

mobile site

A unit or site used for the collection of blood and/or blood components, operating temporarily or at movable locations off-site from a permanent collection site, under the responsibility of a blood establishment.

nucleic acid amplification techniques (NAT)

A testing method to detect the presence of a targeted area of a defined microbial genome that uses amplification techniques such as polymerase chain reaction (PCR).

near-miss event

An incident that, if not detected in a timely manner, would have affected the safety of the recipients or donors.

national regulatory authority (NRA)

WHO terminology for national medicines regulatory authorities. NRAs should promulgate and enforce medicines regulations.

plasma for fractionation

The liquid part of human blood remaining after separation of the cellular elements from blood collected in a container containing an anticoagulant, or separated by continuous filtration and/or centrifugation of anticoagulated blood in an apheresis procedure, intended for further manufacturing.

production

All operations involved in the preparation of blood components, from collection through processing to completion as a finished product (blood component).

qualification

A set of actions used to provide documented evidence that any piece of equipment, critical material or reagent used to produce the final product and that might affect the quality or safety of a product works reliably as intended or specified and leads to the expected results.

quality

The total set of characteristics of an entity that affect its ability to satisfy stated and implied needs, and the consistent and reliable performance of services or products in conformity with specified requirements. Implied needs include safety and quality attributes of products intended both for therapeutic use and as starting materials for further manufacturing.

quality assurance

A part of quality management focused on providing confidence that quality requirements will be met.

quality management

The coordinated activities that direct and control an organization with regard to quality.

quality management system

A management system that directs and controls an organization with respect to quality and that ensures that steps, processes, procedures and policies related to quality activities are being followed.

quality risk management (QRM)

A systematic process for the assessment, control, communication and review of risks to the quality of the product across the product's life cycle.

quarantine

The status of starting or packaging materials, intermediate, bulk or finished products that are isolated physically or by other means while a decision is awaited on their release for use or rejection.

regular donor

A person who routinely donates blood, blood components or plasma in the same blood establishment in accordance with the minimum time intervals.

repeat donor

A person who has donated before in the same establishment but not within the period of time considered as regular donation.

repeatedly reactive

A donation is considered to be repeatedly reactive if it is found reactive in a screening test, is retested in duplicate using the same assay, and at least one of the repeat tests is also reactive.

validation

Actions for proving that any operational procedure, process, activity or system leads to the expected results. Validation work is normally performed in advance according to a defined and approved protocol that describes tests and acceptance criteria.

WNV, West Nile Virus

An enveloped single-stranded RNA virus that is the causative agent of West Nile fever.

3. Quality management

3.1 Principles

Quality is the responsibility of all persons involved in the various processes of the blood establishment. The management of the blood establishment is responsible for a systematic approach to quality and the implementation and maintenance of a quality management system. A quality programme

should be designed to ensure that each product (including plasma for fractionation) is manufactured in the same manner from donor selection through to distribution of the final product.

Quality management involves all activities that determine the quality policy, objectives and responsibilities, and their implementation through quality planning, quality control, quality assurance and quality improvement in order to assure the quality and safety of blood and blood components.

The attainment of the quality policy and objectives is the responsibility of the senior management of the blood establishment and requires the participation and commitment of all staff throughout the entire blood establishment. Senior management should review the quality system at regular intervals to verify its effectiveness and to introduce corrective measures if they are considered necessary.

Within the organizational structure of the blood establishment there should be a quality management unit comprising one or more persons. The quality management personnel should be responsible for ensuring that there is documented evidence that the quality policies, procedures and practices are being fulfilled. Senior management, in coordination with the quality management unit, should develop and implement quality assurance policies and objectives in a manner that provides clear direction to all staff. The quality assurance policies and objectives should be designed to ensure the highest levels of safety and quality in the blood components that are produced from each collection. The policies and procedures should comply with all national and, where appropriate, international regulations and requirements.

Staff should be able to understand the intent of the quality objectives and their own role in accomplishing the objectives. The performance of the quality management system should be evaluated periodically by determining whether the objectives have been or are continuously being met. If there are shortcomings in the quality system, corrections should be made and the quality management unit should be held responsible for monitoring corrective action and continued compliance.

Within any blood establishment there should be independent functions for fulfilling quality assurance and quality control responsibilities. The quality assurance function should be independent of manufacturing operations and should assure that all processes are performed and documented. The quality assurance function should be involved in all quality-related matters and in the review and approval of all quality-related documents.

3.2 Quality assurance

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of the product. It is the

totality of arrangements that are made with the purpose of ensuring that products are of the quality required for their intended use. Quality assurance therefore incorporates GMP, and other elements, including those outside the scope of this guideline — such as product design and development (*7*).

Quality assurance is that part of quality management that ensures that all critical processes are appropriately described in written instructions (see chapter 5), are performed in accordance with the principles of GMP and comply with the appropriate regulations. The quality assurance system should be fully documented, distributed and explained to everyone involved in the manufacturing processes.

All parts of the quality assurance system should be adequately resourced with competent personnel, suitable premises, and suitable and sufficient equipment and facilities to enable the manufacturing steps to be completed in a safe and quality-compliant manner.

3.2.1 *Good manufacturing practice in blood establishments*

GMP is the part of quality assurance that ensures that blood products are consistently produced and controlled to the quality standards appropriate to their intended use, as required by predefined specifications and, if applicable, by the marketing authorization. GMP is aimed primarily at diminishing the risks inherent in any blood establishment operation — such as contamination (including cross-contamination), mix-ups, disease transmission or other unexpected adverse outcomes resulting from the use of blood products. GMP is concerned with both production and quality control.

The basic requirements of GMP are the following:

- All manufacturing processes are clearly defined by policies and standard operating procedures, are systematically reviewed in the light of experience, and are shown to be capable of consistently manufacturing products of the required quality that comply with their specifications.
- Qualification of equipment and reagents and validation of processes and methods are performed prior to use in the manufacture of products intended for transfusion or further manufacturing.
- All necessary resources are provided — including appropriately qualified and trained personnel, adequate premises, suitable equipment, appropriate materials, approved procedures and instructions, suitable storage and transport.
- A system is available to maintain traceability of all released products in order to facilitate recall, if necessary, of any product suspected of not conforming to standards, and there is also a system to handle complaints.
- A system is available that addresses process and quality improvement functions and activities.

3.2.2 *Quality control*

Quality control is that part of GMP which is concerned with specifications, sampling and testing. Quality control is also concerned with the organization, documentation and release procedures which ensure that the necessary and relevant tests are carried out and that neither materials are released for use nor products released for supply until their quality has been judged to be satisfactory (*7*). For quality control programmes in blood establishments, refer to sections 9.5 and 9.6.

3.3 Product quality review

Regular periodic or rolling quality reviews should be conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications in order to highlight trends and to identify improvements in both product and process.

A product quality review may also be considered as an instrument for surveying the overall quality status of a blood component and its manufacturing processes, including the collection of starting materials. Such a review should normally be conducted annually and should be documented. In accordance with international and/or NRA requirements and recommendations it may include:

— review of starting materials;
— review of critical in-process controls;
— review of results of quality control and quality monitoring;
— review of all changes;
— review of the qualification status of equipment;
— review of technical agreements and contracts;
— review of all significant deviations, errors and non-conformances, and the corrective actions implemented;
— review of the findings of internal audits and other inspections, and the corrective actions implemented;
— review of complaints and recalls;
— review of donor acceptance criteria;
— review of donor deferrals;
— review of look-back cases.

3.4 Quality risk management

Blood establishments should ensure that blood components manufactured in their facilities are of the quality required for their intended use, comply with quality standard requirements, and do not place recipients at risk due to inadequate safety, quality or efficacy throughout the life-cycle of the product. In order to reliably achieve the quality objective, there should

be a comprehensively designed and correctly implemented system of quality assurance that incorporates GMP, quality control and quality risk management (QRM).

An effective QRM approach can ensure the quality of a product by providing proactive means to identify and control potential quality issues. It can also facilitate and improve the decision-making process in cases when quality problems or deviations from standard processes and specifications have to be assessed or planned changes need to be evaluated.

The two primary principles of QRM are:

- The evaluation of the risk to quality and safety should be based on scientific knowledge and ultimately linked to the protection of the donor and/or recipient.
- The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk.

Examples of the QRM processes and applications can be found in guidelines on QRM, such as the Q9 guideline of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (*8*). This describes processes and offers a selection of methods and tools for applying the QRM principles.

3.5 Change control

A formal change control system should be in place to plan, evaluate and document all changes that may affect the quality, traceability and availability of blood or blood components or that might have an impact on the safety of blood, blood components, donors or recipients. The change control system should guarantee a formal approval of a change before it is implemented. Furthermore it should ensure that the impact of the proposed change is assessed and that all necessary measures — such as qualification and validation, training of personnel, adoption of working instructions, revision of contracts, definition of maintenance tasks, information for third parties and authorities — are defined and completed at the time the change is put into force. The need for additional testing and validation should be determined on a scientific basis. A risk analysis may be appropriate as part of the QRM.

After the implementation of a change, a post-implementation evaluation should be carried out in order to determine whether the introduction of the change has been successful and effective.

The introduction of new equipment, processes and methods should be treated as a change.

3.6 Deviation evaluation and reporting

Any deviation from standard operating procedures, validated processes, or non-conformances with specifications or other quality-related requirements should be recorded and investigated. The potential impact on the quality of the product in question, or on other products, should be evaluated.

The evaluation of the cause of the deviation and of related processes that may also be implicated in the deviation should be documented. Review and approval of the investigation as completed should be documented by the quality assurance and/or quality control department as appropriate.

All deviations and non-conformances should be logged in a system that allows for appropriate data review. A data review should be carried out periodically in a manner that allows for tracking and trending of data and that facilitates process improvement.

The handling of deviations and non-conformances should be defined in writing. Actions should be taken within a reasonable time frame in order to avoid any impact on other products manufactured within the same establishment.

Under certain circumstances a product may be accepted after evaluation of a deviation. The documentation should include the justification or rationale for accepting a product manufactured in deviation from a specified requirement, and should be signed by the responsible person.

3.7 Corrective and preventive actions

A corrective and preventive action system should be established, implemented and maintained to ensure that there is continuous improvement at the blood establishment. The procedures should include the management of deviations and non-conformances, complaints, events and findings of the quality system management review, inspections and audits, and should ensure the proper recording of all corrective and preventive actions taken.

The corrective and preventive action system should ensure that each quality problem is addressed and corrected and that recurrence of the problem is prevented. Actions should be carried out within a reasonable predefined time frame. The management of the blood establishment should be involved in the review of corrective and preventive actions.

The blood establishment should have methods and procedures in place to collect, document and evaluate data on quality. Product or quality problems should be entered into the corrective and preventive action system. Quality data include all errors, deviations, non-conformances, accidents, near-miss events and complaints. Quality data also include the results of quality control tests

and monitoring activities. Quality data should be reviewed at defined intervals in order to identify product and quality problems that may require corrective action and to identify unfavourable trends that may require preventive action.

3.8 Internal audits

In order to monitor implementation and compliance with the quality management system, regular internal audits should be performed according to an established procedure. Internal audits should be conducted by trained, independent and competent persons under the responsibility of the organization's quality assurance unit.

Internal audits should be arranged according to a schedule and should cover all parts of the operations, including data processing systems. Each audit should be carried out according to an approved audit plan that assesses compliance with internal requirements and applicable national and/or international regulations.

All audit results should be documented and reported to the management. Appropriate corrective and preventive actions should be taken in a timely and effective manner and should be assessed for effectiveness after implementation.

The quality assurance department, where the internal audit function resides, should not audit itself but should be subject to an independent audit.

Internal audits are not a substitute for official inspections performed by the competent national authorities who check compliance with national regulations.

3.9 Complaints and product recall

3.9.1 *Complaints*

There should be a system in place to ensure that all complaints are handled according to written — and approved — standard operating procedures. The review of the complaint should take account of whether the complaint relates to a quality defect in a blood component. The blood establishment should determine whether a recall should be initiated. The process should be defined in a standard operating procedure. Complaints, adverse events or reactions, as well as any information concerning potentially defective products, should be carefully reviewed and thoroughly investigated in order to find the root cause of the problem. Consideration should be given to determining whether other products are also affected. All investigations and actions should be carried out in a timely manner to ensure that the safety of the recipient is not compromised and that other products manufactured within the same establishment are not affected.

Immediate corrective actions should be taken to address the root cause of the problem, and actions should be taken to prevent it from recurring. There should be active follow-up of the implementation of corrective actions (see section 3.7).

Designated personnel should be responsible for managing complaints and coordinating investigations, actions and measures to be taken within a defined time frame. The unit responsible for quality should be included in this process.

All complaints, with the original details, should be recorded. Records should be retained of all the decisions, investigations and measures taken as a result of a complaint. Complaint records should be reviewed regularly in order to check for unfavourable trends or recurring problems and to ensure continuous quality improvement.

Depending on the national requirements the NRA should be informed.

3.9.2 *Recalls*

An effective written recall procedure should be in place, including a description of the responsibilities and actions to be taken. A recall should always be initiated whenever it is discovered that a product does not meet the release criteria of the blood establishment and NRA. This may happen when information is obtained subsequent to the release of a product and, had this information been known in advance, it would have prevented the blood component from being released. A recall may also be indicated when it is discovered that personnel did not follow standard operating procedures. Corrective actions should take place within predefined time periods and should include the traceability of all relevant components and, where applicable, look-back procedures (see section 3.11).

A qualified person within the blood establishment should be nominated to assess the need for product recall and to initiate, coordinate and document the necessary actions.

Recall operations should be initiated promptly and at any time. Therefore the standard operating procedures should include emergency and "out of hours" contact details. Depending on the national requirements the NRA should be informed.

Recalled products should be destroyed. If recalled products are not destroyed, they should be clearly identified and stored separately in a secure area.

3.10 Process improvement

Ideas for potential improvements to any of the systems may come from research, development, brainstorming, or from the management of non-

conformances, events and complaints, from internal or external audit or inspection findings, and from deviations detected during quality monitoring activities.

The process should track corrective or preventive actions that are developed and implemented. An effectiveness check should be in place to determine the impact or effectiveness of any changes. These activities should be documented and reported at least annually to the executive management (in the quality management review report).

3.11 Look-back

A written system should be in place for carrying out a look-back procedure. This process should be able to trace the products collected from a donor to the final recipients and from the recipient back to the donor, preferably by means of a computer database.

This standard operating procedure should be followed when it is determined retrospectively that a blood or plasma donation should have been excluded from processing — for instance, because the unit was collected from a donor who was subsequently rejected for reactive viral marker, high-risk behaviour, exposure to CJD/vCJD or other risks related to infectious diseases (*donor look-back*) (*3*).

If a donor is confirmed to have a disease that is transmissible by blood products or has high-risk behaviour, the donor should be permanently excluded from further donation. All donations from such a donor should be traced and prevented from being used or further manufactured unless they have expired and therefore have already been destroyed. If donations have been used or further processed, procedures should be in place to define appropriate actions. Donor notification and counselling is recommended for purposes of donor health and for the safety of the blood supply.

There should be a process in place for investigating a report of a suspected transfusion-associated reaction in a recipient, in order to identify a potentially implicated donor (*recipient look-back*). The donor of products implicated in transmitting disease or causing recipient harm should be excluded from further donations. All other donations from the implicated donor should be traced and blood components removed from the inventory and recalled, if within the expiry date.

All post-donation information should be recorded and maintained. There should be a system in place to react accordingly and in time to remove unexpired products from distribution in order to assure the safety of recipients.

The recipients of any products identified in the look-back process should be counselled about the risk of having contracted a disease from the potentially contaminated products and should be offered disease marker testing, consultation and medical treatment if indicated. For plasma used for fractionation, the manufacturer of the medicinal product should be notified in case of a look-back (*3*).

4. Personnel

Sufficient personnel should be available and should be qualified to perform their tasks. They should have the appropriate qualifications and experience and should be given initial and continuous training in order to assure the quality and safety of blood and blood components.

Only persons who are competent in the manufacturing process and have read and understood all relevant standard operating procedures should be involved in the manufacturing and distribution processes, including collection, quality control and quality assurance.

4.1 Organization and responsibilities

Tasks and responsibilities should be clearly documented and understood. Personnel should have clear, current and written job descriptions. There should be an organizational chart showing the hierarchical structure of the blood establishment with clear delineation of lines of responsibility and reporting.

Key personnel include the following functions and their substitutes:

— a "responsible person" (see functions and qualifications below);
— a processing or operations manager, responsible for all processing and operations activities;
— a quality control manager, responsible for all quality control activities;
— a quality assurance manager, reporting findings or quality issues directly to the responsible person and empowered to discontinue operations if quality and safety expectations are not being fulfilled;
— a physician with the responsibility to ensure the safety of donors and the safety of the distributed blood components.

The blood establishment should nominate a "responsible person" who will be responsible for:

— ensuring that approved donor selection criteria are followed;
— ensuring that every unit of blood or blood components has been collected, tested, processed, stored and distributed in compliance with the national regulations in force;
— providing information to the competent national authority;

— ensuring that the required initial and ongoing training of personnel is carried out;
— ensuring that a quality management system and a haemovigilance system (ensuring traceability as well as notification of serious adverse events and reactions) is in place in the blood establishment.

The responsible person should fulfil the qualification requirements according to the national regulations, or should fulfil the following minimum conditions of qualification:

- He/she should hold a diploma, certificate or other evidence of formal qualification in the field of medical or biological sciences awarded on completion of a university course of study or a course recognized as equivalent.
- He/she should have practical experience in relevant areas, preferably for at least two years, in one or more establishments which are authorized to undertake activities related to collection, testing, preparation, storage and distribution of blood and blood components.

Depending on the national legislation, the name of the responsible person may need to be communicated to the NRA.

The quality assurance manager and the processing or operations manager should be different persons, functioning independently. The quality assurance manager is responsible for ensuring that there are appropriate quality systems and protocols in place for the safe and secure release of all materials, equipment, reagents and blood and blood components.

The processing or operations manager is responsible for ensuring that there are appropriate manufacturing and technical processes and procedures in place for the production of blood or blood components.

The physician should hold a relevant medical degree awarded on completion of a university course of study and should hold any registration or licensure that is required by the national authority.

Responsibilities should be delegated only to individuals who have been trained for the task. Delegation should be in written form and should be reviewed regularly.

4.2 Training

Personnel should receive initial and continuous training that is appropriate to their specific tasks. This training should be carried out by qualified personnel or trainers and should follow prearranged written programmes. Approved training programmes should be in place and should also include:

— relevant principles of transfusion medicine;
— GMP;
— relevant knowledge in microbiology and hygiene.

Training should be documented and training records should be retained.

4.2.1 *Initial training*

Programmes for the initial training of newly recruited personnel or personnel taking over new functions should take into account all relevant tasks and procedures, including general topics such as quality assurance, GMP and computerized systems. The same topics and principles apply to training aimed to reintroduce personnel after a longer absence from the workplace. The time frames should be defined.

The training records should identify at least the trainer, all the specified tasks (including the relevant standard operating procedures) and when the training was completed. The records should be signed by both the trainee and the trainer. Upon completing the training, the personnel should be competent in the tasks in which they have been trained. If a database is used the personnel training profile should be updated annually.

4.2.2 *Continuous training*

Continuous training programmes (theoretical and/or practical training) should be in place to ensure that personnel keep up the skills to carry out their assigned tasks. Such training programmes should take technical and scientific developments into account. Training should also include any changes to standard operating procedures and personnel requirements. Both internal and external training courses may be useful here.

4.2.3 *Competency*

The overall competency of personnel is a result of education, experience and training. As a key factor for the quality and safety of blood and blood products, competency has to be carefully evaluated and continuously monitored.

Upon completion of the initial training, the competency of the personnel should be evaluated and documented. After the initial competency is determined, there should be periodic assessment of competency. The contents of training programmes and their effectiveness should be periodically reviewed and assessed.

4.3 Personal hygiene

All personnel, prior to being hired and during employment, as appropriate, should undergo health examinations. Any person shown at any time to

have an illness or open lesions that may adversely affect the quality of the products and/or the safety of the donors should be excluded from the establishment's manufacturing processes until that person's condition is no longer judged to be a risk.

All personnel should be trained in personal hygiene. In particular, personnel should be instructed to wash and disinfect their hands before, during and after activities such as blood collection and production.

Special attention should be drawn to the need to protect donors, employees and products from contamination — especially with blood and any other material of human origin.

To ensure protection of products, donors and employees from contamination, personnel should wear clean protective clothing appropriate for the duties they perform. Soiled protective clothing, if reusable, should be stored in a separate closed container until properly laundered and, if necessary, disinfected or sterilized. Where appropriate, disposable or sterile gloves should be worn when handling items that may come in contact with any blood or blood components.

Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material and personal medicines should not be permitted in areas used for production, testing, storage or distribution, or in other areas where they might adversely affect product quality. Personal hygiene procedures, including the use of appropriate protective clothing and equipment, should apply to all persons entering production areas.

5. Documentation

The documentation of procedures and records is essential to the quality assurance system. It ensures that work is performed in a standardized and uniform manner and ensures the traceability of all steps. Written instructions should include all applicable methods and procedures and should be accessible to all authorized personnel.

5.1 Standard operating procedures and records

5.1.1 *Standard operating procedures*

All critical procedures — such as purchase and receipt of starting materials, selection of donors, collection of blood, preparation of blood components, laboratory testing and associated quality control testing, product labelling, storage, release, dispatch, shipping, and recall of final products — should be specified in appropriate written instructions in accordance with the principles of GMP and relevant national regulations. Quality assurance

procedures such as complaint investigations, deviation management, recall of non-conforming products, change control and document control should also be specified in written instructions.

All activities should be carried out according to the standard operating procedures. The standard operating procedures and the processes should be regularly reviewed and updated as necessary in order to improve the quality of products and services delivered. The document review process should itself be documented.

5.1.2 *Records*

Each activity that may affect the quality of blood and blood components should be documented and recorded at the time it takes place. Critical activities should be double-checked, either by a second person or electronically. There should be documentation to ensure that work is performed in a standardized manner according to standard operating procedures and that all critical steps in the process are traceable — especially those that have the potential to affect the quality of the product. The documentation should allow all steps and all data to be confirmed by independent review. All documentation should indicate the person performing the action, the date of the action and the equipment used in the action, where applicable.

Records should be legible, accurate, reliable and a true representation of the results and entries. The legibility of records is of great importance. Handwritten entry of data should be clear. Corrections to any records should be made in a manner that permits the reading and review of the previous entry, the correction, the date of correction and the person responsible for the correction.

Critical manufacturing and laboratory testing records should be reviewed frequently for completeness, legibility and, when appropriate, accuracy by the manager or other designated person.

5.2 Document control

All documents should be laid out in an orderly manner with a unique title and reference number, and should indicate the version and the effective date. The content of the document should be clear and should not include superfluous information. Title, nature, purpose and scope should be clearly outlined. Documents should be reviewed, approved, signed and dated by authorized persons. An audit trail should indicate the person responsible for each step of document control.

5.2.1 *Document management*

A document management system should be in place. Documents that outline specific manufacturing steps or other critical steps should be readily

available to the personnel performing these tasks. A document control standard operating procedure should be established for the development, review, approval, distribution, implementation, revision and archival of documents. When a document has been revised, the document management system should function in such a way as to prevent the inadvertent use of documents that have been superseded.

There should be a record of the distribution of each document which also shows at least the work areas or tasks affected by the document. All changes to documents should be acted upon promptly and should be reviewed, dated and signed by a person authorized to do so. Standard operating procedures should be designed, developed and approved, and personnel trained in a consistent manner, prior to implementation.

5.2.2 *Record retention and archiving*

All records, including raw data, which are critical to the safety and quality of blood or blood components, should be kept in a secured storage area according to national regulations, or preferably for at least 10 years. A longer period for retention of records may be required by NRAs, international requirements or by specific contractual agreements. Records of permanently deferred donors should be kept indefinitely.

Outdated standard operating procedures should also be kept in a historic file system. Documents should be archived in a secured area and should be readily accessible for retrieval by authorized personnel if required. The archival and retrieval process, especially if computerized systems are used, should be validated to ensure that all information can be retrieved and read at any time until the end of the required period of retention.

6. Premises and equipment

6.1 Premises

6.1.1 *Design and construction*

Premises should be located, constructed, adapted and maintained to suit the operations that are to be carried out in them. Premises should be designed to permit effective cleaning and maintenance to minimize risk of contamination. The workflow should be designed and arranged to allow for a logical flow of staff, donors and products in order to minimize the risk of errors. Working areas should not be used as passageways or storage areas.

Ancillary areas should be separated from the donor evaluation area, and from the screening, collection and manufacturing areas. Washing and toilet facilities and, if required, facilities for changing or eating should be maintained in a hygienic and tidy condition.

Production, testing and storage areas should be secured against entry by unauthorized persons.

Lighting, temperature, humidity and ventilation should be appropriate and should not adversely affect production or storage. Premises should be designed and equipped so as to afford maximum protection against the entry of animals, including insects.

Premises should be carefully maintained and cleaned (see sections 6.2.2 and 6.2.3) and where appropriate disinfected according to detailed written standard operating procedures. Cleaning records should be retained.

6.1.2 *Donor areas*

The area for blood donors should be separated from all production and testing areas.

The design of premises should be adequate for the conduct of operations and should allow for the logical flow of donors, in one direction if possible, so that donors who have passed reception, screening and donation do not have to return to a previous area.

The area for donor selection should permit confidential personal interviews to take place with due consideration for the safety of donors and personnel.

Rest and refreshment rooms for donors should be separated from donation or storage areas.

6.1.3 *Production areas*

Blood processing should be carried out in adequate facilities that are suitable for the purpose. The donor area, and production and testing areas should be separated from each other.

Whenever possible, closed systems should be used. Using a validated sterile connecting device creates a functionally closed system.

When the use of a closed system is not possible or not appropriate, the risk of contamination or cross-contamination needs to be minimized. Therefore, the premises used for the processing of blood components in an open process should be designed and qualified as a grade A environment with a grade B background, as defined in the WHO GMP for sterile pharmaceutical products (*12*). A less stringent environment may be acceptable if the preparation of the product is directly combined with additional safety measures — such as immediate transfusion within a defined and limited time period after processing, or placing the product immediately into storage conditions that prohibit microbial growth. Personnel performing open processing should wear appropriate clothing (i.e. suitable coats, masks or gloves) and should

receive regular training in aseptic manipulations. Aseptic processing should be validated. Environmental monitoring protocols should be applied and evaluated by the quality assurance unit.

The premises used for processing blood components should be kept in a clean and hygienic condition. Monitoring of the microbiological contamination load should be considered for critical equipment surfaces and environments where appropriate, according to a risk-based assessment of the process. Records should be available.

Each area of processing and storage should be secured against entry by unauthorized persons and should be used only for the intended purpose.

6.1.4 *Storage areas*

Storage areas should provide adequate space and should be arranged in a way that allows for dry and orderly placement of stored materials.

Storage conditions should be controlled, monitored and documented to show compliance with the specifications. Equal distribution of temperature throughout the storage facility should be guaranteed and documented. This is particularly important for the critical materials used in processing blood and blood components. Temperature checks should be carried out and recorded at least daily. Appropriate alarms at upper and lower temperature limits should be present and should be regularly checked; the checks should be recorded. Appropriate actions to be taken when there is an alarm should be defined in writing.

Intermediate storage and transport should be carried out under defined conditions to ensure that specifications are met.

Storage areas should provide effective segregation of quarantined and released materials or components. There should be a separate area for rejected components and materials.

6.1.5 *Laboratories*

Testing laboratories should be designed and constructed so as to minimize the risk of errors and contamination. Laboratory areas should be separated from the processing and final product storage areas. Where nucleic acid amplification testing (NAT) technology warrants, separate premises (rooms) and air handling systems should be considered for performing NAT. Consideration should be given to constructing a separate room for specimen sampling and another room for amplification and nucleic acid detection in order to minimize the risk of contamination or false-positive test results.

6.1.6 *Mobile collection sites*

Premises for mobile collection sites should be adequate in design for the conduct of operations and should allow for the logical flow of staff, donors and products in order to minimize the risk of errors. The blood collection at mobile sites should be planned thoroughly. Ancillary areas (rest and refreshment rooms) should be separated from donation or storage areas, but observation of donors during post-donation refreshment should still be ensured.

Before premises are accepted for mobile donor sessions their suitability should be assessed against the following criteria:

— sufficient size to allow proper operation and ensure donor privacy;
— safety for staff and donors;
— ventilation, electrical supply, lighting, hand-washing facilities, reliable communication, sufficient space for blood storage and transport, and suitable temperature conditions.

Each site should have an approved plan that details the site layout. The set-up of the mobile collection site should be carried out according to the approved plan.

6.2 Equipment

6.2.1 *Design and construction*

All equipment should be designed and installed to suit its intended purpose and should not present any hazard to donors, personnel or blood components. It should allow for effective cleaning, and disinfection is recommended for all surfaces in direct contact with the bag system.

Equipment should be located in a suitable position (e.g. a balance should be positioned on a suitable even surface) where there is no negative impact from the surrounding environment (e.g. direct sunlight may have an impact on optical instruments such as apheresis systems or balances).

6.2.2 *Maintenance*

Maintenance, cleaning and calibration should be performed regularly and should be recorded. Maintenance of equipment should be carried out at intervals according to a documented schedule.

The maintenance programmes should be established on the basis of qualification activities. The intervals should be defined according to the instructions of the manufacturer of the equipment. Where intervals are not defined by the equipment manufacturer, maintenance should be carried out at least annually. Different intervals may be defined on the basis of a risk

assessment. If no regular maintenance activities are recommended by the manufacturer, at least a functional control should be performed according to documented procedures. All maintenance activities should be documented. The maintenance reports of external technical services should be checked and countersigned by the staff of the blood establishment in order to decide if action needs to be taken as a result of the maintenance outcome. The maintenance documents should include sufficient information to determine what types of checks have been performed.

Maintenance should also be carried out on equipment that is not in regular use, including back-up systems.

Instructions for use, maintenance, service, cleaning and sanitization should be available in a language that is understood by the user. There should be written procedures for each type of equipment, detailing the actions to be taken when malfunctions or failures occur. Defective equipment, or equipment that is not in service, should be clearly labelled and if possible removed from the working area.

The maintenance of sterile connecting devices should include a check of the tensile strength. Furthermore, as it is a very critical piece of equipment, there should be regular functional checks of the integrity of the tubing weld.

In general, functional tests should also be considered for other pieces of equipment — such as for balances before use after they have been moved or transported to a mobile site.

A regular maintenance programme, including appropriate intervals, should be in place for all critical laboratory equipment or systems. A procedure should be implemented for releasing equipment after maintenance or intervention.

If the maintenance is contracted out (e.g. to the supplier) the work should be documented. Equipment should be evaluated to determine if it is still capable of expected performance prior to returning it to service for manufacturing blood components.

6.2.3 *Cleaning*

Cleaning procedures should be established and described in a standard operating procedure. Cleaning of equipment should take into consideration the instructions of the manufacturer. A schedule for regular cleaning and disinfection, if necessary, is recommended for all surfaces with direct contact with the bag system (e.g. centrifuge, separator, storage shelves).

Disinfectant solutions with sufficient and approved antimicrobial activity should be used. A cleaning plan should be established that specifies the cleaning intervals and methods to be used for the different equipment and

premises. The cleaning procedures should not impact negatively on the equipment or blood components. Cleaning activities should be documented.

6.2.4 *Calibration*

Measuring instruments and measuring systems used for the collection and further separation of blood and for quality control testing should be calibrated regularly according to the instructions of the manufacturer. Calibration should be carried out and documented according to established standard operating procedures and national regulations. Regular calibration is necessary for temperature probes (e.g. in refrigerators), pipettes, balances, timing devices and haemoglobinometer devices (using control blood and/or cuvettes from the manufacturer). The devices used for calibration, such as the control weight used for the calibration of balances, should be certified for accuracy (by testing against a known standard). If the calibration consists of using a comparison measurement approach with a second device, then the maximum allowed deviation between the two measurements should be defined.

6.3 Computerized systems

A computerized system may be described as a functional unit consisting of one or more computers and associated peripheral input and output devices, and associated software that uses common storage for all or part of a programme and for all parts of the data necessary for the execution of the programme (*9*). A computerized system executes user-written or user-designated programmes, performs user-designated data manipulation (including arithmetic operations and logic operations), and it can execute programmes that modify themselves during their execution. A computer system may be a stand-alone unit or may consist of several interconnected units.

Hardware and software should be protected against unauthorized use or changes.

Critical computerized systems should be validated before use. The system is considered critical if:

— it is directly linked to the decision-making process for blood product manufacturing, blood or blood product testing (donor/recipient), labelling and release;
— it is used to handle or manipulate the related information;
— it has an impact on product quality, information management, storage, or tools for operational decision-making and control.

Periodic revalidation or annual checks to ensure reliability should be performed on the basis of a risk assessment.

There should be procedures for each type of software and hardware, detailing the action to be taken when malfunctions or failures occur. A back-up procedure should be in place to prevent loss of records in case of expected or unexpected downtime or function failures. The archival and retrieval process should be validated to ensure the accuracy of the stored and retrieved data.

Once in routine operation, critical computer systems should be maintained in a validated state. Any change should be handled through the formal change control system which includes qualification and/or validation activities. Applicable documentation should be revised and personnel should be trained before the change is introduced into routine use. Any software updates should be evaluated in advance and there should be procedures to validate or verify the acceptability of the update installation.

The manual entry of critical data, such as laboratory test results, should require independent verification and release by a second person. When a computerized system is used, an audit trail should be guaranteed.

7. Qualification and validation

7.1 Qualification of equipment

All equipment should be qualified and used in accordance with validated procedures.

New and repaired equipment should meet qualification requirements when installed and should be authorized before use. Qualification results should be documented.

The extent of qualification depends on the critical nature and complexity of the equipment. For some equipment, installation qualification and calibration may be sufficient. More complex equipment may need a more thorough approach to qualification and validation and should include the instruments, the associated operation(s) and the software involved.

Further guidance on qualification and validation is given in the WHO guidelines on validation (*10*) and in the Pharmaceutical Inspection Co-operation Scheme (PIC/S) *Recommendations on validation master plan, installation and operational qualification, non-sterile process validation, cleaning validation* (*11*).

7.2 Validation of manufacturing processes

All critical processes in the manufacture of blood and blood components should be validated before implementation according to a predefined protocol of tests and acceptance criteria. Critical processes include donor

selection and determination of suitability, component preparations, donor testing for infectious diseases (see also section 7.3), ABO blood typing and antibody screening where applicable (e.g. for red-cell concentrates), labelling, storage and distribution.

Validation studies, including statistically based sampling where feasible, should be conducted to ensure that products are produced with consistent quality characteristics. Acceptance criteria should be based on a defined set of specifications for each blood component, including a set of quality control tests — such as measurement of weight respective to volume, residual blood cells (depending on product specifications), haemoglobin, and relevant coagulation factors (e.g. Factor VIII) and/or total protein/IgG content where applicable — established by the blood establishment or the NRA (see also sections 9.4.3 and 9.6). Data should be available to ensure that the final product is able to meet specifications.

Likewise, apheresis systems, including software, should be qualified and maintained. Apheresis procedures should be validated. Validation criteria with regard to the quality of blood components may, depending on the product, include weight, yield, content of residual white blood cells, haemoglobin and relevant coagulation factors. Validation studies of new apheresis procedures should also evaluate possible risks of activation of the coagulation, fibrinolysis, and complement systems potentially induced by the material in contact with blood. Such studies are usually performed by the manufacturer of the apheresis systems to support the licensing by the regulatory authorities.

7.3 Choosing an appropriate test system to screen for infectious disease

The quality of the screening of blood donations for markers of infection depends on a number of conditions being fulfilled:

- Only test systems designed and validated for blood donor screening should be used. Other systems, such as tests validated for diagnostic purposes only, should not be used.
- All test systems should be validated by the manufacturer.
- Before implementing a test system for routine analysis, the laboratory should prove by validation that the manufacturer's specifications are met (in principle this also applies if in-house tests are used).
- The laboratory should show that, on routine application of test systems, specified performance is reached and is consistently maintained.

Screening of blood donations generally requires such test systems to aim for high sensitivity even though this may be achieved at the expense of specificity. Although this may result in an increased proportion of false-

positive results, it is important in ensuring that all components with true-positive test results are detected and not released. In case of new assays or techniques, precise specifications must be established by testing samples of appropriate populations (e.g. donors, recipients, seroconverted recipients) and by comparing the results generated by the existing test system and by the new one.

Validation of a test system involves four main elements:

— assay reagents which should include quality control material (e.g. positive quality control sample, negative quality control sample, calibrators);
— equipment;
— software, if applicable;
— procedure and handling (test method).

Validation records should not only present proof that the scope and desired specifications are met, but should also provide precise descriptions of all key material, key equipment and conditions of processing (e.g. temperature and time of incubation, rounds per minute in centrifugation). In addition, instructions for handling and processing, by which assay specifications are met, should be put in writing and should be provided with the test system.

Test system specifications that need to be established and/or met by the manufacturer are:

— specificity;
— sensitivity;
— accuracy (degree of closeness of measurements to the true value);
— repeatability (replicates of series);
— reproducibility (replicates of series, variation by operator, by day or by lot of reagents);
— known interferences (e.g. haemolytic sera, lipemic sera);
— lower and upper limits of detection (serial dilution).

Apart from testing appropriate donor/recipient populations, appropriate reference materials should be used to define the performance specifications of a test system. These reference materials should be traceable to the WHO international standard or reference reagents, when available for a specific marker.

The necessary documentation should be available for each test system and should include at least the following information:

— a description of the test system (reagents, controls, devices etc.), equipment and diluents (if applicable);
— safety instructions;

— a description of the assay principle;
— specifications;
— a description of the sampling procedure, sampling plan, sample handling and test procedure;
— internal quality controls (positive and negative), run with every series of donor samples;
— recommended calibration material and calibration frequency (e.g. change of reagent lot);
— primary reading of measurement (format e.g. optical density);
— interpretation of the measurement and/or conversion to result;
— acceptance criteria, cut-off, reference values, limits, pro-zone, grey zone.

Where feasible, the test system should be approved for blood screening by the NRA.

7.4 Assay performance validation

In addition to the validation of the test system by the manufacturer, an on-site validation of the test system in the laboratory is required prior to its use in routine testing. This validation should demonstrate, that:

— the performance specifications of the system established by the kit manufacturer are met by the laboratory;
— laboratory personnel are thoroughly instructed, trained and competent to operate the test system.

Prior to first-time use, critical equipment, including related computer systems, should be thoroughly qualified. Installation qualification, operational qualification and performance qualification should be carried out and fully documented. This work may involve suppliers and/or third parties. It is strongly recommended that any performance qualification should be performed by the end-user (and not by a third party) since this is intended to demonstrate that the process works as designed.

In addition, a demonstration showing that the test system performance specifications are constantly met in routine donor testing is required. The means by which this may be achieved are:

— inclusion of internal and external quality control materials with every test series;
— previously tested samples collected for use as an internal panel for periodical in-process quality control;
— monitoring measurements of controls (for instance, graphically by using a Levi-Jennings diagram);
— statistically establishing the standard deviation of control measurements;

— implementation of deviation rules (warning range, control range, Westgard rules) to govern corrective actions;
— monitoring trends in control measurements on external standard or reference material;
— successful participation in external quality assessment schemes (proficiency testing) by all qualified members of staff.

8. Management of materials and reagents

8.1 Materials and reagents

Only reagents and materials from approved suppliers that meet documented requirements and specifications should be used. Materials and reagents should meet the legal requirements for medical devices. The management procedures for materials, reagents and supplies should define the specifications for acceptance of any elements that may influence the quality of the final blood component. Receipt logs or records for these critical materials should indicate their acceptability on the basis of the defined specifications and should identify the person accepting them.

8.2 Receipt and quarantine

Appropriate checks (e.g. attached certificates, expiry date, lot number, defects) should be performed on received goods in order to confirm that they correspond to the order and meet the specifications. Damaged containers should be carefully checked to detect possibly affected materials. Incoming critical materials (such as sterile solutions, blood bag systems and testing reagents) should be physically or administratively quarantined immediately after receipt and until they are released for use. Where the quarantine status is ensured by storage in separate areas, these areas should be clearly marked and their access restricted to authorized personnel. When labels are applied to the containers to indicate their status, the use of different colours may be helpful. Any system replacing physical quarantine (e.g. a computerized system) should provide equivalent security.

8.3 Release of incoming production material and test reagents

Critical material should be received under quarantine and then evaluated for acceptability. After acceptability has been determined, the materials should be released by an authorized person for use in manufacture. The actual release may be performed by an authorized person or under the guidance of a validated computer system. The minimum criteria for the release should be the availability — and check of — certificates or other acceptability records generated by the manufacturer and containing sufficient information to determine product acceptance.

Similarly, each new lot of testing kits should be evaluated by the laboratory to check compliance with predetermined performance standards before release for routine analysis.

The manufacturers of sterile materials (e.g. blood bag systems, anticoagulant solutions) should provide a certificate of release for each batch. The blood establishment should define acceptance criteria for such certificates in writing, and should include at least the name of the material, the manufacturer, compliance with the relevant requirements (e.g. pharmacopoeia or medical device regulations) and confirmation that the materials are sterile and pyrogen-free.

8.4 Storage

Materials and reagents should be stored under the conditions established by the manufacturer and in an orderly manner that permits segregation by batch or lot and stock rotation. Storage and use should follow the "first-expiring first-out" principle (i.e. the material that entered storage first should be used first). The use of the expiry date as an alternative inventory management technique is also acceptable.

Where special storage temperature conditions are required, these should be provided, checked and regularly monitored.

8.5 Traceability of materials and reagents

Inventory records should be kept for traceability. The records should document which batch or lot of materials or reagents have been used for the collection, processing or testing of the blood units or blood components. Inventory of critical supplies such as donation labels with serial numbers should be strictly controlled to avoid mix-ups or mislabelling due to uncontrolled excess labels.

8.6 Supplier/vendor management

All materials and reagents relevant for the quality of the products should be purchased or obtained only from qualified suppliers. The relationship between the two parties (i.e. contract giver and contract acceptor) should be defined in a contract. The blood establishment as contract giver is responsible for assessing the competence of the supplier (contract acceptor).

The contracting process should include:

— a qualification review prior to awarding the contract to ensure that the supplier meets the organizational needs and complies with GMP requirements;

— the setting of appropriate specifications that adequately define the quality of the service or goods;
— appropriate checks on received goods to confirm that they meet specifications;
— checks to ensure that goods in use continue to meet specifications;
— notification of changes to requirements from either party prior to implementing any changes that may affect the quality of the services or goods provided;
— regular contact with suppliers in order to help understand and resolve problems.

9. Manufacturing

9.1 Donor registration

Upon presentation at the blood establishment, donors should positively identify themselves by stating their full name, address and date of birth. Each donor should also provide proof of a permanent place of residence, including a telephone number where appropriate, so that they can be contacted after donation, if necessary.

Proof of identity with a photograph — such as an identity card, passport or driver's licence — should be provided, especially in the case of first-time donors. A careful check of the identity of the donor should be repeated prior to each step that is relevant to the quality of the products and the safety of donors, but at least before donor selection and venipuncture.

If electronic databases are used to maintain donor information, double checks or another validated method to confirm accuracy of information entered manually should be implemented.

9.2 Donor selection

Blood and blood components should be obtained from healthy donors who are carefully selected using a systematic and validated process consisting of review of the donor's health assessment, social behaviour history (the donor questionnaire) and medical examination. This evaluation, along with a review of the results of the infectious disease screening laboratory test, should be used to make sure, prior to the release of any blood component, that the donor presents no increased risk for transmission of infectious agents. NRAs are pivotal in establishing a harmonized framework for donor selection criteria, taking into consideration the types of products, the relevant infectious risks, and the epidemiological data for disease prevalence in the country. The review of these combined data may be used in developing donor selection criteria. The NRA should also be part of

any decision-making process intended to modify the donor selection and donation-testing procedures.

Regulatory agencies and professional organizations have respectively published regulations and recommendations on the criteria for the selection of donors of whole blood and blood components (see, for instance, the Council of Europe's *Guide to the preparation, use and quality assurance of blood components*) that can be used as a reference (*13*). Such guidance documents also explain critical points that should be considered when processing blood and blood components.

Whenever possible, blood donations should be collected through a donation system involving regular and repeat donors. Obtaining blood from regular and repeat donors is a major contribution to ensuring optimal historical medical information about the donors, and therefore to detecting potential risk factors.

9.2.1 *Epidemiological surveillance of the donor population*

To ensure optimal long-term safety of blood components, blood establishments should maintain continuous epidemiological surveillance of the donor population. The objective of this surveillance is to know, as precisely as possible, the prevalence and incidence, and their respective trends, of infectious markers that are relevant to the safety of blood components. This enables countermeasures to be taken in a timely manner. The system should be able to gather epidemiological data not only at national/regional levels but also among donor populations that provide blood at individual blood establishments within a country or region. Consideration should be given to the travelling patterns of the donor population with respect to possible transmission of infectious diseases (i.e. malaria, Chagas disease, vCJD, etc.).

The information from epidemiological surveillance can furthermore be used:

— to detect, among donor populations of various collection centres, differences that may be associated with objective differences in viral markers within donor populations;
— to detect differences in the donor selection and screening processes at collection centres;
— to detect trends in infectious markers which may reflect either a change in the rate of viral markers in the population or a possible deviation in the donor selection or screening process at specific collection sites;
— to assess the relevance of any preventive measures such as a strengthened donor selection process, additional deferral criteria, or implementation of additional screening tests to avoid contamination of blood components.

When donations from first-time donors are used to prepare blood components, epidemiological data on this specific donor group should be included in the estimate of the risk for infectious diseases transmitted by blood. It has been shown that first-time donors, who may occasionally include test-seeking persons, constitute a group that in some situations is more likely to have bloodborne viral markers than regular donors who have already gone through a selection/deferral process.

It is currently advisable to collect and analyse epidemiological data at the collection sites for HIV1/HIV2, hepatitis C virus (HCV) and hepatitis B virus (HBV) since they historically represent the major pathogenic risks associated with blood components. It is the responsibility of the NRA to define whether this list should be modified or should include additional criteria such as emerging infectious agents, on the basis of local or regional epidemiology. For the current three recommended markers, only confirmed positive tests (i.e. tests which are repeatedly reactive in a screening test and positive in at least one confirmatory test) should be recorded, reported and analysed.

9.2.2 *Information to donors*

Potential new donors should be informed (ideally both verbally and in writing) that it is necessary to respond to questions about their medical history and personal behaviour so that it can be determined whether they are eligible for blood donation. Written information can be a leaflet explaining infectious risks associated with blood products, and the impact of social behaviour on infectious risks or infectious risk factors. This information is usually provided by a licensed physician, or by a designated qualified person under the direct supervision of a licensed physician. The information should clearly explain the deferral criteria that exclude a donor from donating blood or plasma. It is important to ensure that the reasons for deferral are well understood by the candidate donor.

The candidate donor should be asked to sign a form of informed consent to give blood in which he/she acknowledges understanding the moral and legal responsibilities and possible risks associated with donating blood, as well as the occasional complications that may occur. The declaration of consent should also include a statement that the donor authorizes the release of his/her blood and blood components for transfusion or further manufacturing.

Donors should be informed to contact the blood establishment if there is an unexpected event after the donation, such as illness or the discovery of new information not disclosed during the health screening.

9.2.3 *Questionnaire and interview*

The interview assessment of each donor should be carried out by a qualified person who is trained in the use of donor selection criteria using a validated

written questionnaire with direct questions if necessary. In order to obtain relevant and consistent information about the donor's medical history (concerning illnesses and drug use) and general health, it is recommended that the donor should review, complete and sign a predefined questionnaire that is adapted to the type of donor (e.g. first-time donor or repeat donor). The questionnaire should cover questions about the medical history of the donor, his/her travel habits, risk behaviours, use of medication, and other medical treatment. A list of countries may be provided to assist the donor to complete the questionnaire with regard to earlier residency or travel. Similarly, a list of drugs that may pose a threat to the recipient or may be an indication of poor donor health may also be provided. The NRA may provide requirements for such lists.

The questions should be drafted in such a way that donors may easily identify whether they are in good health. The questionnaire may be administered in several ways, such as:

— by a person reading questions to the donor and recording the responses;
— by the donor reading the questions and recording the responses;
— by computerized written questions presented to the donor with the donor recording the responses;
— by the computer reading the questions to the donor and the donor recording the responses;
— by other validated methods that ensure that the donor understands the question, how to completely answer the question and how to record the response to the question.

There should be a link between the donor, the donor questionnaire and the collected products. After the donor's history has been reviewed, the collected components should be identified in a way that links the products to the history records but maintains the confidentiality of the donor. The product should be identified by a unique donation number linked to the donor name but the product information should not include the donor name except as required by the NRA in cases such as autologous donations.

After reading the donor information and/or answering the questionnaire, donors who are at risk of carrying a disease transmissible by blood should be able to exclude themselves voluntarily and confidentially. Such confidential self-exclusion should also be possible after the donation (e.g. by phone). There should be a means of documenting both the reason for self-deferral and the determination of the need for temporary or permanent deferral. These records should be retained in a similar manner to all donor screening records.

Donor identification and information, the donor selection interview and the donor assessment should all take place before each donation. The premises

and layout of the blood establishment (or the mobile collection unit) should allow for adequate confidentiality during the donor interview and selection process so as not to discourage the candidate donor from answering questions about personal or private behaviour; otherwise the safety of the blood donation could be compromised.

The minimum intervals between two donations should be defined and should then be audited or reviewed for compliance with the waiting period prior to each donation.

9.2.4 *Deferral policy and deferral criteria*

As part of the blood establishment's deferral policy, a list of permanent or temporary deferral criteria used for potential donors should be clearly defined, made public, and incorporated in the educational material for donors and the establishment's procedures. It should also be determined whether the donor has previously been deferred, and reasons for any deferral should be reviewed so that a decision may be made on whether to accept the donor for current donation. A donor who is deferred should be informed of the reason for deferral, encouraged not to donate at other facilities while deferred and informed that the reason for the deferral may be shared with other health professionals or government agencies according to NRA recommendations or other legal requirements.

Both acceptance and deferral criteria for the donation of blood should be formulated by the NRA and should be national requirements that are applied nationwide. Within the scope of their role of establishing and implementing effective national regulations, NRAs should enforce such criteria.

Examples of the major permanent deferral criteria found in international guidelines include:

— clinical or laboratory evidence of bloodborne infectious diseases such as acute or chronic infection with HIV, HCV or HBV (in certain jurisdictions donors with elevated titres of anti-HBs may be acceptable);
— past or present intravenous drug use;
— persistent bacterial or protozoal infections.

Other deferral criteria, either permanent or temporary, may include:

— a sexual relationship between men;
— men or women who are engaged in prostitution;
— subjects with haemophilia or other clotting-factor defects;
— sexual partners of any of the above or of someone the donor suspects may carry the above risk factors;
— jaundice within the 12 months prior to donation, since this may be a clinical sign of hepatitis A, B or C;

— transfusion with blood, blood components, plasma products, cellular therapy products or vascularized tissue transplant in the 12 months prior to donation, as blood transfusion and transplantations are risk factors for all bloodborne infections;
— exposure to someone else's blood, including an accidental needle stick in the 12 months prior to donation;
— tattooing, scarification, ear-piercing or acupuncture in the 12 months prior to donation (since these practices may be vehicles for transmission of viral diseases) unless clear evidence is provided that it was carried out under sterile conditions;
— risk factors for Human T-cell lymphotropic virus (HTLV) infection;
— risk factors for malaria infection (e.g. travel in countries where the prevalence is high);
— a confirmed family history of CJD;
— imprisonment longer than three days within the 12 months prior to donation.

When temporary deferral criteria are used, a specific procedure involving trained personnel should be in place for the reinstatement of donors. There are deferral criteria that are temporary (as long as a risk factor has been identified) but that can be waived after additional controls have been carried out on the donor or the period of deferral has passed. NRAs may recommend or define different deferral criteria and timelines, e.g. when implementing NAT testing for the relevant viruses.

9.2.5 *Physical examination, donor health criteria and donor acceptance*

A targeted physical examination should be carried out by a licensed physician according to an established procedure prior to the first donation and thereafter before subsequent blood donations, and in case of special apheresis programmes at regular intervals. Depending on national regulations established by the NRA, the physical examination may be performed by a suitably educated and trained physician substitute under the supervision of a licensed physician. NRAs should, usually after consultation with the blood establishment, determine the health criteria and the acceptable limits taken into account during the physical examination — such as measurement of haemoglobin, blood pressure, weight, age, pulse rate and temperature, or any other criteria considered to be of concern for the safety of blood components or donors.

A written standard operating procedure based on the relevant acceptance/deferral criteria should be in place at the blood establishment to control donor acceptance and deferral criteria, in compliance with the NRA. Abnormal donor findings should be referred to the physician who has the

responsibility of making the final decision about the donor's eligibility on the basis of current medical knowledge and national regulations. If the physician has any doubt about the donor's eligibility, the donor should be deferred.

An appropriate computerized record system (or, if that is not available, a manual system) should be in place for donor records (including their medical history and health status), and for the purpose of ensuring traceability of all donations. Such information provides historical perspective of the health status of donors, including previous temporary deferrals, and contributes to reinforcing the judgement about whether the donation would create a risk to the quality and safety of the blood components.

Records should be kept for each activity associated with the selection of the donor. The record should reflect the decision to accept the donor, taking into consideration the medical history, donor deferral history, the donation interval, the answers given in the interview or questionnaire, and the results of the physical examination. The rejection of a donor and the reason for the deferral should be recorded. An authorized interviewer should sign the donor selection records and the final assessment of the donor's suitability.

As with all other manufacturing steps under GMP, donor selection and acceptability procedures should be followed at all times using the validated methods. Any deviations from established procedures and processes may result in products not meeting specifications so such products should be considered as non-conforming products and must not be released for distribution.

9.3 Collection

9.3.1 *Whole blood collection*

Donors should confirm their identity (by a method such as stating name and date of birth) immediately prior to venipuncture. Also prior to venipuncture, a check should be made to ensure that the collection system to be used is not damaged or contaminated, and that it is appropriate for the intended collection. Any abnormal moisture or discoloration suggests a defect and in such a case the collection system should be discarded. An investigation should be conducted to evaluate the extent of the problem and appropriate corrective actions should be taken. The collection systems should be used in accordance with the instructions of the manufacturer. Appropriate hand disinfection and personal hygiene procedures should be in place and should be performed by the personnel before each donation.

A standardized and validated procedure for the preparation of the phlebotomy site should be followed using a suitable disinfection solution

which should be allowed to dry depending on the type of disinfectant. The expiry date of the disinfectant should be checked. If refillable bottles are used, they should be cleaned before being refilled. The date of manufacture and the date of opening of in-house disinfectants should be stated on the label. The prepared skin area should not be touched after the disinfection and before the needle has been inserted. Care should be taken not to lean over or speak over the disinfected skin.

For blood donations, laboratory samples should be taken at the time of donation. Procedures should be designed to minimize the risk of microbial contamination to the unit, such as diverting at least the first 10 ml collected in the tubing into test tubes for testing. Methods should be implemented to minimize the deterioration of the sample, such as refrigeration of the sample if required by the manufacturer's instructions for the sample tube or test kit. The sample labelling process should include steps (such as labelling the tubes immediately at the chair side) to prevent the misidentification of samples. The test samples should be labelled immediately in a manner that links the donor, the samples and the blood component without breaching the confidentiality of the donor.

As soon as the collection process starts, good mixing of the blood with the anticoagulant solution should be ensured to avoid risks of activation of the coagulation cascade. The collection bag should be mixed gently at regular intervals thereafter. The mixing can be done by using a continuously running automatic mixing balance or by periodic manual mixing of the unit at least every 90 seconds. Collection of one standard unit of whole blood should be achieved within 12–15 minutes (depending on the component to be prepared later on), as longer durations may result in activation of the coagulation factors and cellular components.

Records should be kept for each activity associated with the donation, including identification of the person who performed the venipuncture. Records should also show any unsuccessful donation, adverse reactions or adverse events.

The maximum collection time for acceptance of the donation for component processing should be specified and controlled. Donations that exceed the maximum time period should be recorded and discarded.

The integral blood bag collection tubing should be sealed off at the end as close as possible to the blood bag and then removed.

A system of unique donation numbers should be used to identify each donor and the related donation, all associated components, samples and records, and to link each one to the others.

When the donation is completed, all records, blood bags and laboratory samples should be checked for the donation number issued. Donation

number labels that have not been used should be discarded using a controlled procedure. Procedures to exclude misidentification should be in place. After blood collection, the blood bags should be handled in a way that maintains the quality of the blood (see section 9.4.3.1).

A standard operating procedure should be in place describing the actions to be taken following an unsuccessful donation. It should specify how to handle already labelled material and the circumstances under which a second venipuncture might be possible.

As with other GMP manufacturing steps, the donor product collection process should be followed at all times using the validated methods. Any deviations from these established procedures and processes may result in products not meeting specifications and therefore such products should be considered non-conforming products and should not be released for distribution.

9.3.2 *Collection by apheresis*

In automated procedures, whole blood is collected from the donor, mixed with anticoagulant, and passed through an automated apheresis device. The blood component of choice is separated from the other blood components which are returned to the donor in a series of collection/separation and return cycles. The operational parameters of the apheresis system should be implemented in compliance with the instructions of the equipment manufacturer and in compliance with any specified safety requirements of the NRA. In general, the anticoagulant — often 4% sodium citrate or anticoagulant citrate dextrose solution A (ACD-A) — is delivered at a rate that will yield a specified ratio of anticoagulant to blood. The volume of the component collected from the donor during one procedure and over a period of time should be regulated by internal policies based on current medical knowledge and on national regulations set by the NRA. The number of collection/separation and return cycles for each donor depends on the total volume of the component that is to be harvested. To determine the number of cycles to be employed, the equipment requires programming with data inputs such as donor weight, height and haemoglobin values, and the pre-donation platelet count if platelets are to be collected. The amount of time required for the donation procedure depends on the number of cycles. An adequately trained physician should be available during apheresis sessions.

The donor apheresis collection process should be followed at all times using validated methods. Any deviations from the established procedures and processes may result in products not meeting specifications and therefore they should be considered non-conforming products and must not be released for distribution.

9.3.3 *Safety of donors*

All measures should be taken to avoid anything that could adversely affect the donor before, during and after the donation. Special attention should be drawn to the potential risk of transmission of diseases or infections during the collection and sampling processes.

Donors should be given post-donation instructions regarding a period of recovery, such as refraining from certain activities for a while, drinking more fluids than usual and making sure to eat appropriately after the donation. Donors should be advised to refrain from activities such as heavy lifting, operating large items of equipment and other strenuous activities for a period of time until their blood volume has recovered. Donors should also be provided with information on how to obtain medical advice if they experience an adverse donor reaction after leaving the blood establishment.

Throughout the procedure of withdrawal of blood or blood components, the donor should be monitored. Personnel should be educated to provide appropriate aid in case of any adverse reaction. Donors should be kept under post-donation observation (e.g. for 15 minutes or more) prior to leaving the blood establishment and should be offered refreshment to replace fluid loss. If medically required, drinks may be provided to donors during collection (e.g. apheresis). In these circumstances, a suitable container for the drink is required. Donors should remain under observation for anticipated reactions to donation until they are able to articulate that they feel well enough to leave and be unattended. Immediate care should be given to the donor if there is a donor reaction. Information regarding donor reactions and a process to track and trend reactions should be in place in order to evaluate the number, type and severity of reactions. This information should be used to improve donor safety.

9.4 Component preparation

The quality of the components is assured by control of all stages of manufacture, including donor identification, collection, separation of components, labelling, storage, packaging and dispatch. The standard operating procedures should describe the specifications for materials that will influence the quality of the final blood component. In particular, specifications should be in place for blood and blood components (intermediate and final components), starting materials, additive solutions, primary package material (bags) and equipment.

The standard operating procedures for component preparation should be followed at all times using the validated methods. Any deviations from these established procedures and processes may result in products not meeting specifications and such products should be considered as non-conforming products and must not be released for distribution.

9.4.1 *Starting material*

The starting materials for preparation of blood components are blood donations collected from suitable donors. Conditions of storage or transport, and the time prior to processing, are contributing factors to the quality of the product. Delays in preparation or unsuitable conditions of storage or transport may adversely affect the quality of the final product. Blood and blood components should be placed in controlled and validated conditions as soon as possible after venipuncture.

Donations and samples should be transported to the processing site in accordance with procedures that ensure both a constant approved temperature and secure confinement. This is especially important when blood is transported from distant collection sites.

Product transport or shipping at appropriate temperatures and temperature monitoring are important to ensure optimal quality. One way to ensure the temperature of products is to use packaging methods validated to keep the blood within the required temperature limits. There should be validation data to demonstrate that the method of transport maintains the blood within the specified temperature range throughout the period of transportation. Alternatively, portable temperature loggers may be used to record the temperature during the transportation of blood to the processing site. Where the blood is not transported by the processing establishment itself, the responsibilities of the transport company should be clearly defined and periodic audits should be conducted to ensure compliance.

9.4.2 *Methods of production*

Blood components may be prepared by using a centrifugation step with subsequent separation, by using another validated preparation method, or by apheresis technology during collection.

Although the use of closed systems is strongly recommended for all steps in component processing, open systems may exceptionally be necessary due to local constraints in an environment specifically designed to minimize the risk of bacterial contamination. When open systems are used, careful attention should be given to the use of aseptic procedures (*12*).

Where sterile connecting devices are used to maintain a functionally closed system they should be correctly used in accordance with a validated procedure. The resulting weld should be checked for satisfactory alignment and for validated integrity.

The critical equipment used for the preparation of blood components should be traceable to the corresponding manufacturing records.

9.4.2.1 *Centrifugation*

The centrifugation parameters (revolutions per minute, temperature, time, acceleration, deceleration) are important for the composition and characteristics of the specific components. These critical parameters should be defined on the basis of validation data that demonstrate a process that consistently produces quality products. For each run, the centrifugation records should identify the operator and confirm that the centrifugation process was performed according to specifications.

9.4.2.2 *Separation*

After centrifugation, the bag system should be carefully removed from the centrifuge and placed into a plasma expressor or blood separation system. The different layers of the components (red cells, platelets, plasma) should be transferred to the satellite bags within the closed systems, in a manner designed to optimize the harvest of the intended component while minimizing the carry-over of other component fractions.

Alternatively, blood components can be separated during collection by apheresis technology (see section 9.3.2.).

9.4.2.3 *Freezing*

Freezing is an important processing step that has an impact on quality, especially of plasma. The rate at which freezing proceeds and the core temperature are both considered to be important parameters. Rapid plasma freezing prevents or reduces the loss of critical constituents such as Factor VIII in frozen plasma that is either recovered or obtained by apheresis.

A system should be in place for ensuring that plasma is frozen to the specified core temperature within the time limit, keeping in mind that the freezing speed will be influenced by the type of plasma container, the freezing equipment and the loading pattern, as well as by the volume of plasma. The validation of the freezing process should consider worst-case scenarios that take into account both minimum and maximum loads and positions in the freezer. Recording the temperature of plasma units and the freezing time during a freezing process allows one to evaluate the freezing capacity of the equipment and ensures a standardized freezing process. Validation studies should be available and should demonstrate that the temperature of a frozen pack reaches the proposed storage temperature following the specifications. As indicated above, the aim is to achieve rapid freezing and thereafter to minimize temperature changes to the frozen plasma.

Freezing of cellular components such as red cells or cellular therapy should follow a well defined, validated procedure that ensures the recovery

and viability of the intended cellular product during thawing and final preparation steps.

9.4.2.4 *Leukocyte reduction*

Whole blood may be filtered for leukocyte reduction prior to centrifugation. Filtration of whole blood reduces the level of platelet and leukocyte contamination in plasma and red-cell concentrate preparations. Alternatively, components (e.g. red cells, platelets) may be filtered after separation. The introduction of any leukocyte reduction process either by filtration or special centrifugation technique requires careful validation that takes national requirements into account.

In addition to filter properties, the final result of filtration is influenced by several process parameters (e.g. flow rate, temperature, priming and rinsing) and by the properties of the component to be filtered (e.g. storage history of the component, number of leukocytes and number of platelets). The filtration procedure should incorporate manufacturing specifications such as height and temperature. The method should be fully validated under the conditions to be used. Careful attention should be given to the rate of filtration. Rapid or slow filtration may indicate process failures.

Special centrifugation or filtration techniques of leukocyte reduction are used in several apheresis systems. When a standardized procedure is established on the apheresis system, the method should be validated under the conditions to be used.

An appropriate method should be used for leukocyte counting after leukocyte reduction. The method should be validated to ensure linearity, accuracy and reproducibility.

9.4.2.5 *Irradiation*

Regular dose-mapping of irradiation equipment should be performed. The exposure time should be set to ensure that all blood and blood components receive the specified recommended minimum dose, with no part receiving more than the maximum recommended dose. The common recommended minimum dose is 25 Gy (2500 cGy).

Care should be taken regarding the increased potassium leakage from red cells after their irradiation, either by limiting the shelf-life of the red-cell concentrate or by further manufacturing steps such as washing.

For the radioactive source, allowance should be made at least annually for source decay. A second independent timing device should be used to monitor exposure time.

Radiation indicators should be used as aids to differentiating between irradiated and non-irradiated blood and blood components. A defined

procedure should ensure the separation of components that have not been irradiated from those that have been irradiated, and should ensure they have distinctive labelling.

9.4.3 *Blood and blood components*

Blood components may be obtained using the methods described in section 9.4.2. However, the sequence and the combination of the methods used in the production of blood components may vary from one product to another.

The collection process itself is already crucial for the quality of blood components. Measures such as a reliable arm-cleaning and disinfection procedure, the use of closed and sterile collection systems, and appropriate microbiological controls should be implemented. Time limits should be defined for the processing of blood components.

There are detailed recommendations concerning the preparation and quality assurance of blood components. See for instance *Guide to the preparation, use and quality assurance of blood components* of the Council of Europe (*13*). In the following sections, examples of the most important blood components are described. Where NRA requirements exist, they should be followed. Specifications of a number of products are described below.

9.4.3.1 Whole blood

Whole blood for transfusion is blood that is taken from a donor who has been assessed and found suitable as meeting the blood establishment and NRA acceptance criteria. Whole blood is collected in sterile and pyrogen-free containers with a suitable anticoagulant. It may be used without further processing. In some cases, whole blood for transfusion may also be used after leukocyte reduction.

The temperature of whole blood stored for transfusion should remain controlled between 1° and 6°C or in a more stringent range defined by the NRA. The storage time depends on the anticoagulant/preservative solution used.

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). At a minimum, the following critical parameters should be checked during the quality control assays:

— volume;
— haemoglobin or haematocrit;
— haemolysis at the end of storage.

The primary use of whole blood is as a source material for the preparation of blood components. Transportation and further manufacturing processes

should be developed to maximize the number of components that may be produced from a whole blood donation. After collection, whole blood should be kept at a controlled temperature appropriate to the intended component manufacture and should be delivered to the production site as quickly as possible. If whole blood is collected away from the production site, the validated transport systems should ensure that correct temperatures are maintained throughout the process and that the product is delivered within 24 hours. The period between collection and further processing depends on the product but should not exceed 24 hours.

The whole blood may also be filtrated to reduce leukocyte content prior to further processing.

Components should be manufactured by a method validated as meeting the predefined product specifications.

9.4.3.2 Red-cell concentrate

Red-cell concentrates are obtained from whole blood by centrifugation and removal of plasma with or without buffy coat, depending on the centrifugation parameters. After subsequent addition of an appropriate nutrient solution, the red cells should be stored at 1–6°C as soon as possible. Alternatively, red-cell concentrates may be obtained using an apheresis system and likewise stored at 1–6°C. Red-cell units that exceed 10°C after reaching the storage temperature should be discarded. The red-cell concentrate may be used for transfusion without further processing.

To obtain leukocyte-reduced red-cell concentrates, either whole blood filtration can be applied prior to separation or there can be a post-separation filtration of the red-cell concentrate. A fully validated procedure should be established to determine optimum conditions for use of a leukocyte reduction method.

Red-cell concentrates are stored under the same storage conditions as whole blood. The storage time depends on the anticoagulant/preservative solution used.

Further methods of preparation, such as irradiation or washing, are applied to obtain specific red-cell products, depending on the clinical indication.

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). Parameters measured depend on the type of red-cell concentrate product obtained. At a minimum, the following critical parameters should be checked during the quality control assays:

— volume;
— haemoglobin or haematocrit;
— haemolysis at the end of storage;
— residual leukocytes, if leukocyte reduction is performed.

9.4.3.3 *Platelet concentrate*

Platelet concentrates are derived from whole blood or are obtained by apheresis.

After collection, whole blood can be kept for up to 24 hours in conditions that are consistent with the preparation of plasma (see section 9.4.3.4.) and validated to maintain a temperature between 20°C and 24°C, following international or NRA recommendations. The whole blood unit is centrifuged so that an optimal number of platelets remain in plasma (platelet-rich plasma, or PRP). Platelet concentrates are then obtained by hard-spin centrifugation of PRP and are then resuspended.

However, if whole blood is centrifuged so that the blood platelets are primarily sedimented to the buffy coat layer, the buffy coat is separated and further processed to obtain a platelet concentrate. Either a single buffy coat or a pool of buffy coats is diluted with plasma or an appropriate nutrient solution, and platelets are concentrated by further centrifugation. The platelet content per unit depends on the method of preparation. Similarly, the residual leukocyte content will vary according to the centrifugation parameters.

Platelet concentrates (both from whole blood and apheresis) should be stored in conditions that guarantee that viability and haemostatic activities are optimally preserved. The storage temperature should be 20–24°C. Continuous gentle agitation of platelets during storage should be sufficient to guarantee the availability of oxygen to the platelets (but should be as gentle as possible). A storage time should be defined in accordance with national regulations set by the NRA; it should normally not exceed five days in the absence of additional measures.

In special circumstances, volume-reduced, split, washed or irradiated platelet concentrates can be prepared for specific treatments.

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). At a minimum, the following critical parameters should be checked during the quality control assays:

— volume;
— platelet content;
— residual leukocytes, if leukocyte reduction is performed;
— pH, measured at the end of the recommended shelf-life.

9.4.3.4 *Plasma for transfusion and Plasma for fractionation*

Plasma for transfusion is prepared either from whole blood or from plasma collected by apheresis, and is frozen within a defined period of time to a temperature that should adequately maintain the labile coagulation factors

in a functional state, consistent with the intended use of the plasma. In particular, Factor VIII content is critical both as a quality indicator and to assure the efficacy of cryoprecipitate.

If plasma is separated from a unit of whole blood that is refrigerated to 4°C, centrifugation should preferably take place within eight hours of collection (*14*,*15*,*16*).

If the whole blood unit is rapidly cooled to 20–24°C and maintained at this constant temperature after collection, separation can take place within 18–20 hours because such conditions have been found to protect Factor VIII (*17*).

If plasma is collected by apheresis, the freezing process should begin as soon as possible, and ideally not later than six hours after the completion of the apheresis process. In compliance with NRA requirements, consideration should be given to the time frames of processing with respect to the anticoagulant and device used and the product to be manufactured.

The freezing process should be validated and should take place in a system that will allow complete freezing to a predefined core temperature in a predefined time (see section 9.4.2.3).

Product stability is dependent on the storage temperature. Storage temperature and shelf-life depend on the intended use of the product. For long-term storage (more than one year) the optimal storage temperature is minus 25°C or colder (*18*).

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). At a minimum, the following critical parameters should be checked during the quality control assays:

— volume;
— Factor VIII activity (especially if plasma is used to treat Factor VIII deficiencies);
— residual leukocytes, if leukocyte reduction is performed;
— leakage;
— visual changes.

Virus inactivation and/or quarantine of plasma for transfusion are applied in some countries. Further complementary guidance with respect to virus inactivation is available in *WHO guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products* (*2*), and in other publications (*19*,*20*).

Plasma for transfusion is suitable as source material for the production of fractionated products, and particularly Factor VIII concentrates or other labile factors. Plasma prepared in other ways should meet the specifications of the plasma fractionators and the requirements of the pharmacopoeia

and NRA. Further complementary guidance with respect to the production of plasma for fractionation is available in *WHO recommendations for the production, control and regulation of human plasma for fractionation* (*3*).

9.4.3.5 *Cryoprecipitate and Cryo-poor plasma*

Cryoprecipitate is the cryoglobulin fraction of plasma and contains a major portion of the Factor VIII, von Willebrand factor, fibrinogen, Factor XIII and fibronectin present in plasma. Cryoprecipitate is obtained from fresh frozen plasma that is prepared in a way that protects Factor VIII stability. Plasma is allowed to thaw either overnight at 2–6°C or by a rapid-thaw technique. Following thawing, the supernatant cryo-poor plasma and the cryoprecipitate are separated by hard-spin centrifugation. The cryo-poor plasma is then expressed into a transfer bag. The two components are refrozen to the appropriate core temperature.

Stability during storage depends on the storage temperature. Storage temperature and shelf-life depend on the intended use of the product. For long-term storage (for two years or longer) the optimal storage temperature is minus 25°C or colder.

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). At a minimum, the following critical parameters should be checked during the quality control assays of cryoprecipitate:

— volume;
— Factor VIII activity;
— clottable fibrinogen;
— von Willebrand factor activity (if applicable).

Virus inactivation and/or quarantine are applied in some countries.

Under certain circumstances the use of small pool preparations of cryoprecipitate (by pooling single-donor cryoprecipitate units) may be desired.

9.5 Laboratory testing

9.5.1 *Screening tests for infectious disease markers*

9.5.1.1 *Testing requirements*

The following tests, which are considered mandatory by all regulatory agencies, are relevant to the preparation of blood components and should be performed on each individual blood donation:

— an approved test for Hepatitis B surface antigen (HBsAg);
— an approved test for anti-HIV1/HIV2;
— an approved test for anti-HCV.

All three tests have to be negative. Initially reactive donations should be retested in duplicate by the same assay. Products from a repeatedly reactive donation should not be used for therapeutic applications and should normally be destroyed unless useful for non-therapeutic purposes or investigations. A sample of the donation should be evaluated by a confirmatory test. There should be a system for notifying and counselling the donor if confirmation is positive. It is recommended that national algorithms should be developed and used to enable consistent resolution of discordant/indeterminate or unconfirmed results.

In some countries, additional serological testing is required — for instance, anti-HBc testing may be performed on whole blood donations in order to further reduce the risk of exposure of recipients to HBV by contaminated blood or blood components (*3*). Additional testing for other agents or markers — such as anti-HTLV I/II, anti-T.cruzi or West Nile Virus (WNV) — may be required by the NRA, taking into account the epidemiological situation in any given region or country or the frequency of donating blood. In addition to testing for immunochemical-serological infectious disease markers, NAT testing of blood donations for the virus genomes has been introduced in some countries to increase the chance of identifying infected donors.

During the natural course of infection, viraemia usually occurs significantly at a point earlier than that at which immunochemical markers (antibodies) can be detected in the infected serum. Thus, infection may be detected by NAT up to 50–60 days before seroconversion (i.e. to HCV) occurs. Testing for the presence of nucleic acid may be performed for viruses such as HCV, HBV, HIV, HAV, WNV (where appropriate) and/or Parvovirus B19, and the application of this technology may be extended to other transmissible microbes. NATs require a particularly sophisticated laboratory environment, special equipment and specially trained laboratory personnel. Mainly because of an extraordinary risk of false-positive results due to the so-called "carry-over" (inadvertent transfer of the amplification product DNA to neat donor samples), very stringent handling and logistics are mandatory.

In contrast to testing for the serological markers of individual donor specimens, NAT testing may be performed following current practices by assembling various samples in mini-pools. However, this requires a thoroughly validated system of sample labelling/identification, a validated strategy and pooling process, and a validated algorithm to resolve pool results to individual donors. Hence, a specific logistics system may have to be established not only in the laboratory but also at the blood establishment in order to collect and suitably label samples. Contiguously tracing samples through the whole process from the donor, through pooling (if applicable), testing and release of the donation may present a particularly demanding challenge.

A system should exist in the country or region for approval of test systems, such as an official approval system by the NRA or a delegated laboratory. The required minimal sensitivity of tests for the different antigens/antibodies or nucleic acids should be defined by the NRA.

9.5.1.2 *Handling of samples and data*

Multiple specimens may be collected from a donor in order to meet all testing requirements (i.e. ABO typing, viral markers, NAT testing). There should be written standard operating procedures that clearly describe the collection, transportation and labelling of donor samples (i.e. whole blood, sera, anti-coagulant, container tubes etc.) and which define the sampling procedure performed on material for analysis (e.g. how and by whom it is done, transfer of samples, accountability of samples). All screening activities, handling of donor specimens, sampling, analysis and data processing should be separated from patient diagnostic testing (*21*).

Sample labelling at the site of collection and identification during all subsequent processing is critical and should be under control at all times. Each step of handling and processing should be described, as should the conditions of pre-analytical treatment of specimens (e.g. centrifugation), storage and transportation (duration, temperature, type of container, storage after testing).

Serological testing should be performed on samples transferred directly into the analyser from the original sample tube.

Secondary aliquot samples may be used for NAT testing of mini-pools of individual samples.

The following practical points should be considered in order to ensure the traceability and integrity of samples and data:

- At receipt of specimens at the laboratory, positive identification of those received versus those expected should be performed. The integrity of the sample should be checked for compliance with the recommendations made by the manufacturer of the test kit.
- Aliquot samples for analysis should be withdrawn from the donor sample preferably by automated pipetting equipment.
- To provide for positive identification of all aspects (donation, donor specimen, aliquot samples etc.) it may be advisable to use a barcode system. Hence, starting with the donation, barcodes should be used for labelling. In case of failure of the automatic barcode reader system and/or data processors, an appropriate system should be available for manual entry and tracing of data throughout the whole process until release of donations for transfusion. Manual handling of data should include independent repeat entry into the database; the data format should include a check-digit algorithm or an automated test for identity of the two sets of data.

- Pipetting devices and machines should be validated before routine use, and validation reports should be available.
- Calibration of the pipetting devices should be performed periodically and should be documented.

9.5.1.3 *Testing and post-analytical procedures*

Testing of blood components should be carried out in accordance with the recommendations of the manufacturer of reagents and test kits. Modifications to the manufacturer's instructions or reagents for donor screening tests should be validated. Where required, prior approval of the NRA should be obtained before the modified method is used for release of a blood component. Laboratory reagents intended for prolonged use should be marked with the preparation date, expiry date, specific storage conditions and signature of the person who prepared them. Instructions for use and storage should be followed.

Screening algorithms should be precisely defined in writing (i.e. standard operating procedures) to deal with initially reactive specimens and to resolve discrepancies in results after retesting. All available measures should be taken to ensure that blood and blood components that are repeat reactive upon screening for an infectious disease marker are excluded from therapeutic use. Repeat reactive material should be stored away from all other blood components in a separate dedicated storage area. Such material should eventually be destroyed to prevent inadvertent re-entry into the transfusion chain.

Test algorithms should provide details for appropriate confirmatory testing. In the case of repeatedly reactive results, clearly defined follow-up instructions should be followed. Actions include:

— notification and deferral of the donor;
— disposal of the indicated donation and of concurrent products;
— tracing and destruction of products which have not yet expired.

If products from the donor have been processed for further manufacture, there should be a procedure in place to assess both the safety of the manufactured products and whether a recall is needed.

Procedures for donor- and/or recipient-initiated look-backs should also be defined. Look-backs should be designed in such a way that the transfusion chain of donor–blood (or blood product)–recipient can be unequivocally reconstructed. The procedure should comprise notification and counselling action where indicated.

The following practical points should be considered in order to ensure that the equipment used for virology testing performs appropriately:

- There should be a mechanism to ensure positive sample identification and linkage to the donor. The preferred method is by sample tubes with barcodes.
- Ideally, the addition of reagent and samples and the testing process should be automated, in order to minimize risk of human errors and to ensure full traceability of the testing process.
- If addition of reagents and samples or preparation of test plates are done manually, full documentation of each addition step should be kept, ensuring identification of the test plate and the location of the reaction well.

9.5.1.4 *Test interpretation and follow-up of reactive results*

The transfer and interpretation of raw data is a critical step and should therefore be documented and reviewed by a responsible person, as should the test parameters. Traceability and archiving of raw data should be guaranteed (see section 5.2).

The data should be examined by the supervisor, or by another person authorized to do so, before being officially accepted. If computerized systems are used, accepted data should be downloaded directly to the server, or there should be a secure system for manual download which ensures positive release. Manual transcription of results is discouraged as mistakes may be introduced. Acceptance and rejection criteria should be specified.

The following should be given special attention:

- Initial reactive results should be identified by means of a secure and validated system.
- An acceptable system should be in place to confirm repeat reactive results, including sampling, labelling, testing and entry of results.
- Computer algorithms should edit reactive status to repeat reactive, or the editing should be performed by two authorized staff members.
- An appropriate deferral system should exist for repeat reactive results.
- There should be appropriate documentation justifying the re-entry of deferred donors.
- Donors should be informed of the reason for deferral and should be counselled about social behaviours and their status as a future donor.

9.5.2 Blood group typing

Each donation should be tested for ABO and RhD blood groups and at least all first-time donors should be tested for clinically significant irregular red-cell antibodies. When plasma is used for fractionation it should be tested in compliance with the specifications of the fractionator as agreed by the relevant NRA (*3*).

Testing should be carried out in accordance with the recommendations of the manufacturer of reagents and test kits. Molecular methods may be used to determine blood groups, as necessary.

The ABO and RhD blood group should be verified on each subsequent donation. A comparison should be made with the historically determined blood group. If a discrepancy is found, the applicable blood components should not be released until the discrepancy has been unequivocally resolved.

Donors with a history of transfusions or pregnancy since the last donation should be tested for clinically significant irregular red-cell antibodies. If clinically significant red-cell antibodies are detected, and where applicable, the blood or blood component should be labelled accordingly

NRAs may set different (stronger) requirements.

The ABO/RhD labelling of the red-cell concentrates of all first-time donations should be based on two independent ABO/RhD tests.

9.5.3 *Retention samples*

As specified by the NRA, an aliquot of the original testing sample should be retained from each donation and stored under conditions recommended by the test manufacturer that would permit retesting if indicated. The procedure for additional testing should be validated to ensure the integrity of the sample (including storage conditions) and the test results. The sample volume, the retention vial, the kind of specimen (serum or plasma), the storage conditions and length of storage should each be defined and should be included in the validation to ensure the integrity of test results.

9.6 Quality monitoring of blood and blood components

Quality control data should demonstrate that critical manufacturing processes are under control. Blood and blood components should comply with specifications and their testing should be performed using test methods approved by the NRA.

All processes — including data transfers and computerized systems — that have an influence on the quality of the products in the area of collection, preparation or testing of blood and blood components should be validated. For critical processes such as rapid freezing of plasma, the need for revalidation should be defined.

Quality control of blood and blood components should be carried out according to a defined sampling plan based on statistical methods. The sampling plan should take into account different collection and production sites, transport, methods of preparation and equipment used. Acceptance criteria should be based on a defined specification for each type of blood component. As an example for fresh frozen plasma, these data may include monitoring of weight/volume, sterility, Factor VIII activity and residual cell

counts (platelets, leukocytes, erythrocytes). The sampling plan for testing of blood or blood components should take into account that most components are derived from one donor, and should be considered as a single batch.

Whole blood or blood components should not be released for use if the quality control test indicates that the integrity of the product has been compromised.

The work record should identify the test(s) employed so as to ensure that entries, such as the calculation of results, are available for review.

Test results that do not meet the acceptance criteria should be clearly identified to ensure that blood components of that donation remain in quarantine and that relevant samples are selected for further testing. An investigation should be conducted into the cause of failure prior to additional or repeat testing. Where possible, the performance of the test procedures should be regularly assessed by participation in a formal system of proficiency testing.

Where applicable, the practice of pooling samples before testing should be clearly stated and the donations used in the pooled sample should be recorded. Pooling of samples, such as for the measurement of Factor VIII activity in plasma, is acceptable only where comparative data of pooled samples and individual samples have demonstrated assurance of equivalence.

The results of quality monitoring testing should be subject to periodic review and trend analysis. If the results of quality monitoring suggest that the process is not meeting validated parameters and specifications, then corrective and preventive actions should be taken to correct identified problems before product manufacturing and distribution is continued.

9.7 Labelling

9.7.1 *Label information*

The collected blood, as well as intermediate and finished blood components, should be labelled with relevant information regarding their identity and release status. The type of label to be used, as well as the labelling methodology, should be established in written standard operating procedures. Whenever possible, machine-readable labels (barcodes) should be used.

The label for a finished blood component should comply with the requirements of the NRA or contain at least the following information:

— the unique donation number (through the use of this number there should be traceability to the donor and all records of the manufacturing steps through to the final product);
— the product name (see section 9.7.2.);

— the required storage conditions;
— the expiry date and, where appropriate, time (see section 9.7.3.);
— the date of collection of the donation(s) from which the blood component was prepared and/or the production date and time (where appropriate);
— the date and time of irradiation (where applicable);
— the ABO and RhD blood group (where appropriate);
— the name or other identification of the component preparation site.

Information regarding the use of the blood product may also be applicable.

For autologous blood components, the label should additionally contain the name and unique identification of the patient as well as the statement "Autologous donation". In some countries the signature of the donor is also required.

9.7.2 *Product name*

The name of the blood component should be clearly stated on the label and should indicate any further processing such as leukocyte reduction or irradiation.

In addition, the anticoagulant and/or any nutrient or preservative solution should be mentioned on the label.

9.7.3 *Expiry date*

Any final blood product should have its expiry date on its label. It should be also kept in mind that certain processing steps, such as irradiation, have an influence on the expiry date so that relabelling becomes necessary.

The definition of an expiry date should be validated and based on scientific data according to the processing steps applied and the storage conditions, or should be the subject of stability studies.

9.8 Release of product

Each blood establishment should be able to demonstrate that a blood component has been evaluated and approved for release by an authorized person, preferably assisted by validated computerized systems. The release criteria and specifications of blood components should be defined, validated, documented and approved by quality assurance. There should be a standard operating procedure that details the actions and criteria that determine whether the blood or blood component can be released. The decision to release the blood components should be made by the responsible person of the establishment; it should be clearly documented and traceability should be ensured. Electronic release of products should be fully validated.

The documented manufacturing processes should be followed at all times using validated methods and procedures. Any deviations from these established procedures and processes may result in products not meeting specifications, in which case they should be considered non-conforming products and must not be released for distribution.

A review of the donor health record, collection and phlebotomy records, consent forms, records of production and test results should be performed and accepted (and should be recorded) prior to the release of the components. The release of products should be arranged in such a way that each component from the donation has been evaluated to ensure conformance with product specifications — such as platelet content in apheresis units, volume in plasma products or appearance for red blood cells — prior to release for distribution. The decision to release the component should not be made on the basis of a review of the collection processes alone.

There should be a system of administrative and physical quarantine for blood and blood components to ensure that components cannot be released until all mandatory requirements have been met.

In the absence of a computerized system for product status control:

— the label of a blood component should identify the product status and should clearly distinguish released products from non-released (quarantined) ones;
— records should demonstrate that, before a component is released, all current donor health records, collection and phlebotomy records, consent forms and test results have been verified and accepted by an authorized person.

If blood or blood components have been prepared from a donor who has donated on previous occasions, a comparison with previous records — specifically the ABO/RhD and infectious disease marker test results — should be made before final product release to ensure that current records accurately reflect the donor history.

Where release is subject to computer-derived information, the following points should be checked:

- Computer systems should be validated so that they are fully secure against the possibility of blood and blood components which do not fulfil all test or donor selection criteria being released.
- The manual entry of critical data, such as laboratory test results, should require independent verification by a second authorized person.
- There should be a hierarchy of permitted access to enter, amend, read or print data. Methods of preventing unauthorized entry should be in place, such as personal identity codes or passwords which are changed on a regular basis.

- Computer systems should prevent the release of all blood or blood components considered not acceptable for release. It should be possible to prevent the release of any future donation from a donor.

In the event that the final product fails release due to noncompliance with the specified requirements and therefore due to potential impact on recipient safety, all other implicated components should be identified and appropriate action should be taken. A check should be made to ensure that (if relevant) other components from the same donation(s) and components prepared from previous donations given by the donor(s) are identified. There should be an immediate updating of the donor record(s) to ensure that the donor(s) cannot make any further donation, if appropriate.

There should be a defined procedure for the exceptional release of nonstandard blood and blood components under a planned non-conformance system. The decision to allow such a release should be made by the responsible person; the decision should be clearly documented and traceability should be ensured. Products that cannot be released should be destroyed and the record of destruction should be retained.

9.9 Storage

Standard operating procedures should describe the receipt, handling and storage of material, blood and blood components. There should be a system in place to maintain and control storage conditions, including any transportation that may be required. Autologous blood and blood components should be stored separately. Storage areas for blood components to be dispatched should be located near an entrance or exit to facilitate dispatch and to limit the number of persons entering the main working areas. Only authorized persons should have access to storage areas.

Storage conditions should be controlled, monitored and checked. The personnel authorized should be trained to be aware of the correct storage temperature ranges and alarm settings. Temperature records should be available to demonstrate that the blood components are stored at the required temperature throughout the storage area. A temperature monitoring and recording system that is independent from the temperature regulation system should be in place. Appropriate alarms should be present (upper and lower limits) and regularly checked; the checks should be recorded. Depending on the method of measuring the temperature, a delay of the alarm may be acceptable in order to avoid an alarm being triggered by opening a door or taking out a product, but any such delay should be reasonably justified. If the temperature sensor is placed in a reference solution, no delay of the alarm should be accepted. Appropriate actions on alarms should be defined, and a person should be authorized to decide on the use or rejection of affected

products. Temperature excursions may occur and each event should be evaluated using the deviation management system (see section 3.5).

An alternative storage area of appropriate temperature is recommended for recovery in case of temperature control failure of the primary system. Areas for storage should be secured against the entry of unauthorized persons and should be used only for the intended purpose. Storage areas should provide effective segregation of quarantined and released materials or components. There should be a separate area for rejected components and material. If a temporary mechanical or electrical failure affects control of storage temperatures, an examination of the records should be made to evaluate the impact on plasma or blood component quality.

For the main blood components, the common storage temperatures are as follows:

— red-cell concentrate: 1–6°C;
— plasma for transfusion: minus 25°C or colder;
— platelets: 20–24°C;
or in a more stringent range defined by the NRA.

Higher storage temperatures (e.g. minus 20°C) might be acceptable for plasma for transfusion but may result in a significantly shorter shelf-life.

Storage of platelets should also be controlled. Besides the temperature, the continuous agitation is very important. Based on the manufacturer's instructions, the moving velocity should be set in a way that obtains an optimal quality of the product. The moving velocity should be part of the qualification of the equipment.

During the whole collection and manufacturing process it should be ensured that blood or blood components are never placed in direct sunlight or near a heating source.

All storage equipment should be subject to qualification, cleaning and preventive maintenance. Thermometers or temperature sensors should be calibrated annually. The temperature deviation to the standard measuring device should not exceed 1°C.

9.10 Distribution

Prior to distribution, blood components should be visually inspected. There should be a record that identifies the person distributing and the customer receiving the components. Dispatch of blood components should be made by authorized personnel.

At the time of dispatch, there should be a procedure in place to ensure that all blood components being issued have been formally released for

use. A standard operating procedure on packaging should be available stating how the contents should be packaged, the materials to be used, and the amount of any cooling elements and their storage conditions before use.

9.11 Shipping

Distribution should take place in a safe and controlled way in order to assure product quality during transport. All transportation and intermediate storage actions, including receipt and distribution, should be defined by written standard operating procedures and specifications.

The shipping containers should be of sturdy construction in order to resist damage and should be validated to maintain acceptable storage conditions for the blood and blood components (e.g. by using appropriate cooling elements or insulation during transport). The transportation and storage conditions for blood components, the packaging format and the responsibilities of the persons involved should be in accordance with standard operating procedures agreed between the sites in question.

9.12 Returns

Blood components should not be returned to stock for subsequent distribution, unless:

— the procedure for return of a blood component is regulated by contract;
— for each returned blood component, it is proven that the agreed storage conditions have consistently been met;
— the integrity of the container has been maintained (i.e. unopened);
— sufficient material is available for compatibility testing.

In case of medical urgency, components may be returned and subsequently distributed using a defined procedure.

The records should indicate that the blood component has been inspected and found to be acceptable before re-issue.

10. Contract manufacturing, analysis and services

In blood establishments, all tasks that have an influence on the quality of collected blood and the manufacture of blood components — such as component processing, testing or information technology support — and which are performed externally by another party, should be subject to a specific written contract. The contract should ensure that the contract acceptor meets GMP requirements in all disciplines relevant to the contract giver's activities.

The contract giver is ultimately responsible for ensuring that processes are in place to assure the control of outsourced activities and the quality of purchased materials. These processes should incorporate QRM and should include:

— assessing (prior to outsourcing operations or selecting material suppliers) the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g. audits, material evaluations, qualification);
— defining the responsibilities and communication processes for quality-related activities of the parties concerned;
— monitoring and review of the performance of the contract acceptor or the quality of the material from the provider, and identification and implementation of any improvements needed;
— monitoring of incoming ingredients and materials to ensure that they are from approved sources using the agreed supply chain.

Details should be specified in a technical quality agreement or contract.

The contract or agreement should:

— clearly establish the duties of each party;
— state the responsibilities of each party;
— mention any technical arrangements;
— define the flow of information, especially regarding deviations and changes;
— define the handling and archiving of documents, samples and other relevant materials and information;
— state that any of the duties given to the contract acceptor should not be passed to a third party without evaluation and approval of the contract giver;
— permit the contract giver and competent authorities to visit and inspect the facilities of the contract acceptor.

The contract giver should provide the contract acceptor with all necessary information to enable compliance with expectations regarding services or goods. This assures that the work or service is performed in compliance with existing regulations. The overall responsibility for the work and duties carried out externally lies always with the contracting company.

The contract should be agreed and signed by quality assurance representatives from both parties and should be kept up to date.

11. Authors and acknowledgements

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Annex 5

Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms

1. Introduction

Heating, ventilation and air-conditioning (HVAC) play an important role in ensuring the manufacture of quality pharmaceutical products. A well designed HVAC system will also provide comfortable conditions for operators.

These guidelines mainly focus on recommendations for systems for manufacturers of solid dosage forms. The guidelines also refer to other systems or components which are not relevant to solid dosage form manufacturing plants, but which may assist in providing a comparison between the requirements for solid dosage-form plants and other systems.

HVAC system design influences architectural layouts with regard to items such as airlock positions, doorways and lobbies. The architectural components have an effect on room pressure differential cascades and cross-contamination control. The prevention of contamination and cross-contamination is an essential design consideration of the HVAC system. In view of these critical aspects, the design of the HVAC system should be considered at the concept design stage of a pharmaceutical manufacturing plant.

Temperature, relative humidity and ventilation should be appropriate and should not adversely affect the quality of pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

This document aims to give guidance to pharmaceutical manufacturers and inspectors of pharmaceutical manufacturing facilities on the design, installation, qualification and maintenance of the HVAC systems. These guidelines are intended to complement those provided in *Good manufacturing practices for pharmaceutical products (1)* and should be read in conjunction with the parent guide. The additional standards addressed by the present guidelines should, therefore, be considered supplementary to the general requirements set out in the parent guide.

2. Scope of document

These guidelines focus primarily on the design and good manufacturing practices (GMP) requirements for HVAC systems for facilities for the manufacture of solid dosage forms. Most of the system design principles for facilities manufacturing solid dosage forms also apply to other facilities such as those manufacturing liquids, creams and ointments. These guidelines do not cover requirements for manufacturing sites for the production of sterile pharmaceutical products. These guidelines do not cover the specific requirements relating to facilities handling hazardous products. Guidelines for hazardous product facilities are covered in a separate WHO guideline.

These guidelines are intended as a basic guide for use by pharmaceutical manufacturers and GMP inspectors.

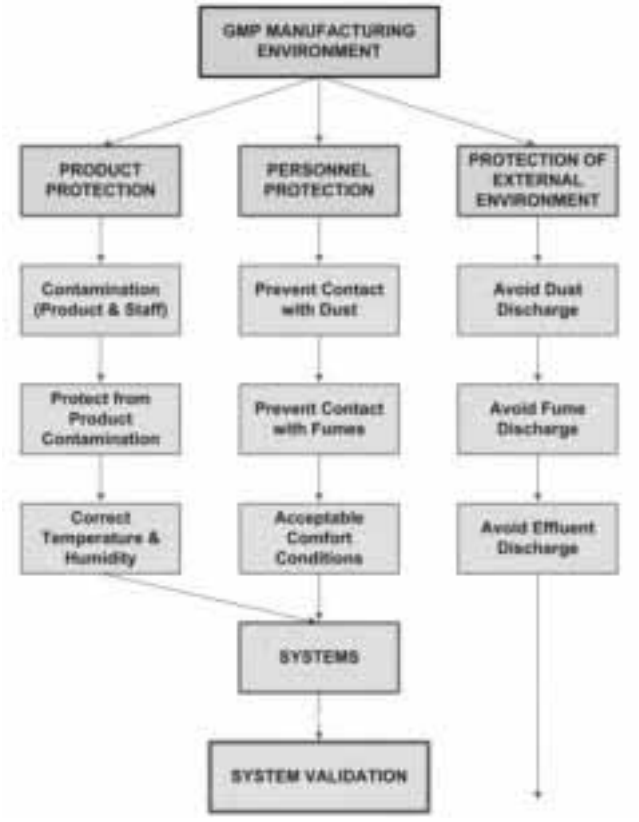
They are not intended to be prescriptive in specifying requirements and design parameters. There are many parameters affecting a clean area condition and it is, therefore, difficult to lay down the specific requirements for one particular parameter in isolation.

Many pharmaceutical manufacturers have their own engineering design and qualification standards and requirements may vary from one manufacturer to the next. Design parameters and user requirements should, therefore, be set realistically for each project, with a view to creating a cost-effective design, yet still complying with all regulatory standards and ensuring that product quality and safety are not compromised. The three primary aspects addressed in this manual are the roles that the HVAC system plays in product protection, personnel protection and environmental protection (Figure 1).

Cognisance should be taken of the products to be manufactured when establishing system design parameters. A facility manufacturing multiple different products may have more stringent design parameters with respect to cross-contamination control, compared with a single product facility.

Figure 1

The guidelines address the various system criteria according to the sequence set out in this diagram



3. Glossary

The definitions given below apply to terms used in these guidelines. They may have different meanings in other contexts.

acceptance criteria

Measurable terms under which a test result will be considered acceptable.

action limit

The action limit is reached when the acceptance criteria of a critical parameter have been exceeded. Results outside these limits will require specified action and investigation.

air changes per hour (ACPH)

The volume of air supplied to a room, in m^3/hr, divided by the room volume, in m^3.

air-handling unit (AHU)

The air-handling unit serves to condition the air and provide the required air movement within a facility.

airlock

An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods (PAL, personnel airlock; MAL, material airlock).

alert limit

The alert limit is reached when the normal operating range of a critical parameter has been exceeded, indicating that corrective measures may need to be taken to prevent the action limit being reached.

as-built

Condition where the installation is complete with all services connected and functioning but with no production equipment, materials or personnel present.

at-rest

Condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.

central air-conditioning unit (see air-handling unit)

change control

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated

status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

clean area (cleanroom)[1]

An area (or room or zone) with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

closed system

A system where the product or material is not exposed to the manufacturing environment.

commissioning

Commissioning is the documented process of verifying that the equipment and systems are installed according to specifications, placing the equipment into active service and verifying its proper action. Commissioning takes place at the conclusion of project construction but prior to validation.

containment

A process or device to contain product, dust or contaminants in one zone, preventing it from escaping to another zone.

contamination

The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.

controlled area

An area within the facility in which specific environmental facility conditions and procedures are defined, controlled, and monitored to prevent degradation or cross-contamination of the product.

critical parameter or component

A processing parameter (such as temperature or relative humidity) that affects the quality of a product, or a component that may have a direct impact on the quality of the product.

critical quality attribute (CQA)

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality.

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[1] Note: Clean area standards, such as ISO 14644-1, provide details on how to classify air cleanliness by means of particle concentrations, whereas the GMP standards provide a grading for air cleanliness in terms of the condition (at-rest or operational), the permissible microbial concentrations, as well as other factors such as gowning requirements. GMP and clean area standards should be used in conjunction with each other to define and classify the different manufacturing environments.

cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

design condition

Design condition relates to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system.

design qualification (DQ)

Design qualification is the documented check of planning documents and technical specifications for conformity of the design with the process, manufacturing, GMP and regulatory requirements.

direct impact system

A system that is expected to have a direct impact on product quality. These systems are designed and commissioned in line with good engineering practice (GEP) and, in addition, are subject to qualification practices.

exfiltration

Exfiltration is the egress of air from a controlled area to an external zone.

facility

The built environment within which the clean area installation and associated controlled environments operate together with their supporting infrastructure.

good engineering practice (GEP)

Established engineering methods and standards that are applied throughout the project life-cycle to deliver appropriate, cost-effective solutions.

hazardous substance or product

A product or substance that may present a substantial risk of injury to health or to the environment

indirect impact system

This is a system that is not expected to have a direct impact on product quality, but typically will support a direct impact system. These systems are designed and commissioned according to GEP only.

infiltration

Infiltration is the ingress of air from an external zone into a controlled area.

installation qualification (IQ)

Installation qualification is documented verification that the premises, HVAC system, supporting utilities and equipment have been built and installed in compliance with their approved design specification.

no-impact system

This is a system that will not have any impact, either directly or indirectly, on product quality. These systems are designed and commissioned according to GEP only.

non-critical parameter or component

A processing parameter or component within a system where the operation, contact, data control, alarm or failure will have an indirect impact or no impact on the quality of the product.

normal operating range

The range that the manufacturer selects as the acceptable values for a parameter during normal operations. This range must be within the operating range.

operating limits

The minimum and/or maximum values that will ensure that product and safety requirements are met.

operating range

Operating range is the range of validated critical parameters within which acceptable products can be manufactured.

operational condition

This condition relates to carrying out room classification tests with the normal production process with equipment in operation, and the normal staff present in the room.

operational qualification (OQ)

Operational qualification is the documentary evidence to verify that the equipment operates in accordance with its design specifications in its normal operating range and performs as intended throughout all anticipated operating ranges.

oral solid dosage (OSD)

Usually refers to an OSD plant that manufactures medicinal products such as tablets, capsules and powders to be taken orally.

pass-through-hatch (PTH) or pass box (PB)

A cabinet with two or more doors for passing equipment or product, whilst maintaining the pressure cascade and segregation between two controlled zones. A passive PTH has no air supply or extract. A dynamic PTH has an air supply into the chamber.

performance qualification (PQ)

Performance qualification is the documented verification that the process and/or the total process related to the system performs as intended throughout all anticipated operating ranges.

point extraction

Air extraction to remove dust with the extraction point located as close as possible to the source of the dust.

pressure cascade

A process whereby air flows from one area, which is maintained at a higher pressure, to another area at a lower pressure.

qualification

Qualification is the planning, carrying out and recording of tests on equipment and a system, which forms part of the validated process, to demonstrate that it will perform as intended.

quality critical process parameter (CPP)

A process parameter which could have an impact on the critical quality attribute.

relative humidity

The ratio of the actual water vapour pressure of the air to the saturated water vapour pressure of the air at the same temperature expressed as a percentage. More simply put, it is the ratio of the mass of moisture in the air, relative to the mass at 100% moisture saturation, at a given temperature.

standard operating procedure (SOP)

An authorized written procedure, giving instructions for performing operations, not necessarily specific to a given product or material, but of a more general nature (e.g. operation of equipment, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

turbulent flow

Turbulent flow, or non-unidirectional airflow, is air distribution that is introduced into the controlled space and then mixes with room air by means of induction.

unidirectional airflow (UDAF)

Unidirectional airflow is a rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (see also turbulent flow).

validation

The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

validation master plan (VMP)

Validation master plan is a high-level document which establishes an umbrella validation plan for the entire project, and is used as guidance by the project team for resource and technical planning (also referred to as master qualification plan).

4. Protection

4.1 Products and personnel

4.1.1 Areas for the manufacture of pharmaceuticals, where pharmaceutical starting materials and products, utensils, primary packing materials and equipment are exposed to the environment, should be defined as "clean areas", "clean zones", "controlled areas" or "cleanrooms".

4.1.2 The achievement of a particular clean area condition depends on a number of criteria that should be addressed at the design and qualification stages. A suitable balance between the different criteria will be required in order to create an efficient clean area.

4.1.3 Some of the basic criteria to be considered which affects room cleanliness should include:

- building finishes and structure
- air filtration
- air change rate or flushing rate
- room pressure
- location of air terminals and directional airflow
- temperature
- relative humidity
- material flow
- personnel flow
- gowning procedures
- equipment movement
- process being carried out (open or closed system)
- outside air conditions
- occupancy
- type of product
- cleaning standard operating procedures (SOPs).

4.1.4 Air filtration and air change rates should be set to ensure that the defined clean area condition is attained.

4.1.5 The air change rates should be determined by the manufacturer and designer, taking into account the various critical parameters using a risk based approach with due consideration of capital and running costs and

energy usage. Primarily the air change rate should be set to a level that will achieve the required clean area condition.

4.1.6 Air change rates are normally determined by the following considerations (could normally vary between 6 and 20 air changes per hour):

- area condition required: whether a specific room cleanliness condition is in fact required and whether the room condition is rated for an "at rest" condition or an "operational" condition (air change rate should be selected on need rather than tradition)
- the product characteristics (e.g. odours, hygroscopicity, etc)
- the quality and filtration of the supply air
- particulates generated by the manufacturing process
- particulates generated by the operators
- configuration of the room and air supply and extract locations
- sufficient air to achieve containment effect and to clean up the area
- sufficient air to cope with the room heat load
- sufficient air to balance extract rates
- sufficient air to maintain the required room pressure.

4.1.7 If a cleanroom classification is specified the manufacturer should state whether this is achieved under "as-built" (Figure 2), "at-rest" (Figure 3) or "operational" (Figure 4) conditions.

4.1.8 Room classification tests in the "as-built" condition should be carried out on the bare room, in the absence of any equipment or personnel.

4.1.9 Room classification tests in the "at-rest" condition should be carried out with the equipment operating where relevant, but without any operators. Because of the amounts of dust usually generated in a solid dosage facility, the clean area classifications would be rated for the "at-rest" condition.

4.1.10 Room classification tests in the "operational" condition are normally carried out during the normal production process with equipment operating, and the normal number of personnel present in the room. Generally a room that is tested for an "operational" condition should be able to be cleaned up to the "at-rest" clean area classification after a short clean-up time. The clean-up time should be determined through validation and is generally of the order of 20 minutes.

4.1.11 Materials and products should be protected from contamination and cross-contamination during all stages of manufacture (see also section 4.5 for cross-contamination control).

Note: contaminants may result from inappropriate premises (e.g. poor design, layout or finishing), poor cleaning procedures, contaminants brought in by personnel, poor manufacturing process and a poor HVAC system.

Figure 2
“As-built” condition

Figure 3
“At-rest” condition

Figure 4
"Operational" condition

4.1.12 Airborne contaminants should be controlled through effective ventilation and filtration.

4.1.13 External contaminants should be removed by effective filtration of the supply air (see Figure 5 for an example of a shell-like building layout to enhance containment and protection from external contaminants).

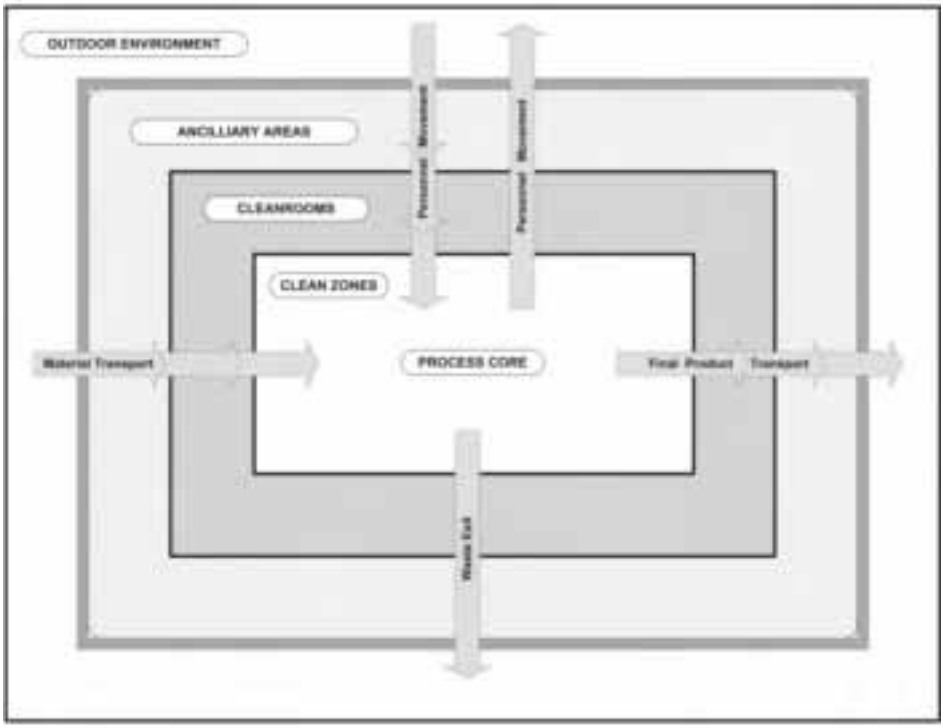
4.1.14 Internal contaminants should be controlled by dilution and flushing of contaminants in the room, or by displacement airflow (See Figures 6 and 7 for examples of methods for the flushing of airborne contaminants).

4.1.15 Airborne particulates and the degree of filtration should be considered critical parameters with reference to the level of product protection required.

4.1.16 Personnel should not be a source of contamination.

4.1.17 The level of protection and air cleanliness for different areas should be determined according to the product being manufactured, the process being used and the product's susceptibility to degradation (Table 1).

Figure 5
Shell-like containment control concept



4.2 Air filtration

Note: The degree to which air is filtered plays an important role in the prevention of contamination and the control of cross-contamination.

4.2.1 The type of filters required for different applications depends on the quality of the ambient air and the return air (where applicable) and also on the air change rates. Table 2 gives the recommended filtration levels for different levels of protection in a pharmaceutical facility. Manufacturers should determine and prove the appropriate use of filters.

4.2.2 Filter classes should always be linked to the standard test method because referring to actual filter efficiencies can be very misleading (as different test methods each result in a different value for the same filter). (Referring to filter classifications such as an 85% filter or a 5 μm filter are not valid classifications and should not be used, as this can lead to the incorrect filter being installed. Only the EN 779 and EN 1822 classifications, as per the table below, should be used.)

Figure 6
Turbulent dilution of dirty air

Low-level extract is ideal for dust suppression purposes, but is not essential. (Low-level extract is essential for Grade A, B & C areas.)

Figure 7
Unidirectional displacement of dirty air

Table 1

Examples of levels of protection (based on ISPE oral solid dosage (OSD) Guideline criteria)

Level	Condition	Example of area
Level 1	General	Area with normal housekeeping and maintenance where there is no potential for product contamination, e.g. warehousing.
Level 2	Protected	Area in which steps are taken to protect the pharmaceutical starting material or product from direct or indirect contamination or degradation, e.g. secondary packing, warehousing, first stage change rooms.
Level 3	Controlled	Area in which specific environmental conditions are defined, controlled and monitored to prevent contamination or degradation of the pharmaceutical starting material or product, e.g. where product, starting materials and components are exposed to the room environment; plus equipment wash and storage areas for equipment product contact parts.

Table 2

Levels of protection and recommended filtration

Level of protection	Recommended filtration
Level 1	Primary filters only (e.g. EN 779 G4 filters)
Level 2	Protected areas operating on 100% outside air: primary plus secondary filters (e.g. EN 779 G4 plus F8 or F9 filters)
Level 3	Production facility operating on recirculated plus ambient air, where potential for cross-contamination exists: Primary plus secondary plus tertiary filters (e.g. EN 779 G4 plus F8 plus EN 1822 H13 filters) (for full fresh air system, without recirculation, G4 and F8 or F9 filters are acceptable)

Note: The filter classifications referred to above relate to the EN 1822 and EN 779 test standards (EN 779 relates to filter classes G1 to F9 and EN 1822 relates to filter classes E10 to U17). Refer to Figure 8 for comparative classifications of other filter standards.

4.2.3 In selecting filters, the manufacturer should have considered other factors, such as particularly contaminated ambient conditions, local regulations and specific product requirements. Good pre-filtration extends the life of the more expensive filters downstream.

4.2.4 Materials for components of an HVAC system should be selected with care so that they do not become a source of contamination. Any component with the potential for liberating particulate or microbial contamination into the air stream should be located upstream of the final filters.

Figure 8

Comparison of filter test standards

Eurovent 4/5 Rating	ASHRAE 52.2	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	EN 779 & EN 1822		
(superseded)	Merv Rating	Average Arrestance A_m (%)	Average Dust Spot Efficiency E_m (%)	MPPS Integral Overall Efficiency (%)	EN Rating	
				99.999995	U17	EN 1822: 2009
				99.99995	U16	
EU 14				99.9995	U15	
EU 13	Merv 18			99.995	H14	
EU 12	Merv 17			99.95	H13	
EU 11				99.5	E12	
EU 10				95	E11	
EU 9	Merv 16		>95	85	E10	
EU 9	Merv 15		95		F9	EN779: 2002
EU 8	Merv 14		90		F8	
	Merv 13	>98	85	MPPS = Most Penetrating Particle Size	F7	
EU 7		>98	80			
	Merv 12	>95	75			
EU 6		>95	70		F6	
	Merv 11	>95	65			
		>95	60			
	Merv 10	>95	55			
EU 5	Merv 9	>95	50		F5	
	Merv 8	>95	45			
		>95	40			
	Merv 7	>90	35			
EU 4		>90	30		G4	
	Merv 6	90	25			
EU 3	Merv 5	85	20		G3	
		80	<20			
	Merv 4	75				
EU 2	Merv 3	70			G2	
	Merv 2	65				
EU 1	Merve 1	<65			G1	

4.2.5 Where possible ventilation dampers, filters and other services should be designed and positioned so that they are accessible from *outside* the manufacturing areas (service voids or service corridors) for maintenance purposes.

4.2.6 Directional airflow within production or primary packing areas should assist in preventing contamination. Airflows should be planned in conjunction with operator locations, so as to minimize contamination of the product by the operator and also to protect the operator from dust inhalation.

4.2.7 HVAC air distribution components should be designed, installed and located to prevent contaminants generated within the room from being spread.

4.2.8 Supply air diffusers should be selected with care taking consideration of, e.g. room requirements and positions of equipment and operators in the room. Supply air diffusers of the high induction type (e.g. those typically used for office-type air-conditioning) should where possible not be used in clean areas where dust is liberated. Air diffusers should be of the non-induction type, introducing air with the least amount of induction so as to maximize the flushing effect. In rooms where the process results in high dust liberation; perforated plates or low induction swirl diffusers with low level extract or return should be used (to contain the dust at the lower level of the room) (see Figures 9–11 for illustrations of the three types of diffuser). In cases where dust liberation is low, ceiling return air grilles may be acceptable.

4.2.9 Induction and certain swirl diffusers induce room air vertically up to the diffuser to mix with the supply air. These diffusers create good dilution of contaminants in the room and may be used in rooms where there is low dust liberation. However, if used in rooms where excessive dust is generated, the distribution of dust in the room could be hazardous for the operators in the room.

4.3 Unidirectional airflow

4.3.1 Unidirectional airflow (UDAF) should be used for weighing booths or sampling booths to provide operator and product protection and should also have a slight air in-flow from the room to enhance containment. Dust containment at the weigh booth should be demonstrated by smoke airflow pattern tests, or other appropriate tests. UDAF can also be used to provide protection of other dusty processes.

4.3.2 Sampling of materials such as starting materials, primary packaging materials and products, should be carried out in the same environmental conditions that are required for the further processing of the product.

Figure 9
Induction diffuser

Figure 10
Perforated plate diffuser

Figure 11
Swirl diffuser

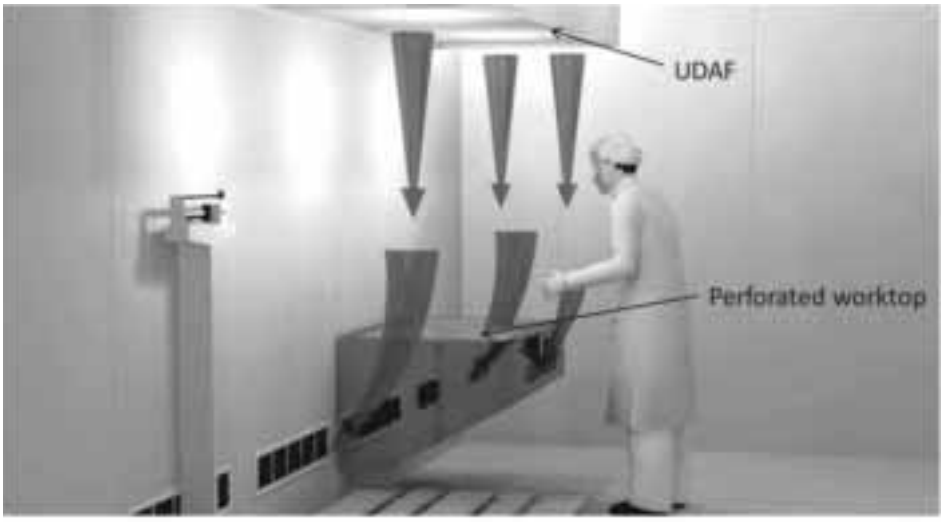
4.3.3 In a weighing booth situation, the aim of the UDAF is to provide dust containment and operator protection.

Example: In Figure 12 the dust generated at the weighing station is immediately extracted through the perforated worktop, thus protecting the operator from dust inhalation, but at the same time protecting the product from contamination by the operator by means of the vertical unidirectional airflow stream.

4.3.4 The unidirectional flow velocity should be such that it does not disrupt the sensitivity of balances in weighing areas. Where necessary the velocity may be reduced to prevent inaccuracies during weighing, provided that sufficient airflow is maintained to provide containment. Conventional unidirectional airflow systems, where a Grade A condition is required, have a guidance airflow velocity of 0.36 to 0.54 m/s. However, in a weigh booth or sampling booth a lower velocity can be used as a Grade A condition is not required. It is often necessary to reduce velocities to a lower level in order not to influence balance readings. The airflow velocity and directional flow should still ensure product containment. For this type of application it is sometimes better to refer to the unit as an airflow protection booth (APB) rather than a UDAF, in order to avoid confusion, with a Grade A requirement.

4.3.5 The position in which the operator stands relative to the source of dust liberation and airflow should be determined to ensure that the operator is not in the path of an airflow that could lead to contamination of the product (Figure 13).

Figure 12
Operator protection at weighing station



4.3.6 Once the system has been designed and qualified with a specific layout for operators and processes, this should be maintained in accordance with an SOP.

4.3.7 There should be no obstructions in the path of a unidirectional flow air stream that may cause the operator to be exposed to dust.

Figure 14 illustrates the incorrect use of a weighing scale which has a solid back. The back of the weighing scale should not block the return air path as this causes air to rise vertically, resulting in a hazardous situation for the operator.

Figure 15 illustrates a situation where an open bin is placed below a vertical unidirectional flow distributor. The downward airflow should be prevented from entering the bin, and then being forced to rise again, as this would carry dust up towards the operator's face. In such an occurrence it may be necessary to add a partial cover over the bin to limit the entry of air. Point extraction could also be used but this can result in the excessive loss of product.

Figure 16 shows that a solid worktop can sometimes cause deflection of the vertical unidirectional airflow resulting in a flow reversal. A possible solution would be to have a 100 mm gap between the back of the table and the wall, with the air being extracted here.

Figure 13
Operator protection by horizontal airflow

4.3.8 The manufacturer should select either vertical or horizontal unidirectional flow (Figure 17) and an appropriate airflow pattern to provide the best protection for the particular application.

4.3.9 Return or exhaust air grilles in rooms or at weigh or sampling booths should preferably be of the perforated grille types, which are easy to clean. Return/exhaust air filters can either be installed at the room terminal or in the air-handling unit. Maintenance and cleaning of filters and ducts should be addressed to ensure constant airflow.

4.4 Infiltration

4.4.1 Air infiltration of unfiltered air into a pharmaceutical plant should not be a source of contamination.

Figure 14

Operator subject to powder inhalation due to obstruction

Figure 15

Operator subject to powder contamination due to airflow reversal in bin

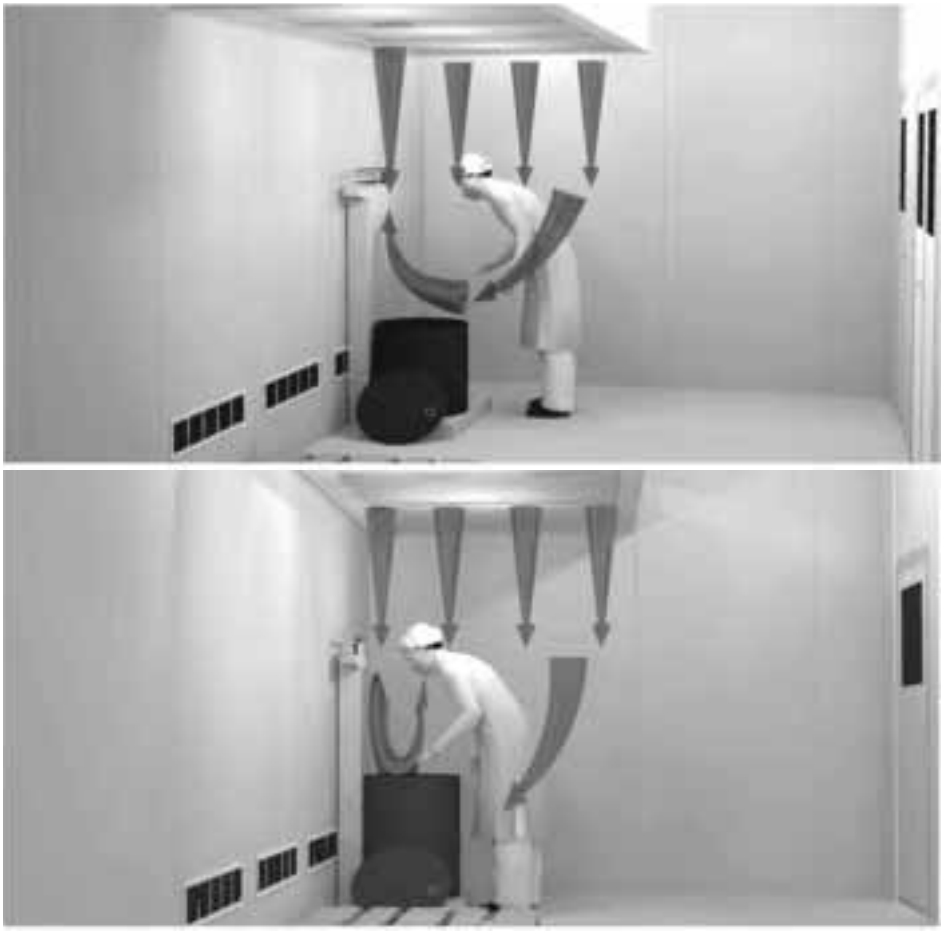


Figure 16
Operator subject to powder inhalation due to worktop obstruction

4.4.2 Manufacturing facilities should normally be maintained at a positive pressure relative to the outside, to limit the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to the ambient pressure, special precautions should be taken. Refer to the WHO guideline for hazardous products, for further guidance on negative pressure facilities.

4.4.3 The location of the negative pressure facility should be carefully considered with reference to the areas surrounding it, particular attention being given to ensuring that the building structure is well sealed.

4.4.4 Negative pressure zones should, as far as possible, be encapsulated by surrounding areas with clean air supplies, so that only clean air can infiltrate into the controlled zone.

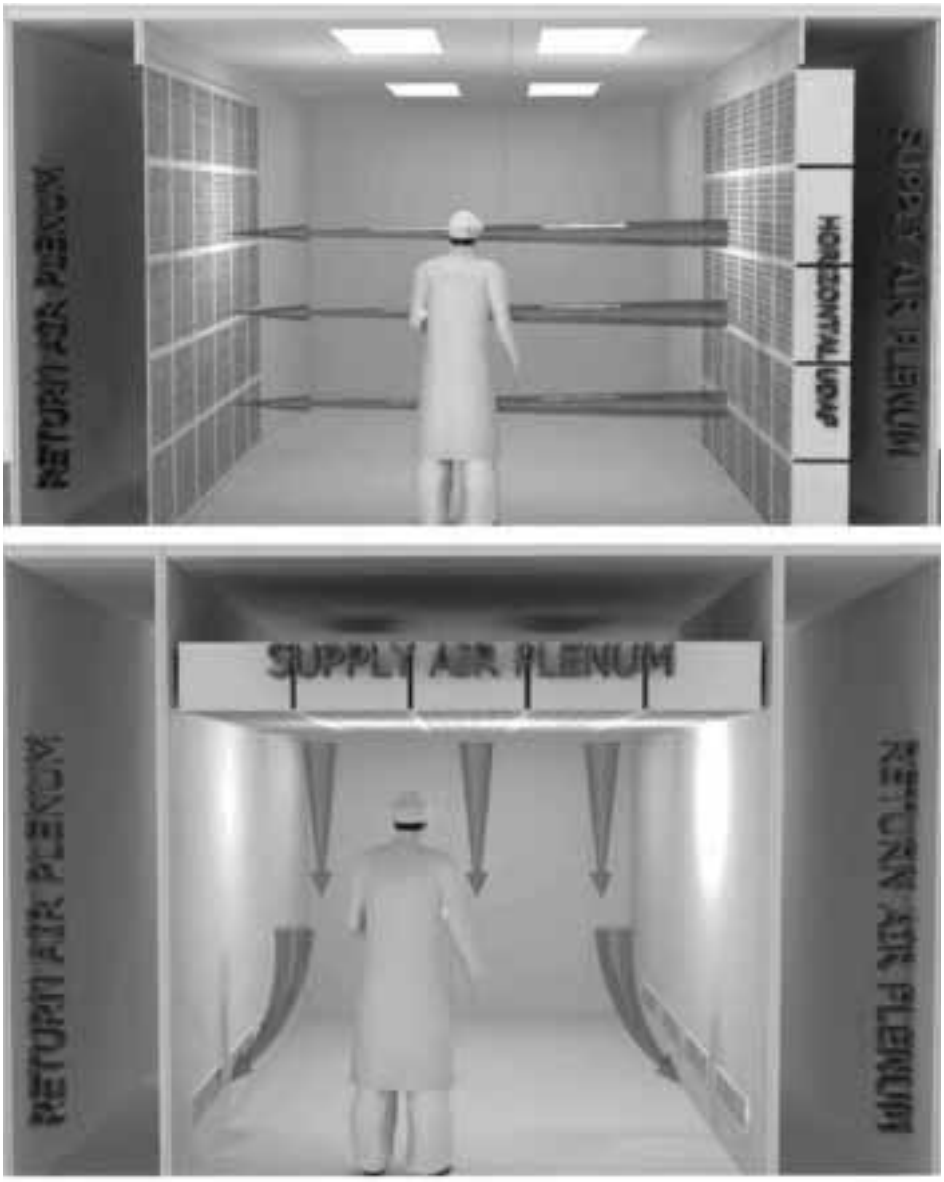
4.5 Cross-contamination

4.5.1 Where different products are manufactured at the same time, in different areas or cubicles, in a multiproduct OSD manufacturing site, measures should be taken to ensure that dust cannot move from one cubicle to another.

4.5.2 Correct directional air movement and a pressure cascade system can assist in preventing cross-contamination. The pressure cascade should be such that the direction of airflow is from the clean corridor into the cubicles, resulting in dust containment.

4.5.3 The corridor should be maintained at a higher pressure than the cubicles, and the cubicles at a higher pressure than atmospheric pressure.

Figure 17
Diagram indicating horizontal and vertical unidirectional flow



4.5.4 Containment can normally be achieved by application of the displacement concept (low pressure differential, high airflow), or the pressure differential concept (high pressure differential, low airflow), or the physical barrier concept.

4.5.5 The pressure cascade regime and the direction of airflow should be appropriate to the product and processing method used.

4.5.6 Highly potent products should be manufactured under a pressure cascade regime that is negative relative to atmospheric pressure.

4.5.7 The pressure cascade for each facility should be individually assessed according to the product handled and level of protection required.

4.5.8 Building structure should be given special attention to accommodate the pressure cascade design.

4.5.9 Ceilings and walls, close fitting doors and sealed light fittings should be in place, to limit ingress or egress of air.

4.6 Displacement concept (low pressure differential, high airflow)

Note: This method of containment is not the preferred method, as the measurement and monitoring of airflow velocities in doorways is difficult. This concept is commonly found in production processes where large amounts of dust are generated.

4.6.1 Under this concept the air should be supplied to the corridor, flow through the doorway, and be extracted from the back of the cubicle. Normally the cubicle door should be closed and the air should enter the cubicle through a door grille, although the concept can be applied to an opening without a door.

4.6.2 The velocity should be high enough to prevent turbulence within the doorway resulting in dust escaping.

4.6.3 This displacement airflow should be calculated as the product of the door area and the velocity, which generally results in fairly large air quantities.

Note: Although this method of containment may still exist on older facilities, it is not the preferred method, as the measurement and monitoring of doorway velocities is difficult. In addition, simultaneously maintaining the correct room pressure and the correct room air change rate is often not achieved.

4.7 Pressure differential concept (high pressure differential, low airflow)

Note: The pressure differential concept may normally be used in zones where little or no dust is being generated. It may be used alone or in combination with other containment control techniques and concepts, such as a double door airlock.

4.7.1 The high pressure differential between the clean and less clean zones should be generated by leakage through the gaps of the closed doors to the cubicle.

4.7.2 The pressure differential should be of sufficient magnitude to ensure containment and prevention of flow reversal, but should not be so high as to create turbulence problems.

4.7.3 In considering room pressure differentials, transient variations, such as machine extract systems, should be taken into consideration.

4.7.4 A pressure differential of 15 Pa is often used for achieving containment between two adjacent zones, but pressure differentials of between 5 Pa and 20 Pa may be acceptable. Where the design pressure differential is too low and tolerances are at opposite extremities, a flow reversal can take place. For example, where a control tolerance of ± 3 Pa is specified, the implications of rooms being operated at the upper and lower tolerances should be evaluated. It is important to select pressures and tolerances such that a flow reversal is unlikely to occur.

4.7.5 The pressure differential between adjacent rooms could be considered a critical parameter, depending on the outcome of risk analysis. The limits for the pressure differential between adjacent areas should be such that there is no risk of overlap in the acceptable operating range, e.g. 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in the failure of the pressure cascade, where the first room is at the maximum pressure limit and the second room is at its minimum pressure limit.

4.7.6 Low pressure differentials may be acceptable when airlocks (pressure sinks or pressure bubbles) are used to segregate areas.

4.7.7 The effect of room pressure tolerances are illustrated in Figure 18.

4.7.8 The pressure control and monitoring devices used should be calibrated and qualified. Compliance with specifications should be regularly verified and the results recorded. Pressure control devices should be linked to an alarm system set according to the levels determined by a risk analysis.

4.7.9 Manual control systems, where used, should be set up during commissioning, with set point marked, and should not change unless other system conditions change.

4.7.10 Airlocks can be important components in setting up and maintaining pressure cascade systems and also to limit cross-contamination.

4.7.11 Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock (Figures 19–21):

- cascade airlock: higher pressure on one side of the airlock and lower pressure on the other;
- sink airlock: lower pressure inside the airlock and higher pressure on both outer sides;

Figure 18

Examples of pressure cascades

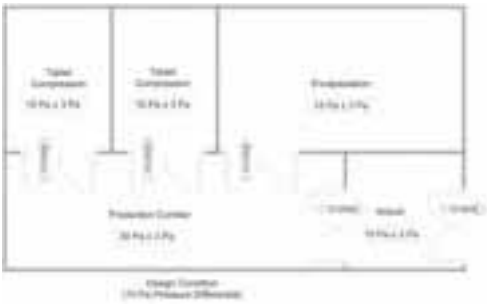


Image of room pressure gauge indicating colour coded normal, alert & action parameters

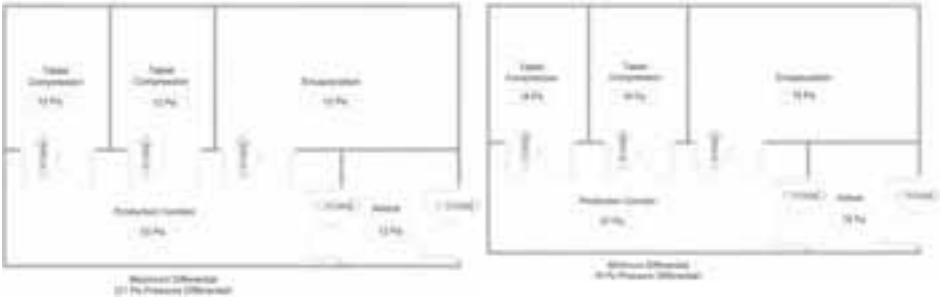


Figure 19

Example of cascade airlock

(In most cases the internal pressure of the airlock is not critical. The pressure differential between the two outer sides is the important criteria.)

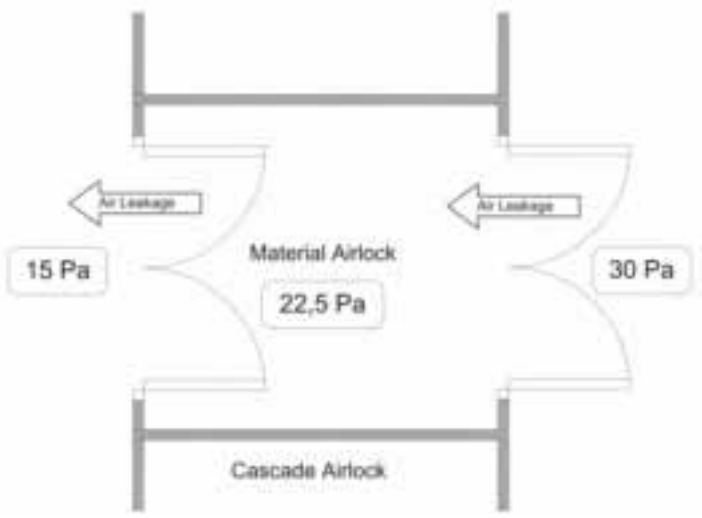


Figure 20
Example of sink airlock

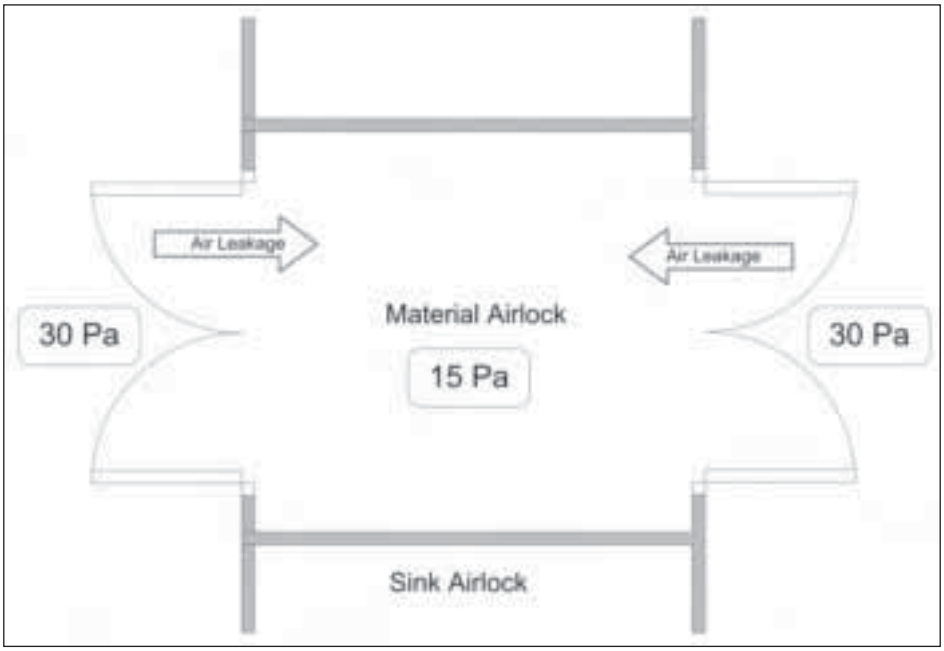
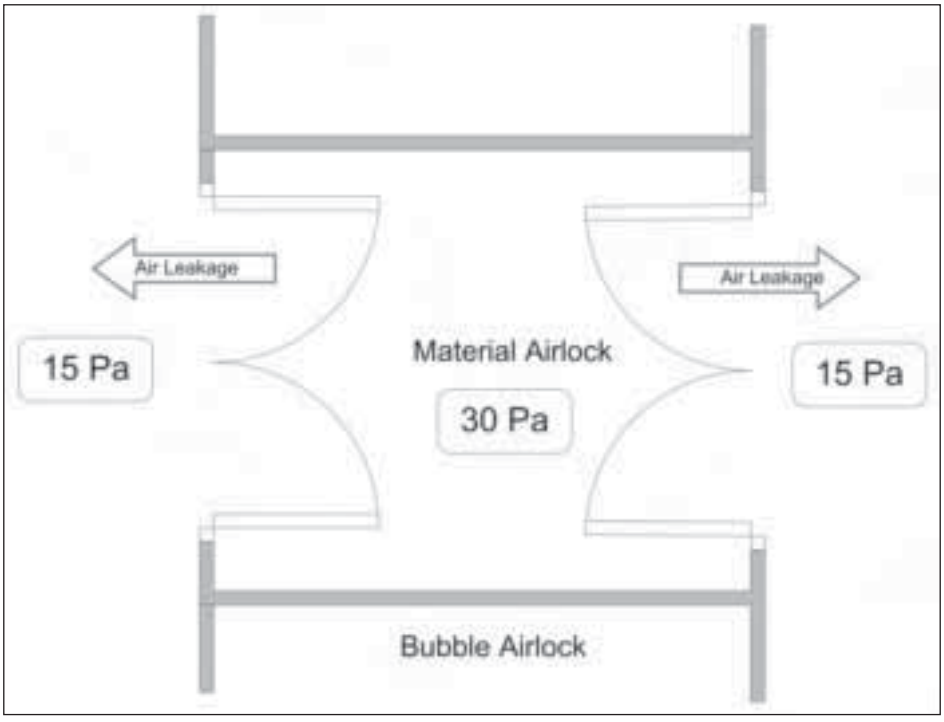


Figure 21
Example of bubble airlock



- bubble airlock: higher pressure inside the airlock and lower pressure on both outer sides.

Note: The diagrams above and the differential pressures shown here are for illustration purposes only. Pressures indicated in these examples are absolute pressures, whereas the local pressure indication would most likely be pressure differential from room to room.

4.7.12 Doors should open to the high pressure side, so that room pressure assists in holding the door closed and in addition be provided with self-closers. Should the doors open to the low pressure side, the door closer springs should be sufficient to hold the door closed and prevent the pressure differential from pushing the door open. There should be a method to indicate if both doors to airlocks are open at the same time, or alternatively these should be interlocked. The determination of which doors should be interlocked should be the subject of a risk assessment study.

4.7.13 Central dust extraction systems should be interlocked with the appropriate air-handling systems, to ensure that they operate simultaneously.

4.7.14 Room pressure differential between adjacent cubicles, which are linked by common dust extraction ducting, should be avoided.

4.7.15 Air should not flow through the dust extraction ducting or return air ducting from the room with the higher pressure to the room with the lower pressure (this would normally occur only if extract or return systems were inoperative). Systems should be designed to prevent dust flowing back in the opposite direction in the event of component failure or airflow failure.

4.7.16 Adequate room pressure differential indication should be provided so that each critical room pressure can be traced back to ambient pressure (by summation of the room pressure differentials), in order to determine the room actual absolute pressure. Room pressure indication gauges should have a range and graduation scale which enables the reading to an accuracy, as appropriate; normal operating range, alert and action limits should be defined and displayed at the point of indication. A colour coding gauge may be helpful.

Room pressure indication may be either analogue or digital, and may be represented as either pressure differentials or absolute pressures. Which ever system is used any out-of-specification condition should be easily identifiable.

4.7.17 Material pass-through-hatches (PTH) or pass boxes (PB) can also be used for separating two different zones. PTHs fall into two categories, namely a dynamic PTH or a passive PTH. Dynamic PTHs have an air supply to or extraction from them, and can then be used as bubble, sink or cascade PTHs.

4.8 Physical barrier concept

4.8.1 Where appropriate, an impervious barrier to prevent cross-contamination between two zones, such as closed systems, pumped or vacuum transfer of materials, should be used.

4.9 Temperature and relative humidity

4.9.1 Where appropriate, temperature and relative humidity should be controlled, monitored and recorded, where relevant, to ensure compliance with requirements pertinent to the materials and products and provide a comfortable environment for the operator where necessary.

4.9.2 Maximum and minimum room temperatures and relative humidity should be appropriate. Alert and action limits on temperatures and humidities should be set, as appropriate.

4.9.3 The operating band, or tolerance, between the acceptable minimum and maximum temperatures should not be made too close. Tight control tolerances may be difficult to achieve and can also add unnecessary installation and running costs.

4.9.4 Cubicles, or suites, in which products requiring low relative humidity are processed, should have well-sealed walls and ceilings and should also be separated from adjacent areas with higher relative humidity by means of suitable airlocks.

4.9.5 Precautions should be taken to prevent moisture migration that increases the load on the HVAC system.

4.9.6 Humidity control should be achieved by removing moisture from the air, or adding moisture to the air, as relevant.

4.9.7 Dehumidification (moisture removal) may be achieved by means of either refrigerated dehumidifiers or chemical dehumidifiers.

4.9.8 Appropriate cooling media for dehumidification such as low temperature chilled water/glycol mixture or refrigerant should be used.

4.9.9 Humidifiers should be avoided if possible as they may become a source of contamination (e.g. microbiological growth). Where humidification is required, this should be achieved by appropriate means such as the injection of steam into the air stream. A product-contamination assessment should be done to determine whether pure or clean steam is required for the purposes of humidification.

4.9.10 Where steam humidifiers are used, chemicals such as corrosion inhibitors or chelating agents, which could have a detrimental effect on

the product, should not be added to the boiler system. Only appropriate additives should be added to the boiler system.

4.9.11 Humidification systems should be well drained. No condensate should accumulate in air-handling systems.

4.9.12 Other humidification appliances such as evaporative systems, atomizers and water mist sprays, should not be used because of the potential risk of microbial contamination.

4.9.13 Duct material in the vicinity of the humidifier should not add contaminants to air that will not be removed by filtration further downstream.

4.6.14 Air filters should not be installed immediately downstream of humidifiers, as moisture on the filters could lead to bacterial growth.

4.9.15 Cold surfaces should be insulated to prevent condensation within the clean area or on air-handling components.

4.9.16 When specifying relative humidity, the associated temperature should also be specified.

4.9.17 Chemical driers using silica gel or lithium chloride are acceptable, provided that they do not become sources of contamination.

5. Dust control

5.1 Wherever possible, dust or vapour contamination should be removed at source. Point-of-use extraction, i.e. as close as possible to the point where the dust is generated, should be employed. Spot ventilation or capture hoods may be used as appropriate.

5.2 Point-of-use extraction should be either in the form of a fixed high velocity extraction point or an articulated arm with movable hood or a fixed extraction hood.

5.3 Dust extraction ducting should be designed with sufficient transfer velocity to ensure that dust is carried away, and does not settle in the ducting. Periodic checks should be performed to ensure that there is no build up of the dust in the ducting.

5.4 The required transfer velocity should be determined: it is dependent on the density of the dust (the denser the dust, the higher the transfer velocity should be, e.g. 15–20 m/s).

5.5 Airflow direction should be carefully chosen, to ensure that the operator does not contaminate the product, and also so that the operator is not put at risk by the product.

5.6 Point extraction alone is usually not sufficient to capture all of the contaminants, and general directional airflow should be used to assist in removing dust and vapours from the room.

5.7 Typically, in a room operating with turbulent airflow, the air should be introduced from ceiling diffusers, located at the door entry side of the room and extracted from the rear of the room at low level to help give a flushing effect in the room. Correct flushing of the rooms may be verified by airflow visualization smoke tests.

5.8 When dealing with particularly harmful products, additional steps, such as handling the products in glove boxes or using barrier isolator technology, should be used.

6. Protection of the environment

6.1 General

6.1.1 It should be noted that protection of the environment is not addressed in this guideline, and discharges into the atmosphere should be compliant with relevant local and national environmental legislation and standards.

6.1.2 Dust, vapours and fumes could be possible sources of contamination; therefore, care should be taken when deciding on the location of the inlet and exhaust points relative to one other.

6.2 Dust in exhaust air

6.2.1 Exhaust air discharge points on pharmaceutical equipment and facilities, such as from fluid bed driers and tablet-coating equipment, and exhaust air from dust extraction systems, carry heavy dust loads and should be provided with adequate filtration to prevent contamination of the ambient air.

6.2.2 Where the powders are not highly potent, final filters on a dust exhaust system should be fine dust filters with a filter classification of F9 according to EN 779 filter standards.

6.2.3 Where reverse-pulse dust collectors are used for removing dust from dust extraction systems, they should usually be equipped with cartridge filters containing a compressed air lance, and be capable of continuous operation without interrupting the airflow.

6.2.4 Alternative types of dust collectors (such as those operating with a mechanical shaker, requiring that the fan be switched off when the mechanical shaker is activated) should be used in such a manner that there is no risk of cross-contamination. There should be no disruption of airflow during a production run as the loss of airflow could disrupt the pressure cascade.

6.2.5 Mechanical-shaker dust collectors should not be used for applications where continuous airflow is required, in order to avoid unacceptable fluctuations in room pressures, except in the case where room pressures are automatically controlled.

6.2.6 When wet scrubbers are used, the dust-slurry should be removed by a suitable means, e.g. a drainage system or waste removal contractor.

6.2.7 The quality of the exhaust air should be determined to see whether the filtration efficiency is adequate with all types of dust collectors and wet scrubbers.

6.2.8 Where necessary, additional filtration may be provided downstream of the dust collector.

6.3 Vapour and fume removal

6.3.1 Vapour should be extracted at the point of generation. When planning the system for the extraction of residual vapours, the density of the vapour should be taken into account. If the vapour is lighter than air, the extract grilles should be at a high level, or possibly at both high and low levels.

6.3.2 The systems for fume, dust and effluent control should be designed, installed and operated in such a manner that they do not become possible sources of contamination or cross-contamination, e.g. an exhaust-air discharge point located close to the HVAC system fresh air inlet.

6.3.3 Fumes should be removed by means of wet scrubbers or dry chemical scrubbers (deep-bed scrubbers).

6.3.4 Wet scrubbers for fume removal normally require the addition of various chemicals to the water to increase the adsorption efficiency.

6.3.5 Deep-bed scrubbers should be designed with activated carbon filters or granular chemical adsorption media. The chemical media for deep-bed scrubbers should be specific to the effluent being treated.

6.3.6 The type and quantity of the vapours to be removed should be known to enable the appropriate filter media, as well as the volume of media required to be determined.

7. Design of HVAC systems and components

7.1 General

7.1.1 The required degree of air cleanliness in most OSD manufacturing facilities can normally be achieved without the use of high-efficiency particulate air (HEPA) filters, provided the air is not recirculated or

in the case of a single-product facility. Many open product zones of OSD form facilities are capable of meeting ISO 14644-1 Class 8 or Grade D, "at-rest" condition, measured against particle sizes of 0.5 ìm and 5 ìm, but cleanliness may not necessarily be classified as such by manufacturers.

A risk assessment should be carried out to determine the cleanroom conditions required and the extent of validation required.

7.1.2 There are two basic concepts of air delivery to pharmaceutical production facilities: a recirculation system, and a full fresh air system (100% outside air supply). For recirculation systems the amount of fresh air should not be determined arbitrarily on a percentage basis, but, for example, by the following criteria:

- sufficient fresh air to compensate for leakage from the facility and loss through exhaust air systems;
- sufficient fresh air to comply with national building regulations; and[2]
- sufficient fresh air for odour control.

7.1.3 Where automated monitoring systems are used, these should be capable of indicating any out-of-specification condition without delay by means of an alarm or similar system. Sophisticated computer-based data monitoring systems may be installed, which can aide with planning of preventive maintenance and can also provide trend logging.

(This type of system is commonly referred to as a building management system (BMS), building automation system (BAS) or system control and data acquisition (SCADA) system.) If these systems are used for critical decision-making, they should be validated.

7.1.4 Failure of a supply air fan, return air fan, exhaust air fan or dust extract system fan can cause a system imbalance, resulting in a pressure cascade malfunction with a resultant airflow reversal.

7.1.5 All critical alarms should be easily identifiable and visible and/or audible to relevant personnel.

7.1.6 Appropriate alarm systems should be in place to alert personnel if a critical fan fails. A fan interlock failure matrix should be set up, such that if a fan serving a high pressure zone fails, then any fans serving surrounding lower pressure areas should automatically stop, to prevent an airflow reversal and possible cross-contamination.

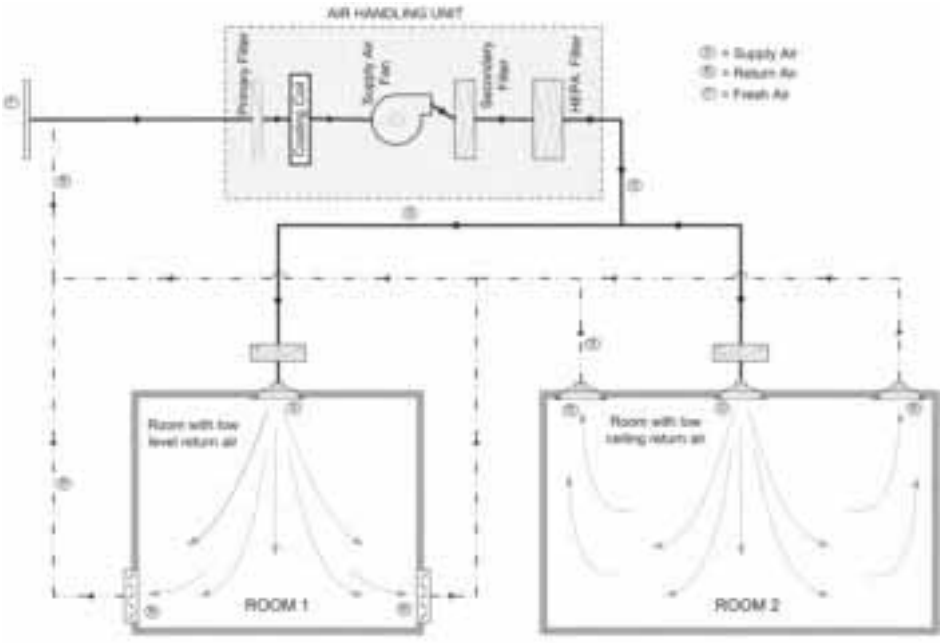
[2] Depending on occupant density, between 1 and ACPH will often satisfy occupancy requirements.

7.2 Air distribution

7.2.1 The positioning of supply and extract grilles should be such as to provide effective room flushing. Low-level return or exhaust air grilles are usually preferred. However, where this is not possible, a higher air change rate may be needed to achieve a specified clean area condition, e.g. where ceiling return air grilles are used.

7.2.2 There may be alternative locations for return air. For example, referring to Figure 22, Room 1 (low-level return air) and Room 2 (ceiling return air). The airflow diagram in Figure 22 is an example of a typical system with a lower clean area condition.

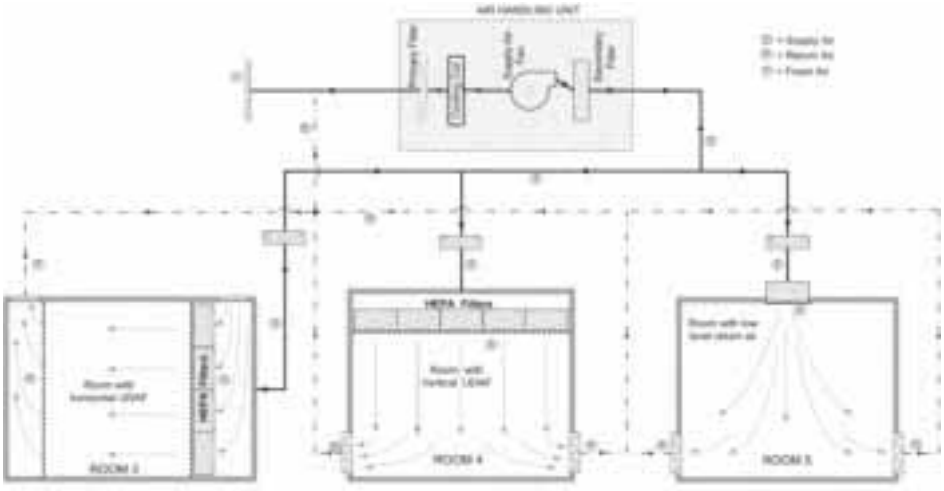
Figure 22
Air-handling system with high-efficiency particulate air filters in air-handling unit



The airflow schematics of the two systems (Figures 22 and 23) indicate air-handling units with return air or recirculated air, having a percentage of fresh air added. Depending on product characteristics and dust loading it is sometimes preferable to fit filters on return air outlets or in return air ducting.

Figure 23 is a schematic diagram of an air-handling system serving rooms with horizontal unidirectional flow, vertical unidirectional flow and turbulent flow, for rooms 3, 4 and 5, respectively.

Figure 23
Horizontal unidirectional flow, vertical unidirectional flow and turbulent flow



7.3 Recirculation system

7.3.1 There should be no risk of contamination or cross-contamination (including by fumes and volatiles) due to recirculation of air.

7.3.2 Depending on the airborne contaminants in the return-air system it may be acceptable to use recirculated air, provided that HEPA filters are installed in the supply air stream (or return air stream) to remove contaminants and thus prevent cross-contamination. The HEPA filters for this application should have an EN 1822 classification of H13.

7.3.3 HEPA filters may not be required where the air-handling system is serving a single product facility and there is evidence that cross-contamination would not be possible.

7.3.4 Recirculation of air from areas where pharmaceutical dust is not generated such as secondary packing, may not require HEPA filters in the system.

7.3.5 HEPA filters may be located in the air-handling unit or placed terminally. Where HEPA filters are terminally mounted they should

preferably not be connected to the ducting by means of flexible ducting. Due to the high air pressure required for the terminal filter, this connection should preferably be a rigid duct connection. Where flexible ducting is used, it should be as short as possible and properly fixed to withstand duct pressure.

7.3.6 Air containing dust from highly toxic processes and/or solvents or flammable vapours should never be recirculated to the HVAC system.

7.4 Full fresh-air systems

Figure 24 indicates a system operating on 100% fresh air and would normally be used in a facility dealing with toxic products or solvents, where recirculation of air with contaminants should be avoided.

7.4.1 The required degree of filtration of the exhaust air depends on the exhaust air contaminants and local environmental regulations. HEPA filters in the exhaust system would normally only be required when handling hazardous materials.

Figure 24
Full fresh-air system

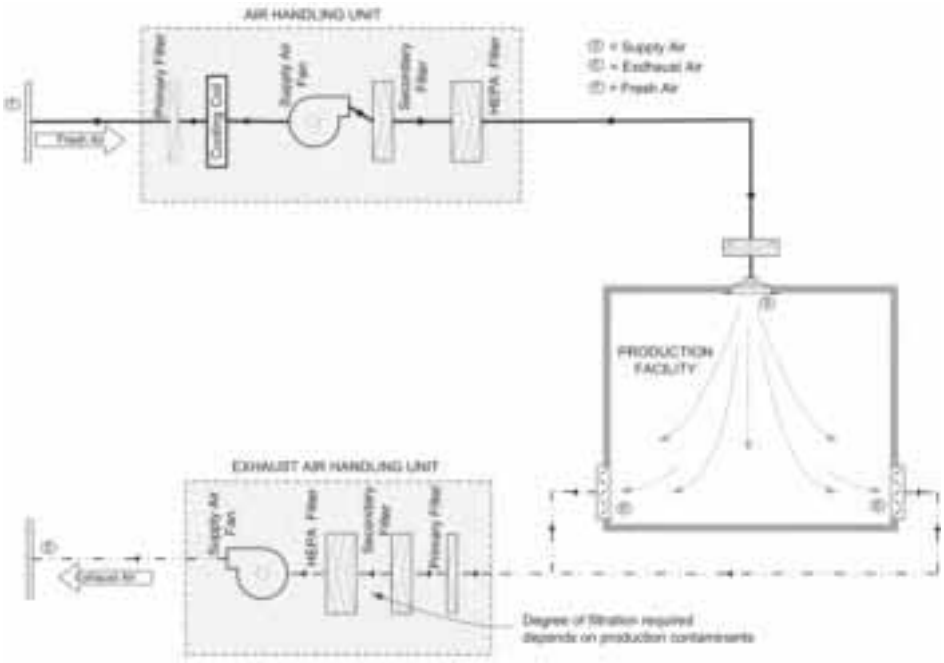
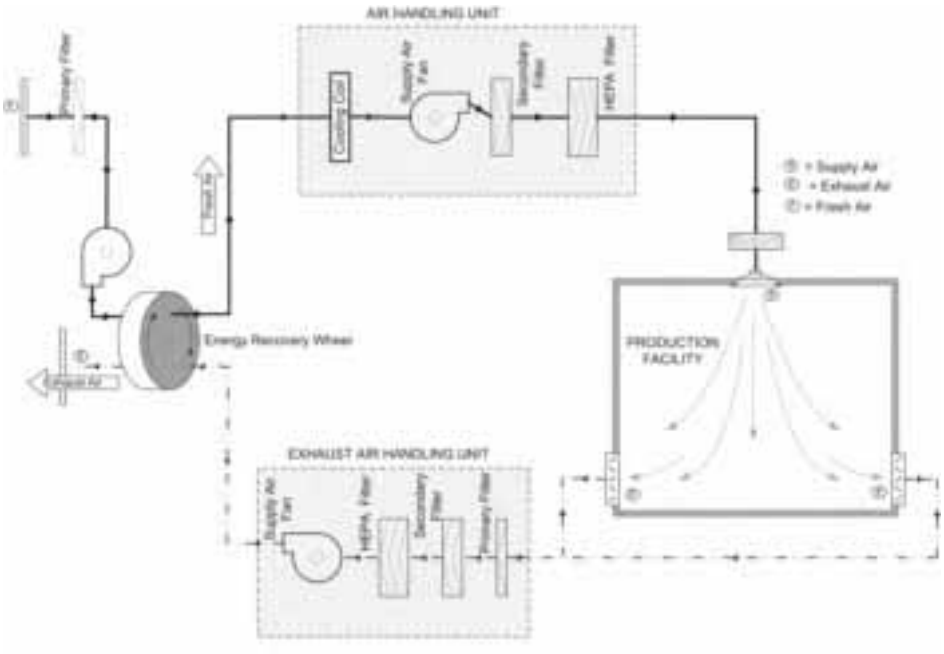


Figure 25
Full fresh-air system with energy recovery



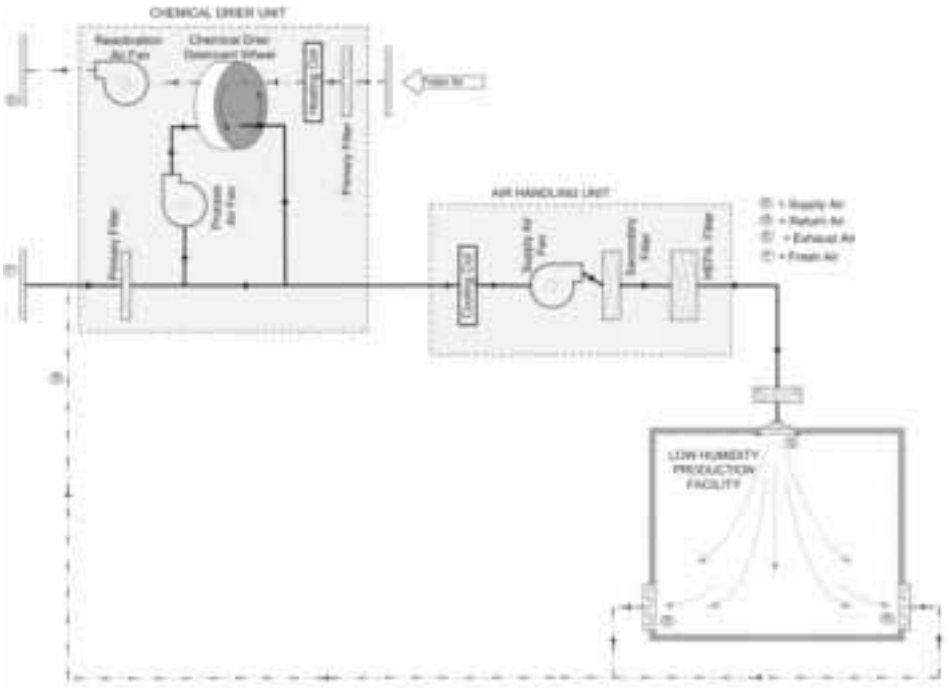
7.4.2 Energy-recovery wheels if used in multiproduct facilities should have been subjected to a risk assessment to determine if there is any risk of cross-contamination. When such wheels are used they should not become a source of possible contamination (see Figure 25). *Note*: *Alternatives to the energy-recovery wheels, such as crossover plate heat exchangers and water-coil heat exchangers, may be used in multiproduct facilities.*

7.4.3 The potential for air leakage between the supply air and exhaust air as it passes through the wheel should be prevented. The relative pressures between supply and exhaust air systems should be such that the exhaust air system operates at a lower pressure than the supply system.

7.5 Additional system components

7.5.1 A schematic diagram of the airflow for a typical system serving a low relative humidity suite is represented in Figure 26. Air can be dried with a chemical drier (e.g. a rotating desiccant wheel which is continuously regenerated by means of passing hot air through one segment of the wheel). Alternative methods of drying air are also available.

Figure 26
Air-handling system with chemical drying



7.5.2 The figure illustrates the chemical drier handling part of the fresh air/return air mixture on a bypass flow. The location of the chemical drier should be considered in the design phase. The practice of locating the complete chemical drier unit in the production cubicle is not recommended as this could be a source of contamination or cross-contamination. Examples of appropriate locations for the drying wheel could include:

— full flow of fresh/return air;
— partial handling of fresh/return air (bypass airflow);
— return air only;
— fresh air only; or
— pre-cooled air with any of the above alternatives.

7.5.3 Possible additional components that may be required in air handling should be considered depending on the climatic conditions and locations. These may include items such as:

— frost coils on fresh air inlets in very cold climates to preheat the air;
— reheaters for humidity control
— automatic air volume control devices
— sound attenuators

— snow eliminators to prevent snow entering air inlets and blocking airflow
— dust eliminators on air inlets in arid and dusty locations
— moisture eliminators in humid areas with high rainfall
— fresh air precooling coils for very hot or humid climates.

8. Commissioning, qualification and maintenance

8.1 Commissioning

8.1.1 Commissioning should include the setting up, balancing, adjustment and testing of the entire HVAC system, to ensure that it meets all the requirements, as specified in the user requirement specification (URS), and capacities as specified by the designer or developer. The commissioning plan should start at the early stages of a project so that it can be integrated with qualification and verification procedures.

8.1.2 The installation records of the system should provide documented evidence of all measured capacities of the system.

8.1.3 Acceptance criteria should be set for all system parameters. The measured data should fall within the acceptance criteria.

8.1.4 Acceptable tolerances for all system parameters should be specified prior to commencing the physical installation.

8.1.5 Training should be provided to personnel after installation of the system, and should include operation and maintenance.

8.1.6 Commissioning should be a precursor to system qualification and process validation.

8.2 Qualification

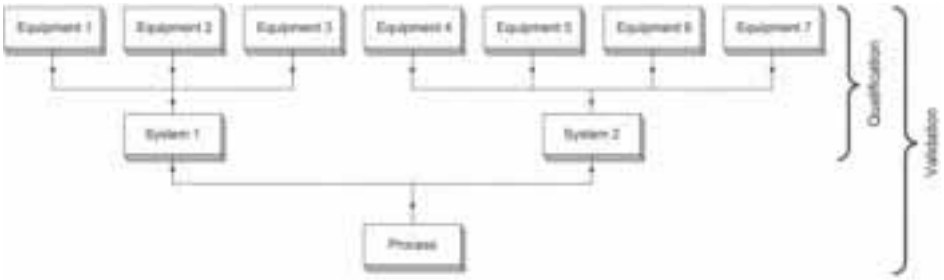
8.2.1 Validation is a many-faceted and extensive activity and is beyond the scope of these guidelines (*2*) (see also Figure 27).

A risk-based approach should be used to identify the extent to which the HVAC system requires qualification and verification. The basic concepts of qualification of HVAC systems are set out below.

8.2.2 The qualification of the HVAC system should be described in a validation master plan (VMP).

8.2.3 It should define the nature and extent of testing and the test procedures and protocols to be followed.

Figure 27
Qualification is a part of validation



8.2.4 Stages of the qualification of the HVAC system should include DQ, IQ, OQ and PQ.

8.2.5 Critical and non-critical parameters should be determined by means of a risk analysis for all HVAC installation components, subsystems and controls.

8.2.6 Any parameter that may affect the quality of the pharmaceutical product, or a direct impact component, should be considered a critical parameter.

8.2.7 All critical parameters should be included in the qualification process. *Note: A realistic approach to differentiating between critical and noncritical parameters is required, to avoid making the validation process unnecessarily complex.*

Example:

- *The relative humidity of the room where the product is exposed should be considered a critical parameter when a humidity-sensitive product is being manufactured. The humidity sensors and the humidity monitoring system should, therefore, be qualified. The heat transfer system, chemical drier or steam humidifier, which is producing the humidity controlled air, is further removed from the product and may not require operational qualification.*
- *A room cleanliness condition is a critical parameter and, therefore, the room air change rates and HEPA filters should be critical parameters and require qualification. Items such as the fan generating the airflow and the primary and secondary filters are non-critical parameters, and may not require operational qualification.*

8.2.8 Non-critical systems and components should be subject to GEP and may not necessarily require qualification.

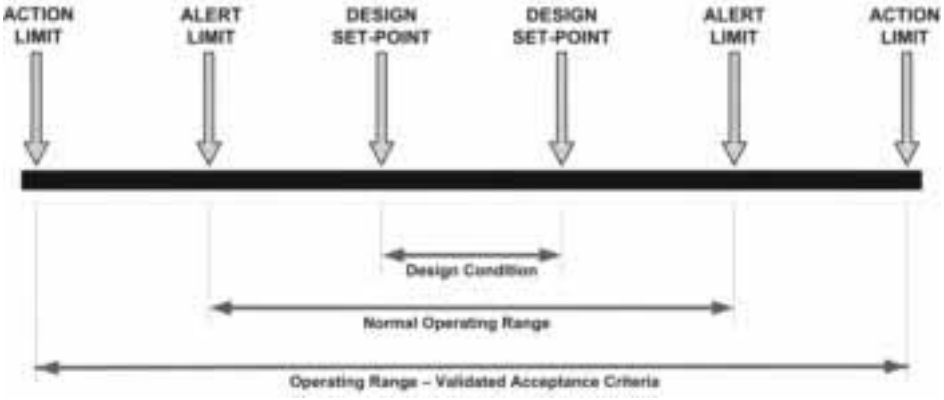
8.2.9 A change control procedure should be followed when changes are planned to the direct impact HVAC system, its components and controls that may affect critical parameters.

8.2.10 The design condition, normal operating ranges, operating range and alert and action limits should be defined and be realistic.

8.2.11 Out-of-limit results (e.g. action limit deviations) should be recorded and their impact should be investigated.

8.2.12 The relationships between design conditions, normal operating range and validated acceptance criteria (also known as proven acceptable range) are given in Figure 28.

Figure 28
System operating ranges



8.2.13 For a pharmaceutical facility, based on a risk assessment, some of the typical HVAC system parameters that should be qualified may include:

— temperature
— relative humidity
— supply air quantities for all diffusers
— return air or exhaust air quantities
— room air change rates
— room pressures (pressure differentials)
— room airflow patterns
— unidirectional flow velocities
— containment system velocities
— HEPA filter penetration tests

— room particle counts
— room clean-up rates
— microbiological air and surface counts where appropriate
— operation of de-dusting
— warning/alarm systems where applicable.

8.2.14 The maximum time interval between tests should be defined by the manufacturer. The type of facility under test and the product level of protection should be considered. Table 3 gives various tests that can be carried out. The required tests and intervals between testing should be determined through risk assessment.

Table 3
Tests to demonstrate compliance

Test parameter	Test procedure
Particle count test (Verification of cleanliness)	Dust particle counts to be carried out and result printouts produced. No. of readings and positions of tests to be in accordance with ISO 14644-1 Annex B5
Air pressure difference (To verify non cross-contamination)	Log of pressure differential readings to be produced or critical plants should be logged daily, preferably continuously. A 15 Pa pressure differential between different zones is recommended. In accordance with ISO 14644-3 Annex B5
Airflow volume (To verify air change rates)	Airflow readings for supply air and return air grilles to be measured and air change rates to be calculated. In accordance with ISO 14644-3 Annex B13
Airflow velocity (To verify unidirectional flow or containment conditions)	Air velocities for containment systems and unidirectional flow protection systems to be measured. In accordance with ISO 14644-3 Annex B4
Filter leakage tests (To verify filter integrity)	Filter penetration tests to be carried out by a competent person to demonstrate filter media, filter seal and filter frame integrity. Only required on HEPA filters. In accordance with ISO 14644-3 Annex B6
Containment leakage (To verify absence of cross-contamination)	Demonstrate that contaminant is maintained within a room by means of: • airflow direction smoke tests • room air pressures. In accordance with ISO 14644-3 Annex B4
Recovery (To verify clean-up time)	Test to establish time that a cleanroom takes to recover from a contaminated condition to the specified cleanroom condition. Should not take more than 15 min. In accordance with ISO 14644-3 Annex B13*

Test parameter	Test procedure
Airflow visualization (To verify required airflow patterns)	Tests to demonstrate air flows: • from clean to dirty areas • do not cause cross-contamination • uniformly from unidirectional airflow units Demonstrated by actual or video-taped smoke tests. In accordance with ISO 14644-3 Annex B7

8.2.15 Requalification should also be done when any change, which could affect system performance, takes place.

8.2.16 Clean-up or recovery times normally relate to the time it takes to "clean up" the room from one condition to another, e.g. the relationship between "at-rest" and "operational" conditions in the clean area may be used as the criteria for clean-up tests. Therefore, the clean-up time can be expressed as the time taken to change from an "operational" condition to an "at rest" condition.

8.2.17 If energy-saving procedures such as reducing the airflow during non-production hours are used, precautionary measures should be in place to ensure that the systems are not operated outside the defined relevant environmental conditions.

These precautionary measures should be based on a risk assessment to ensure that there is no negative impact on the quality of the product.

8.2.18 Documents that should be included in the qualification manuals should include system airflow schematics, room pressure cascade drawings, zone concept drawings, air-handling system allocation drawings, particle count mapping drawings, etc.

8.3 Maintenance

8.3.1 There should be a planned preventive maintenance programme, procedures and records for the HVAC system. Records should be kept.

8.3.2 Operating and maintenance (O&M) manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system. These documents should be kept up to date, containing any system revisions made.

8.3.3 Maintenance personnel should receive appropriate training.

8.3.4 HEPA filters should be changed either by a specialist or a trained person, and then followed by installed filter leakage testing.

8.3.5 Any maintenance activity should be assessed critically to determine any impact on product quality including possible contamination.

8.3.6 Maintenance activities should normally be scheduled to take place outside production hours, and any system stoppage should be assessed with a view to the possible need for requalification of an area as a result of an interruption of the service.

9. Premises

9.1 As the efficient operation of the air-handling system and cleanliness levels attained are reliant on the correct building layout and building finishes, the following items should be considered:

- adequate airlocks, such as personnel airlocks (PAL) and/or material airlocks (MAL), change rooms and passages should be provided to protect passage between different cleanliness conditions . These should have supply and extract air systems as appropriate;
- areas such as airlocks, change rooms and passages, should be designed so that the required pressure cascades can be achieved;
- detailed diagrams depicting pressure cascades, air flow directions and flow routes for personnel and materials should be prepared and maintained;
- where possible, personnel and materials should not move from a higher cleanliness zone to a lower cleanliness zone and back to a higher cleanliness zone; (if moving from a lower cleanliness zone to a higher cleanliness zone, changing /decontamination procedures should be followed); and
- the final stage of the changing room should, in the "at rest" state, be the same GMP classification grade as the area into which it leads.

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WHO Technical Report Series, No. 961, 2011

Annex 6

WHO good manufacturing practices for sterile pharmaceutical products

Introduction

Following implementation of these WHO good manufacturing practices (GMP) guidelines (*1*) within the context of the WHO Prequalification of Medicines Programme, clarifying, editorial modifications have been proposed. These changes were adopted for maintenance purposes. In order to ease reading the full guideline has been reproduced again as an Annex to the current report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

WHO good manufacturing practices for sterile pharmaceutical products

1. General considerations

1.1 The production of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency.

1.2 The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be carried out in separate areas within the clean area. These areas are classified into four grades (see section 4).

1.3 Manufacturing operations are divided here into two categories:

— first, those where the product is terminally sterilized; and
— second, those which are conducted aseptically at some or all stages.

2. Quality control

2.1 The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.

2.2 Samples taken for sterility testing should be representative of the whole of the batch but should, in particular, include samples taken from parts of the batch considered to be most at risk of contamination, for example:

- for products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work;
- for products that have been heat sterilized in their final containers, consideration should be given to taking samples from that part of the load that is potentially the coolest.

2.3 The sterility of the finished product is assured by validation of the sterilization cycle in the case of terminally sterilized products, and by "media simulation" or "media fill" runs for aseptically processed products. Batch-processing records and, in the case of aseptic processing, environmental quality records, should be examined in conjunction with the results of the sterility tests. The sterility test procedure should be validated for a given product. Pharmacopoeial methods should be used for the validation and performance of the sterility test. In those cases where parametric release has been authorized in place of sterility testing special attention should be paid to the validation and the monitoring of the entire manufacturing process.

2.4 For injectable products the water for injection and the intermediate, if appropriate, and finished products should be monitored for endotoxins, using an established pharmacopoeial method that has been validated for each type of product. For large-volume infusion solutions, such monitoring of water or intermediates should always be done, in addition to any tests required by an approved monograph for the finished product. When a sample fails a test, the cause of the failure should be investigated and necessary action should be taken. Alternative methods to those in the pharmacopoeias may be used if they are validated, justified and authorized.

2.5 The use of rapid microbiological methods to replace the traditional microbiological methods, and to obtain earlier results on the microbiological quality of, for example, water, the environment or bioburden, could be considered if appropriately validated and if a comparative assessment of the proposed rapid method is performed against the pharmacopoeial method.

3. Sanitation

3.1 The sanitation of clean areas is particularly important. They should be cleaned frequently and thoroughly in accordance with an approved written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be regularly undertaken to detect contamination or the presence of an organism against which the cleaning procedure is ineffective. Interactions between different cleaning materials should be validated. Appropriate cleaning validation should be carried out to ensure disinfectant residuals can be detected and are removed by the cleaning process.

3.2 Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilized. Disinfectants and detergents used in Grade A and B areas should be sterile before use.

3.3 A disinfectant programme should also include a sporicidal agent since many common disinfectants are ineffective against spores. The effectiveness of cleaning and disinfectant procedures should be demonstrated.

3.4 Fumigation of clean areas may be useful for reducing microbial contamination in inaccessible places.

4. Manufacture of sterile preparations

4.1 Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate level of environmental

cleanliness in the operational state to minimize the risks of particulate or microbial contamination of the product or materials being handled.

4.2 Detailed information on methods for determining the microbiological and particulate cleanliness of air, surfaces, etc., is not given in these guidelines.

ISO 14644-1 (*2*) should be used for classification of cleanliness according to concentration of airborne particles (determination of number of sample locations, calculation of sample size and evaluation of classification from the data obtained). Table 1 should also be used to define the levels to be used as the basis for monitoring clean areas for airborne particles.

4.3 For the manufacture of sterile pharmaceutical preparations, four grades of clean areas are distinguished as follows:

- *Grade A*: The local zone for high-risk operations, e.g. filling and making aseptic connections. Normally such conditions are achieved by using a unidirectional airflow workstation. Unidirectional airflow systems should provide a homogeneous air speed of 0.36–0.54 m/s (guidance value) at a defined test position 15–30 cm below the terminal filter or air distributor system. The velocity at working level should not be less than 0.36 m/s. The uniformity and effectiveness of the unidirectional airflow should be demonstrated by undertaking airflow visualization tests.
- *Grade B*: In aseptic preparation and filling, this is the background environment for the Grade A zone.
- *Grades C and D*: Clean areas for carrying out less critical stages in the manufacture of sterile products or carrying out activities during which the product is not directly exposed (i.e. aseptic connection with aseptic connectors and operations in a closed system).

A unidirectional airflow and lower velocities may be used in closed isolators and glove boxes.

4.4 In order to reach the B, C and D air grades the number of air changes should be appropriate for the size of the room and the equipment and personnel present in it.

4.5 High-efficiency particulate air (HEPA) filters should be subjected to an installed filter leakage test in accordance with ISO 14644-3 (*3*) at a recommended interval of every 6 months, but not exceeding 12 months. The purpose of performing regular leak tests is to ensure the filter media, filter frame and filter seal are free from leaks. The aerosol selected for HEPA leak testing should not support microbial growth and should be composed of a sufficient number or mass of particles. HEPA filter patching is allowed at the filter manufacturer and in situ operation provided that the patch sizes and procedures follow the recommendations of ISO 1822-4 (*4*).

Clean room and clean-air device classification

4.6 Clean rooms and clean-air devices should be classified in accordance with ISO 14644 (*2–3, 5–7*).

4.6.1 Classification should be clearly differentiated from operational process environmental monitoring. The maximum permitted airborne particle concentration for each grade is given in Table 1.

Table 1
Maximum permitted airborne particle concentrat

	Maximum permitted number of particles per m^3 greater than or equal to the tabulated size			
	At rest[a]		In operation[b]	
Grade	**0.5 µm**	**5.0 µm**	**0.5 µm**	**5.0 µm**
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

[a] The "at rest" state is the condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.
[b] The "in operation" state is the condition where the installation is functioning in the defined operating mode and the specified number of personnel is present. The areas and their associated environmental control systems should be designed to achieve both the "at rest" and "in operation" states.

4.6.2 For classification purposes in Grade A zones, a minimum sample volume of 1 m^3 should be taken per sample location. Referring to Table 1, for Grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles ≥ 5.0 µm. For Grade B (at rest) the airborne particle classification is ISO 5 for both particle sizes considered. For Grade C (at rest and in operation) the airborne particle classification is ISO 7 and ISO 8, respectively. For Grade D (at rest) the airborne particle classification is ISO 8. For classification purposes ISO 14644-1 (*2*) methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest particle size considered and the method of evaluation of the data collected. The sample volume should be determined according to ISO 14644-1 (*2*) clause B.4.2. However, for lower grades (Grade C in operation and Grade D at rest) the sample volume per location should be at least 2 litres and the sample time per location should be not less than 1 minute.

4.6.3 Portable particle counters with a short length of sample tubing should be used for classification purposes to avoid the loss of particles ≥ 5.0 µm. Isokinetic sample heads should be used in unidirectional airflow systems.

4.6.4 "In operation" classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation

is required for this. ISO 14644-2 (*6*) provides information on testing to demonstrate continued compliance with the assigned cleanliness classification.

Clean room and clean-air device monitoring

4.7 Clean rooms and clean-air devices should be routinely monitored while in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean-air devices.

4.7.1 For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, for example, live organisms and radiological hazards. In such cases monitoring during routine equipment set-up operations should be undertaken before exposure to the risk. Monitoring during simulated operations should also be performed. The Grade A zone should be monitored at a frequency and sample size such that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of ≥ 5.0 μm particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

4.7.2 It is recommended that a similar system be used for Grade B zones, although the sample frequency may be decreased. The importance of the particle monitoring system should be determined by the effectiveness of the segregation between the adjacent Grade A and B zones. The Grade B zone should be monitored at a frequency and with a sample size such that changes in levels of contamination and any deterioration of the system would be captured and alarms triggered if alert limits are exceeded.

4.7.3 Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or multiple small particle counters located near monitoring points and networked to a data acquisition system. Combinations of systems can also be used. The system selected should be appropriate for the particle size considered.

Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing should be considered in the context of particle losses in the tubing. The selection of the monitoring system should take account of any risk presented by the materials used in the manufacturing operation, for example, those involving live organisms or radiopharmaceuticals.

4.7.4 The sizes of samples taken for monitoring purposes using automated systems will usually be a function of the sampling rate of the system used.

It is not necessary for the sample volume to be the same as that used for formal classification of clean rooms and clean-air devices.

4.7.5 The airborne particle conditions given in Table 1 for the "at rest" state should be achieved in the absence of the operating personnel after a short "clean-up" or "recovery" period of about 15–20 minutes (guidance value), after completion of the operations. The particulate conditions given in Table 1 for Grade A "in operation" should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. The "clean-up" or "recovery" test should demonstrate a change in particle concentration by a factor of 100 within the prescribed time (ISO 14644-3 clause B.12) (*3*).

4.7.6 In order to demonstrate control of the cleanliness of the various clean areas during operation, they should be monitored for airborne particles and microbial contamination. In addition to "at rest" and "in operation" classification, airborne particles should be monitored periodically "in operation" at critical locations. The sampling plan need not be the same as that used for classification. Locations and sample sizes should be determined based on an assessment of the process and contamination risk.

4.7.7 The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended "clean-up period" should be attained.

4.7.8 Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.

4.7.9 Examples of operations to be carried out in the various grades are given in Table 2 (see also sections 4.12–4.20).

Table 2

Examples of operations to be carried out in the various grades

Grade	Examples of operations for terminally sterilized products (see sections 4.12–4.15)
A	Filling of products when unusually at risk
C	Preparation of solutions when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Grade	Examples of operations for aseptic preparations (see sections 4.16–4.20)
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

4.8 To control the microbiological cleanliness of Grades A–D in operation the clean areas should be monitored. Where aseptic operations are performed, monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitization.

4.9 Levels of detection of microbial contamination should be established for the purpose of setting alert and action limits and for monitoring the trends in environmental cleanliness in the facility. Limits expressed in colony-forming units (CFU) for the microbiological monitoring of clean areas in operation are given in Table 3. The sampling methods and numerical values included in the table are not intended to represent specifications, but are for information only.

Table 3

Recommended limits for microbial contamination[a]

Grade	Air sample (CFU/m3)	Settle plates (diameter 90 mm) (CFU/4 hours)[b]	Contact plates (diameter 55 mm) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

CFU, colony-forming units.

[a] These are average values.

[b] Individual settle plates may be exposed for less than 4 hours.

4.10 Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If the action limits are exceeded or a trend is identified in the alert limits, investigation should be initiated and the appropriate corrective actions should be taken, as prescribed in the operating procedures.

4.11 The area grades as specified in sections 4.12 to 4.20 should be selected by the manufacturer on the basis of the nature of the process operations being performed and validation runs (e.g. aseptic media fills or others types of process simulations) are used to establish processing hold times and a maximum fill duration. The determination of an appropriate process area environment and a time limit should be based on the microbial contamination (bioburden) found.

Terminally sterilized products

4.12 Components and most products should be prepared in at least a Grade D environment to ensure low microbial bioburden and particulate counts prior to filtration and sterilization. Where the product is at unusual risk of microbial contamination (e.g. because it actively supports microbial growth, must be held for a long period before sterilization, or is necessarily processed mainly in open vessels), the preparation should generally be done in a Grade C environment.

4.13 The filling of products for terminal sterilization should generally be done in at least a Grade C environment.

4.14 Where the product is at unusual risk of contamination from the environment (e.g. because the filling operation is slow, the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing), the filling should be done in a Grade A zone with at least a Grade C background.

4.15 The preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a Grade C environment before terminal sterilization.

Aseptic preparation

4.16 Components after washing should be handled in at least a Grade D environment. The handling of sterile starting materials and components, unless subjected to sterilization or filtration through a microorganism-retaining filter later in the process, should be undertaken in a Grade A environment with a Grade B background.

4.17 The preparation of solutions which are to be sterile-filtered during the process should be undertaken in a Grade C environment (unless a closed system is used, in which case a Class D environment may be justifiable). If not sterile-filtered (therefore an aseptic manipulation) the preparation of materials and products should be undertaken in a Grade A environment with a Grade B background.

4.18 The handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, should be undertaken in a Grade A environment with a Grade B background.

4.19 The transfer of partially closed containers, as used in freeze-drying, before stoppering is completed, should be undertaken either in a Grade A environment with a Grade B background or in sealed transfer trays in a Grade B environment.

4.20 The preparation and filling of sterile ointments, creams, suspensions and emulsions should be undertaken in a Grade A environment with a Grade B background when the product is exposed and is not subsequently filtered.

Processing

4.21 Precautions to minimize contamination should be taken during all processing stages, including the stages before sterilization.

4.22 In general, preparations containing live microorganisms should not be made, nor should containers be filled in areas used for the processing of other pharmaceutical products. However, if the manufacturer can demonstrate and validate effective containment and decontamination of the live microorganisms, the use of multiproduct facilities may be justifiable. Vaccines consisting of dead organisms or of bacterial extracts may be dispensed into containers in the same premises as other sterile pharmaceutical products, provided that the inactivation procedure has been properly validated.

When multiproduct facilities are used to manufacture sterile preparations containing live microorganisms and other sterile pharmaceutical products, the manufacturer should demonstrate and validate the effective decontamination of the live microorganisms, in addition to precautions taken to minimize contamination.

4.23 Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium.

4.24 The process simulation test should imitate as closely as possible the routine aseptic manufacturing steps except where the activity may lead to any potential microbial contamination.

4.25 Process simulation tests should be performed as part of validation by running three consecutive satisfactory simulation tests. These tests should be repeated at defined intervals and after any significant modification to the heating, ventilation and air-conditioning (HVAC) system, equipment or process. Process simulation tests should incorporate activities and interventions known to occur during normal production as well as the worst-case situation. The process simulation tests should be representative of each shift and shift changeover to address any time-related and operational features.

4.26 The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth and the following should apply:

- when filling fewer than 5000 units, no contaminated units should be detected.
- when filling 5000–10 000 units:
  — one contaminated unit should result in an investigation, including consideration of a repeat media fill;

  - two contaminated units are considered cause for revalidation following investigation;
- when filling more than 10 000 units:
  - one contaminated unit should result in an investigation;
  - two contaminated units are considered cause for revalidation following investigation.

4.27 For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that should be investigated. Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

4.28 Care should be taken to ensure that any validation does not compromise the processes.

4.29 Water sources, water-treatment equipment and treated water should be monitored regularly for chemicals, biological contamination and contamination with endotoxins to ensure that the water complies with the specifications appropriate to its use. Records should be maintained of the results of the monitoring and of any action taken (*8*).

4.30 Activities in clean areas, especially when aseptic operations are in progress, should be kept to a minimum and the movement of personnel should be controlled and methodical, so as to avoid excessive shedding of particles and organisms due to over-vigorous activity. As far as possible, personnel should be excluded from Grade A zones. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn and to reduce the risk of contamination liberated from the personnel.

4.31 The presence of containers and materials liable to generate fibres should be minimized in clean areas and avoided completely when aseptic work is in progress.

4.32 Components, bulk-product containers and equipment should be handled after the final cleaning process in such a way as to ensure that they are not recontaminated. The stage of processing of components as well as the bulk-product containers and equipment should be properly identified.

4.33 The interval between the washing and drying and the sterilization of components, bulk-product containers and equipment, as well as between sterilization and use, should be as short as possible and subject to a time-limit appropriate to the validated storage conditions.

4.34 The time between the start of the preparation of a solution and its sterilization or filtration through a bacteria-retaining filter should be as short as possible. A maximum permissible time should be set for each product that takes into account its composition and the prescribed method of storage.

4.35 Any gas that is used to purge a solution or blanket a product should be passed through a sterilizing filter.

4.36 The bioburden should be monitored before sterilization. There should be working limits on contamination immediately before sterilization, which are related to the efficiency of the method to be used. Bioburden assay should be performed on each batch for both aseptically filled products and terminally sterilized products. Where overkill sterilization parameters are set for terminally sterilized products, bioburden might be monitored only at suitable scheduled intervals. For parametric release systems, bioburden assay should be performed on each batch and considered as an in-process test. Where appropriate, the level of endotoxins should be monitored. All solutions, in particular large-volume infusion fluids, should be passed through a microorganism-retaining filter, if possible sited immediately before filling.

4.37 Components, bulk-product containers, equipment, and any other articles required in a clean area where aseptic work is in progress, should be sterilized and wherever possible passed into the area through double-ended sterilizers sealed into the wall. Other procedures that prevent the introduction of contamination may be acceptable in some circumstances.

4.38 The efficacy of any new processing procedure should be validated and the validation should be repeated at regular intervals thereafter or when any significant change is made in the process or equipment.

5. Sterilization

5.1 Whenever possible products intended to be sterile should be terminally sterilized by heat in their final container. Where it is not possible to carry out terminal sterilization by heating due to the instability of a formulation or incompatibility of a pack type (necessary to the administration of the product, e.g. plastic eye-dropper bottles), a decision should be taken to use an alternative method of terminal sterilization following filtration and/or aseptic processing.

5.2 Sterilization can be achieved by the use of moist or dry heat, by irradiation with ionizing radiation (noting that ultraviolet irradiation is not normally an acceptable method of sterilization), by ethylene oxide (or other suitable gaseous sterilizing agents), or by filtration with subsequent aseptic filling of sterile final containers. Each method has its advantages and disadvantages. Where possible and practicable, heat sterilization is the method of choice. In any case the sterilization process must be in accordance with the marketing and manufacturing authorizations.

5.3 The microbial contamination of starting materials should be minimal and their bioburden should be monitored before sterilization. Specifications

should include requirements for microbiological quality when the need for this has been indicated by monitoring.

5.4 All sterilization processes should be validated. Particular attention should be paid when the adopted sterilization method is not in accordance with pharmacopoeial standards or other national standards, or when it is used for a preparation that is not a simple aqueous or oily solution, for example, colloidal suspensions.

5.5 Before any sterilization process is adopted, its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators, where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

5.6 For effective sterilization the whole of the material should be subjected to the required treatment and the process should be designed to ensure that this is achieved.

5.7 Biological indicators should be considered only as an additional method of monitoring the sterilization process. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls. If they are used, strict precautions should be taken to avoid any transfer of microbial contamination from them.

5.8 There should be a clear means of differentiating products that have not been sterilized from those which have. Each basket, tray, or other carrier of products or components should be clearly labelled with the name of the material, its batch number and an indication of whether or not it has been sterilized. Indicators such as autoclave tape may be used where appropriate to indicate whether or not a batch (or sub-batch) has passed through a sterilization process, but they do not give a reliable indication that the batch is in fact sterile.

5.9 Validated loading patterns should be established for all sterilization processes.

5.10 Sterilization records should be available for each sterilization run. They should be approved as part of the batch-release procedure.

6. Terminal sterilization

Sterilization by heat

6.1 Each heat-sterilization cycle should be recorded by means of appropriate equipment of suitable accuracy and precision, e.g. on a time/temperature chart with a suitably large scale. The temperature should

be recorded by a probe situated at the coolest part of the load or loaded chamber, this point having been determined during the validation; the temperature should preferably be checked against a second independent temperature probe located at the same position. Sterilization records should be available for each sterilization run and should be approved as part of the batch release procedure. Chemical or biological indicators may also be used but should not take the place of physical controls.

6.2 Sufficient time should be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time is started. This time should be determined for each type of load to be processed.

6.3 After the high-temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact with the product should be sterilized.

Sterilization by moist heat

6.4 Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading of the independent temperature indicator should be routinely checked against the reading on the chart recorder during the sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position throughout the sterilization period. There should be regular leak tests on the chamber when a vacuum phase is part of the cycle.

6.5 The items to be sterilized, other than products in sealed containers, should be wrapped in a material that allows the removal of air and the penetration of steam but prevents recontamination after sterilization. Specially designed autoclavable stainless steel containers, that allow steam to enter and air to leave, can also be used. All parts of the load should be in contact with water or saturated steam at the required temperature for the required time.

6.6 Care should be taken to ensure that the steam used for sterilization is of suitable quality (chemical, microbiological and endotoxin analysis of condensate and physical examination of steam (such as dryness, superheat, and non-condensable gases) and does not contain additives at a level that could cause contamination of the product or equipment. Steam used for sterilization should be tested regularly.

Sterilization by dry heat

6.7 Sterilization by dry heat may be suitable for non-aqueous liquids or dry-powder products.

The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. If air is supplied it should be passed through a microorganism-retaining filter (e.g. a HEPA filter). Where sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins are required as part of the validation.

Sterilization by radiation

6.8 Sterilization by radiation is used mainly for heat-sensitive materials and products. Many pharmaceutical products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not an acceptable method for terminal sterilization.

6.9 If sterilization by radiation is done by an outside contractor, the manufacturer is responsible for ensuring that the requirements of section 6.8 are met and that the sterilization process is validated.

6.10 During the sterilization procedure the radiation dose should be measured. The dosimeters used for this purpose should be independent of the dose rate and should provide a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the chamber. Where plastic dosimeters are used they should be used within the time-limit of their calibration. Dosimeter absorbance should be read shortly after exposure to radiation. Radiation-sensitive colour discs may be used to differentiate between packages that have been subjected to irradiation and those that have not; they are not indicators of successful sterilization. The information obtained should constitute part of the batch record.

6.11 Validation procedures should ensure that consideration is given to the effects of variations in the density of the packages.

6.12 Material-handling procedures should prevent any mix-up of irradiated and non-irradiated materials. Each package should carry a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment.

6.13 The total radiation dose should be administered within a predetermined period.

Sterilization by gases and fumigants

6.14 Sterilization by gases and fumigants should only be used for finished products where there is no suitable alternative.

6.15 Various gases and fumigants may be used for sterilization (e.g. ethylene oxide and hydrogen peroxide vapour). Ethylene oxide should be used only when no other method is practicable. During process validation it should be shown that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material concerned. These limits should be incorporated in the specifications.

6.16 Direct contact between gas and microorganisms is essential; precautions should, therefore, be taken to avoid the presence of organisms likely to be enclosed in materials such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the proces.

6.17 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. This requirement should be balanced against the need to minimize the waiting time before sterilization.

6.18 Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information thus obtained should form part of the batch record.

6.19 Biological indicators should be stored and used according to the manufacturer's instructions and their performance checked by positive controls.

6.20 For each sterilization cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration. The pressure and temperature should be recorded on a chart throughout the cycle. The records should form part of the batch record.

6.21 After sterilization, the load should be stored in a controlled manner in ventilated conditions to allow concentrations of residual gas and reaction products to fall to their prescribed levels. This process should be validated.

7. Aseptic processing and sterilization by filtration

7.1 The objective of aseptic processing is to maintain the sterility of a product that is assembled from components, each of which has been sterilized by one of the above methods (see sections 5 and 6).

7.2 The operating conditions should be such as to prevent microbial contamination.

7.3 In order to maintain the sterility of the components and the product during aseptic processing, careful attention needs to be given to:

— the environment;
— personnel;
— critical surfaces;
— container/closure sterilization and transfer procedures;
— the maximum holding period of the product before filling into the final container; and
— the sterilizing filter.

7.4 Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size 0.22 micron (or less), or with at least equivalent microorganism-retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment. Filtration alone is not considered sufficient when sterilization in the final container is possible. Of the methods currently available, steam sterilization is preferred.

7.5 Owing to the potential additional risks of the filtration method as compared with other sterilization processes, a double-filter layer or second filtration through a further sterilized microorganism-retaining filter immediately prior to filling may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.

7.6 The fibre-shedding characteristics of filters should be minimal (virtually zero). Asbestos-containing filters should not be used under any circumstances.

7.7 The integrity of the sterilized filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from these during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals. Consideration should be given to increased monitoring of filter integrity in processes that involve harsh conditions, e.g. the circulation of high-temperature air.

7.8 The same filter should not be used for more than one working day unless such use has been validated.

7.9 The filter should not affect the product either by removing ingredients from it or by releasing substances into it.

8. Isolator technology

8.1 The use of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of microbial contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for each zone can be realized. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from single-door to double-door designs to fully-sealed systems incorporating sterilization mechanisms.

8.2 The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general the area inside the isolator is the local zone for high-risk manipulations, although it is recognized that unidirectional airflow may not exist in the working zone of all isolators and transfer devices.

8.3 The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled, and for aseptic processing it should be at least Grade D.

8.4 Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example, the quality of the air inside and outside (background) the isolator, sanitization of the isolator, the transfer process and isolator integrity.

8.5 Monitoring should be done routinely and should include frequent leak testing of the isolator and the glove/sleeve system.

9. Blow/fill/seal technology

9.1 Blow/fill/seal units are purpose-built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective Grade A air shower may be installed in at least a Grade C environment, provided that Grade A or B clothing is used. The environment should comply with the viable and non-viable limits at rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products which are terminally sterilized should be installed in at least a Grade D environment.

9.2 Because of this special technology, particular attention should be paid to at least the following:

— equipment design and qualification;

— validation and reproducibility of cleaning-in-place and sterilization-in-place;
— background clean room environment in which the equipment is located;
— operator training and clothing; and
— interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

10. Personnel

10.1 Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. As far as possible, inspections and controls should be conducted from outside such areas.

10.2 All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive initial and regular training in disciplines relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.

10.3 Staff who have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed.

10.4 High standards of personal hygiene and cleanliness are essential and personnel involved in the manufacture of sterile preparations should be instructed to report any conditions that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. The action to be taken in respect of personnel who might be introducing undue microbial hazards should be decided by a designated competent person.

10.5 Changing and washing should follow a written procedure designed to minimize the contamination of clean-area clothing or the carry-through of contaminants to clean areas. The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.

10.6 Outdoor clothing should not be brought into changing rooms leading to Grade B and C rooms. For every worker in a Grade A/B area, clean sterile (sterilized or adequately sanitized) protective garments should be provided at each work session. Gloves should be regularly disinfected during

operations. Masks and gloves should be changed at least every working session. Operators working in Grade A and B areas should wear sanitized goggles.

10.7 Wrist-watches, cosmetics and jewellery should not be worn in clean areas.

10.8 The clothing required for each grade is as follows:

- *Grade D*. The hair and, where relevant, beard and moustache should be covered. Protective clothing and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination from outside the clean area.
- *Grade C*. The hair and, where relevant, beard and moustache should be covered. A one-piece jumpsuit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes should be worn. The clothing should shed virtually no fibres or particulate matter.
- *Grades A and B*. Entry of personnel into Grade A areas should be minimized. Headgear should totally enclose the hair and, where relevant, beard and moustache. A one-piece jumpsuit, gathered at the wrists and with a high neck, should be worn. The headgear should be tucked into the neck of the suit. A facemask should be worn to prevent the shedding of droplets. Sterilized, non-powdered gloves of appropriate material and sterilized or disinfected footwear should be worn. Trouser-bottoms should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and should retain particles shed by the body.

10.9 Clothing used in clean areas should be laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. Separate laundry facilities for such clothing are desirable. If fibres are damaged by inappropriate cleaning or sterilization, there may be an increased risk of shedding particles. Washing and sterilization operations should follow standard operating procedures.

11. Premises

11.1 All premises should as far as possible be designed to avoid the unnecessary entry of supervisory or control personnel. Grade A and B areas should be designed so that all operations can be observed from outside.

11.2 In clean areas all exposed surfaces should be smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.

11.3 To reduce the accumulation of dust and to facilitate cleaning, there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be carefully designed to avoid uncleanable recesses; sliding doors may be undesirable for this reason. Swing doors should open to the high-pressure side and be provided with self-closers. Exceptions are permitted based on egress and site environmental, health and safety containment requirements.

11.4 False ceilings should be sealed to prevent contamination from the void space above them.

11.5 Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean. Sanitary pipes and fittings should be used and threaded pipe connections should be avoided.

11.6 Sinks and drains should be avoided wherever possible and should be excluded from Grade A and B areas where aseptic operations are carried out. Where installed they should be designed, located and maintained so as to minimize the risks of microbial contamination; they should be fitted with effective, easily cleanable traps and with air breaks to prevent backflow. Any floor channels should be open and easily cleanable and be connected to drains outside the area in a manner that prevents the ingress of microbial contaminants.

11.7 Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand-washing facilities should be provided only in the first stage of the changing rooms.

There should not be a change of more than one grade between airlocks or passages and changing rooms, i.e. a Grade D passage can lead to a Grade C airlock, which leads to a Grade B changing room, which leads to a Grade B clean room. Changing rooms should be of a sufficient size to allow for ease of changing. Changing rooms should be equipped with mirrors so that personnel can confirm the correct fit of garments before leaving the changing room.

11.8 Airlock doors should not be opened simultaneously. An interlocking system and a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

11.9 A filtered air supply should be used to maintain a positive pressure and an airflow relative to surrounding areas of a lower grade under all operational conditions; it should flush the area effectively. Adjacent rooms

of different grades should have a pressure differential of approximately 10–15 Pascals (guidance value). Particular attention should be paid to the protection of the zone of greatest risk, i.e. the immediate environment to which the product and the cleaned components in contact with it are exposed. The recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain certain materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. The decontamination of the facilities and the treatment of air leaving a clean area may be necessary for some operations.

11.10 It should be demonstrated that airflow patterns do not present a contamination risk; for example, care should be taken to ensure that particles from a particle-generating person, operation or machine are not conveyed to a zone of higher product risk.

11.11 A warning system should be operated to indicate failure in the air supply. Indicators of pressure differentials should be fitted between areas where this difference is important, and the pressure differentials should be regularly recorded and failure alarmed.

11.12 Consideration should be given to restricting unnecessary access to critical filling areas, e.g. Grade A filling zones, by means of a physical barrier.

12. Equipment

12.1 A conveyor belt should not pass through a partition between a Grade A or B clean area and a processing area of lower air cleanliness, unless the belt itself is continuously sterilized (e.g. in a sterilizing tunnel).

12.2 Whenever possible, equipment used for processing sterile products should be chosen so that it can be effectively sterilized by steam or dry heat or other methods.

12.3 As far as possible, equipment fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. Equipment that has to be taken apart for maintenance should be re-sterilized after complete reassembly, wherever possible.

12.4 When equipment maintenance is carried out within a clean area, clean instruments and tools should be used and the area should be cleaned and disinfected again, where appropriate, before processing recommences, if the required standards of cleanliness and/or asepsis have not been maintained during the maintenance work.

12.5 All equipment such as sterilizers, air-handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution

systems should be subject to validation and planned maintenance; their return to use should be approved.

12.6 Water-treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Consideration should be given to including a testing programme in the maintenance of a water system. Water for injection should be produced, stored and distributed in a manner which prevents the growth of microorganisms, e.g. by constant circulation at a temperature above 70 °C or not more than 4 °C (*8*).

13. Finishing of sterile products

13.1 Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules, should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.

13.2 The container closure system for aseptically filled vials is not fully integral until the aluminum cap has been crimped into place on the stoppered vial. Crimping of the cap should, therefore, be performed as soon as possible after stopper insertion.

13.3 As the equipment used to crimp vial caps can generate large quantities of non-viable particulates, the equipment should be located at a separate station equipped with adequate air extraction.

13.4 Vial capping can be undertaken as an aseptic process using sterilized caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a Grade A air supply until the cap has been crimped.

13.5 Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimize microbial contamination.

13.6 Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimizing direct human interventions into the capping operation.

13.7 Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, predetermined period.

13.8 Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is carried

out visually this should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eyesight checks, using personal corrective lenses (e.g. spectacles or contact lenses) as required, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

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Further reading

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Annex 7

WHO guidelines on transfer of technology in pharmaceutical manufacturing

1. Introduction

These guiding principles on transfer of technology are intended to serve as a framework which can be applied in a flexible manner rather than as strict rigid guidance. Focus has been placed on the quality aspects, in line with WHO's mandate.

1.1 Transfer of processes to an alternative site occurs at some stage in the life-cycle of most products, from development, scale-up, manufacturing, production and launch, to the post-approval phase.

1.2 Transfer of technology is defined as "a logical procedure that controls the transfer of any process together with its documentation and professional expertise between development and manufacture or between manufacture sites". It is a systematic procedure that is followed in order to pass the documented knowledge and experience gained during development and or commercialization to an appropriate, responsible and authorized party. Technology transfer embodies both the transfer of documentation and the demonstrated ability of the receiving unit (RU) to effectively perform the critical elements of the transferred technology, to the satisfaction of all parties and any applicable regulatory bodies.

1.3 Literature searches revealed little information on the subject originating from national or regional regulatory bodies. Guidance on intracompany transfers was prepared by the International Society for Pharmaceutical Engineering (ISPE) (*1*).

1.4 The ever changing business strategies of pharmaceutical companies increasingly involve intra- and intercompany transfers of technology for reasons such as the need for additional capacity, relocation of operations or consolidations and mergers. The WHO Expert Committee on Specifications for Pharmaceutical Preparations, therefore, recommended in its forty-second report that WHO address this issue through preparation of WHO guidelines on this matter (*2*).

1.5 Transfer of technology requires a documented, planned approach using trained and knowledgeable personnel working within a quality system, with documentation of data covering all aspects of development, production and quality control. Usually there is a sending unit (SU), a receiving unit and the unit managing the process, which may or may not be a separate entity. For "contract manufacturing" please see good manufacturing practices (GMP) (*3*).

1.6 For the transfer to be successful, the following general principles and requirements should be met:

- the project plan should encompass the quality aspects of the project and be based upon the principles of quality risk management;

- the capabilities of the SU and at the RU should be similar, but not necessarily identical, and facilities and equipment should operate according to similar operating principles;
- a comprehensive technical gap analysis between the SU and RU including technical risk assessment and potential regulatory gaps, should be performed as needed;
- adequately trained staff should be available or should be trained at the RU:
  — regulatory requirements in the countries of the SU and the RU, and in any countries where the product is intended to be supplied, should be taken into account and interpreted consistently throughout any transfer programme project; and
  — there should be effective process and product knowledge transfer.

1.7 Technology transfer can be considered successful if there is documented evidence that the RU can routinely reproduce the transferred product, process or method against a predefined set of specifications as agreed with the SU.

1.8 In the event that the RU identifies particular problems with the process during the transfer, the RU should communicate them back to the SU to ensure continuing knowledge management.

1.9 Technology transfer projects, particularly those between different companies, have legal and economic implications. If such issues, which may include intellectual property rights, royalties, pricing, conflict of interest and confidentiality, are expected to impact on open communication of technical matters in any way, they should be addressed before and during planning and execution of the transfer.

1.10 Any lack of transparency may lead to ineffective transfer of technology.

1.11 Some of the principles outlined in this document may also be applicable to manufacturing investigational pharmaceutical products for clinical trials as part of research and development, but this is not the main focus of this guidance and has been excluded due to the complexity of the processes.

1.12 Some of the responsibilities outlined in this document for the SU may also be considered to be part of the management unit responsibilities.

2. Scope

Note: This section specifically provides for transfer of quality control (QC) methods where a technical agreement exists (SU manufacturer to RU manufacturer or SU manufacturer to RU QC laboratory). Where no such technical agreements exist (e.g. testing by national laboratories or testing

for procurement agencies) a number of the points listed in section 2.4 may not be workable, and alternative approaches may be required.

2.1 This document gives guidance in principle and provides general recommendations on the activities necessary to conduct a successful intra- or intersite transfer of technology as described in the Introduction to these guidelines. The intention is to address the basic considerations needed for a successful transfer in order to satisfy the regulatory authority defined for the transfer process.

2.2 The guidelines will be applied to manufacturing active pharmaceutical ingredients (APIs), manufacturing and packaging of bulk materials, manufacturing and packaging of finished pharmaceutical products (FPPs) and/or performing analytical testing.

2.3 The recommendations provided in these guidelines apply to all dosage forms but need to be adjusted on a case-by-case basis (e.g. by using risk management principles). Particularly close control of certain aspects will be required for certain formulations such as sterile products, and metered-dose aerosols. WHO guidance on manufacture of specific pharmaceutical products *(4,5)* will be useful in this regard.

2.4 The guidelines address the following areas at the SU and the RU:

— transfer of development and production (processing, packaging and cleaning);
— transfer of analytical methods for quality assurance and quality control;
— skills assessment and training;
— organization and management of the transfer;
— assessment of premises and equipment;
— documentation; and
— qualification and validation.

2.5 Because each transfer project is unique, the provision of a comprehensive set of guidelines is beyond the scope of this document.

2.6 These guidelines do not provide guidance on any legal, financial or commercial considerations associated with technology transfer projects.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

acceptance criteria

Measurable terms under which a test result will be considered acceptable.

active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

bracketing

An experimental design to test only the extremes of, for example, dosage strength. The design assumes that the extremes will be representative of all the samples between the extremes.

change control (C/C)

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

commissioning

The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer or developer. Commissioning is carried out before qualification and validation.

control strategy

A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related tomaterials and components related to drug substances and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (*6*).

corrective action (C/A)

Any action to be taken when the results of monitoring at a critical control point indicate a loss of control.

critical

Having the potential to impact on product quality or performance in a significant way.

critical control point (CCP)

A step at which control can be applied and is essential to prevent or eliminate a pharmaceutical quality hazard or to reduce it to an acceptable level.

design qualification (DQ)

Documented evidence that the premises, supporting systems, utilities, equipment and processes have been designed in accordance with the requirements of good manufacturing practices (GMP).

design space

The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality (*7*).

drug master file (DMF)

Detailed information concerning a specific facility, process or product submitted to the medicines regulatory authority, intended for incorporation into the application for marketing authorization.

finished pharmaceutical product (FPP)

A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more APIs.

gap analysis

Identification of critical elements of a process which are available at the SU but are missing from the RU.

good manufacturing practices (GMP)

That part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization (*3*).

in-process control (IPC)

Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

installation qualification (IQ)

The performance of tests to ensure that the installations (such as machines, measuring devices, utilities and manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed and operate in accordance with established specifications.

intercompany transfer

A transfer of technology between sites of different companies.

intracompany transfer

A transfer of technology between sites of the same group of companies.

operational qualification (OQ)

Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

performance qualification (PQ)

Documented verification that the equipment or system operates consistently and gives reproducibility within defined specifications and parameters for prolonged periods. (In the context of systems, the term "process validation" may also be used.)

process validation

Documented evidence which provides a high degree of assurance that a specific process will consistently result in a product that meets its predetermined specifications and quality characteristics.

qualification

Action of proving and documenting that any premises, systems and equipment are properly installed, and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation.

qualification batches

Those batches produced by the RU to demonstrate its ability to reproduce the product *(1)*.

quality assurance (QA)

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use.

quality control (QC)

Quality control covers all measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that starting materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

quality planning

Part of quality management focused on setting quality objectives and specifying necessary operational processes and related resources to fulfil the quality objectives *(6)*.

quality policy

Overall intentions and direction of an organization related to quality as formally expressed by senior management *(6)*.

quality risk management (QRM)

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the pharmaceutical product throughout the product life-cycle.

receiving unit (RU)

The involved disciplines at an organization where a designated product, process or method is expected to be transferred.

sending unit (SU)

The involved disciplines at an organization from where a designated product, process or method is expected to be transferred.

spiking

The addition of a known amount of a compound to a standard, sample or placebo, typically for the purpose of confirming the performance of an analytical procedure.

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

technology transfer report

A documented summary of a specific technology transfer project listing procedures, acceptance criteria, results achieved and conclusions. Any deviation should be discussed and justified.

validation

Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.

validation master plan (VMP)

A high-level document that establishes an umbrella validation plan for the entire project and summarizes the manufacturer's overall philosophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer's validation work programme and defines details of and timescales for the validation work to be performed, including a statement of the responsibilities of those implementing the plan.

validation protocol (or plan) (VP)

A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process — or a part thereof — for routine use.

validation report (VR)

A document in which the records, results and evaluation of a completed validation programme are assembled and summarized. It may also contain proposals for the improvement of processes and or equipment.

4. Organization and management

4.1 Transfer comprises an SU and an RU. In some circumstances there may be an additional unit which will be responsible for directing, managing and approving the transfer.

4.2 There is a formal agreement between the parties, which specifies the responsibilities before, during and after transfer.

4.3 Organization and management of a successful technology transfer need to ensure that the main steps have been executed and documented as described in section 1.6.

4.4 There should be a project management plan which identifies and controls all the necessary activities identified at the start of the undertaking.

4.5 The transfer protocol should list the intended sequential stages of the transfer. The protocol should include:

— objective;
— scope;
— key personnel and their responsibilities;
— a parallel comparison of materials, methods and equipment;
— the transfer stages with documented evidence that each critical stage has been satisfactorily accomplished before the next commences;
— identification of critical control points;
— experimental design and acceptance criteria for analytical methods;
— information on trial production batches, qualification batches and process validation;
— change control for any process deviations encountered;
— assessment of end-product;
— arrangements for keeping retention samples of active ingredients, intermediates and finished products, and information on reference substances where applicable; and
— conclusion, including signed-off approval by project manager.

4.6 The SU should provide the necessary validation documentation for the process and its support functions. Usually, an established process is transferred, and such documentation is already available.

4.7 The SU should provide criteria and information on hazards and critical steps associated with the product, process or method to be transferred, to serve as a basis for a quality risk management (QRM) exercise at the RU (*7–10*).

4.8 The SU or third party should assess the suitability and degree of preparedness of the RU before transfer, with regard to premises, equipment and support services (e.g. purchasing and inventory control mechanisms, quality control (QC) procedures, documentation, computer validation, site validation, equipment qualification, water for pharmaceutical production and waste management).

4.9 The SU and the RU should jointly verify that the following, satisfactorily completed, validation protocols are available:

- installation qualification (IQ) and operational qualification (OQ) data for manufacturing and packaging equipment at the RU site and analytical equipment; and
- qualification of the rooms for both manufacture and packaging at the RU site.

4.10 The SU and the RU should jointly implement any training programmes that may be required specific to the product, process or method to be transferred, e.g. on analytical methods or equipment usage, and assess training outcomes.

4.11 The SU and the RU should jointly execute the transfer protocol according to a checklist and or flow diagram showing the sequence of steps to be carried out to effect an efficient transfer.

4.12 Any changes and adaptations made during the course of the technology transfer should be fully documented.

4.13 The SU and the RU should jointly document the execution of the transfer protocol in a transfer of technology summary in a report.

Project team

4.14 Any transfer project will be managed by a team comprising members with clearly defined key responsibilities. The team should be drawn from members of relevant disciplines from both the SU and RU sites.

4.15 The team members should have the necessary qualifications and experience to manage their particular aspect of the transfer.

5. Production: transfer (processing, packaging and cleaning)

5.1 The RU should be able to accommodate the intended production capacity. If possible, it should be established at the outset whether the intention is to perform single-batch manufacture, continuous production or campaigns.

5.2 Consideration should be given to the level and depth of detail to be transferred to support production and any further process development and optimization at the RU as intended under the transfer project plan.

5.3 Consideration should be given to the technical expertise, site technology and site capabilities for the RU. It should be identified upfront by the SU of any process robustness issues so that plans may be put in place at the RU.

5.4 The SU and the RU should jointly develop a protocol for the transfer of relevant information related to the process under consideration from the SU to the RU, as well as the development of a comparable process at the RU.

Starting materials

5.5 The specifications and relevant functional characteristics of the starting materials (APIs and excipients) (*11,12*) to be used at the RU should be consistent with materials used at the SU. Any properties which are likely to influence the process or product should be identified and characterized.

Active pharmaceutical ingredients (API)

5.6 The SU should provide the RU with the open (applicant's) part of the API master file (APIMF or drug master file (DMF) or active substance master file (ASMF)), or equivalent information and any relevant additional information on the API of importance for the manufacture of the pharmaceutical product. The following are examples of the information which may typically be provided; however the information needed in each specific case should be assessed using the principles of QRM:

- manufacturer and associated supply chain;
- step of the API to be transferred;
- flow chart of synthesis pathway, outlining the process, including entry points for raw materials, critical steps, process controls and intermediates;
- where relevant, definitive physical form of the API (including photomicrographs and other relevant data) and any polymorphic and solvate forms;
- solubility profile;

- if relevant, pH in solution;
- partition coefficient, including the method of determination;
- intrinsic dissolution rate, including the method of determination;
- particle size and distribution, including the method of determination;
- bulk physical properties, including data on bulk and tap density, surface area and porosity as appropriate;
- water content and determination of hygroscopicity, including water activity data and special handling requirements;
- microbiological considerations (including sterility, bacterial endotoxins and bioburden levels where the API supports microbiological growth) in accordance with national, regional or international pharmacopoeial requirements;
- specifications and justification for release and end-of-life limits;
- summary of stability studies conducted in conformity with current guidelines, including conclusions and recommendations on retest date;
- list of potential and observed synthetic impurities, with data to support proposed specifications and typically observed levels;
- information on degradants, with a list of potential and observed degradation products and data to support proposed specifications and typically observed levels;
- potency factor, indicating observed purity and justification for any recommended adjustment to the input quantity of API for product manufacturing, providing example calculations; and
- special considerations with implications for storage and or handling, including but not limited to safety and environmental factors (e.g. as specified in material safety data sheets) and sensitivity to heat, light or moisture.

Excipients

5.7 The excipients (*11*) to be used have a potential impact on the final product. Their specifications and relevant functional characteristics should, therefore, be made available by the SU for transfer to the RU site. The following are examples of the information which may typically be provided; however, the information needed in each specific case should be assessed using the principles of QRM:

- manufacturer and associated supply chain;
- description of functionality, with justification for inclusion of any antioxidant, preservative or any excipient;
- definitive form (particularly for solid and inhaled dosage forms);
- solubility profile (particularly for inhaled and transdermal dosage forms);
- partition coefficient, including the method of determination (for transdermal dosage forms);

- intrinsic dissolution rate, including the method of determination (for transdermal dosage forms);
- particle size and distribution, including the method of determination (for solid, inhaled and transdermal dosage forms);
- bulk physical properties, including data on bulk and tap density, surface area and porosity as appropriate (for solid and inhaled dosage forms);
- compaction properties (for solid dosage forms);
- melting point range (for semi-solid or topical dosage forms);
- pH range (for parenteral, semi-solid or topical, liquid and transdermal dosage forms);
- ionic strength (for parenteral dosage forms);
- specific density or gravity (for parenteral, semi-solid or topical, liquid and transdermal dosage forms);
- viscosity and or viscoelasticity (for parenteral, semi-solid or topical, liquid and transdermal dosage forms);
- osmolarity (for parenteral dosage forms);
- water content and determination of hygroscopicity, including water activity data and special handling requirements (for solid and inhaled dosage forms);
- moisture content range (for parenteral, semisolid or topical, liquid and transdermal dosage forms);
- microbiological considerations (including sterility, bacterial endotoxins and bioburden levels where the excipient supports microbiological growth) in accordance with national, regional or international pharmacopoeial requirements, as applicable (for general and specific monographs);
- specifications and justification for release and end-of-life limits;
- information on adhesives supporting compliance with peel, sheer and adhesion design criteria (for transdermal dosage forms);
- special considerations with implications for storage and or handling, including but not limited to safety and environmental factors (e.g. as specified in material safety data sheets (MSDS)) and sensitivity to heat, light or moisture; and
- regulatory considerations, e.g. documentation to support compliance with transmissible animal spongiform encephalopathy certification requirements (where applicable).

Information on process and finished pharmaceutical products information

5.8 The SU should provide a detailed characterization of the product, including its qualitative and quantitative composition, physical description, method of manufacture, in-process controls, control method and specifications, packaging components and configurations, and any safety and handling considerations.

5.9 The SU should provide any information on the history of process development which may be required to enable the RU to perform any further development and or process optimization after successful transfer. Such information may include the following:

- information on clinical development, e.g. information on the rationale for the synthesis, route and form selection, technology selection, equipment, clinical tests, and product composition;
- information on scale-up activities: process optimization, statistical optimization of critical process parameters, critical quality attributes, pilot report and or information on pilot-scale development activities indicating the number and disposition of batches manufactured;
- information or report on full-scale development activities, indicating the number and disposition of batches manufactured, and deviation and change control (sometimes referred to as change management) reports which led to the current manufacturing process;
- the change history and reasons, e.g. a change control log, indicating any changes to the process or primary packaging or analytical methods as a part of process optimization or improvement; and
- information on investigations of problems and the outcomes of the investigations.

5.10 The SU should provide to the RU information on any health, safety and environmental issues associated with the manufacturing processes to be transferred, and the implications, e.g. need for gowning or protective clothing.

5.11 The SU should provide to the RU information on current processing and testing, including but not limited to:

- a detailed description of facility requirements and equipment;
- information on starting materials, applicable MSDS and storage requirements for raw materials and finished products;
- description of manufacturing steps (narrative and process maps or flow charts, and or master batch records), including qualification of in-processing hold times and conditions, order and method of raw material addition and bulk transfers between processing steps;
- description of analytical methods;
- identification and justification of control strategy (e.g. identification of critical performance aspects for specific dosage forms, identification of process control points, product quality attributes and qualification of critical processing parameter ranges, statistical process control (SPC) charts);
- design space, in cases where this has been defined;
- validation information, e.g. validation plans and reports;
- annual product quality reviews;

- stability information;
- an authorized set of protocols and work instructions for manufacturing; and
- environmental conditions or any special requirement needed for the facility or equipment depending on the nature of the product to be transferred.

5.12 During the transfer process, the RU should identify any differences in facilities, systems and capabilities and communicate with the SU about these differences to understand the potential impact on ability to run the process to deliver good product quality. Differences should be understood and satisfactorily addressed to assure equivalent product quality. Based on the information received from the SU, the RU should consider its own capability to manufacture and pack the product to the required standards and should develop relevant plant operating procedures and documentation before the start of production. Process development at the RU should address the following tasks:

- comparison and assessment of suitability and qualification of facility and equipment;
- description of manufacturing process and flow of personnel and of materials at the RU (narrative and or process maps or flow charts);
- determination of critical steps in manufacture, including hold times, end-points, sampling points and sampling techniques (*13*);
- writing and approval of SOPs for all production operations (e.g. dispensing, granulation or blending or solution preparation, tablet compression, tablet coating, encapsulation, liquid filling, primary and secondary packaging and in-process quality control), packaging, cleaning, testing and storage;
- evaluation of stability information, with generation of site-specific stability data if required (*14*); and
- compliance with regulatory requirements for any changes made, e.g. in terms of batch size.

Packaging

5.13 The transfer of packaging operations should follow the same procedural patterns as those of the production transfer.

5.14 Information on packaging to be transferred from the SU to the RU includes specifications for a suitable container or closure system, as well as any relevant additional information on design, packing, processing or labelling requirements and tamper-evident and anti-counterfeiting measures needed for qualification of packaging components at the RU.

5.15 For QC testing of packaging components, specifications should be provided for drawings, artwork and material (for example, glass, card or fibre board).

5.16 Based on the information provided, the RU should perform a suitability study for initial qualification of the packaging components. Packaging is considered suitable if it provides adequate protection (preventing degradation of the medicinedue to environmental influences), safety (absence of undesirable substances released into the product), compatibility (absence of interaction possibly affecting medicine quality) and performance (functionality in terms of drug delivery).

Cleaning

5.17 During the manufacturing process, pharmaceutical products and APIs can be contaminated by other pharmaceutical products or APIs if the plant is processing different products. To minimize the risk of contamination and cross-contamination, operator exposure and environmental effects, adequate cleaning procedures are essential.

5.18 Cleaning procedures and their validation are site-specific. In order for the RU to define its cleaning strategy the SU should provide information on cleaning at the SU to minimize cross-contamination due to residues from previous manufacturing steps, operator exposure and environmental impact, including:

— information on solubility of active ingredients, excipients and vehicles;
— minimum therapeutic doses of active ingredients;
— therapeutic category and toxicological assessment; and
— existing cleaning procedures.

Additional information should be provided, as appropriate and where available, e.g.:

— cleaning validation reports (chemical and microbiological);
— information on cleaning agents used (efficacy, evidence that they do not interfere with analytical testing for residues of APIs, removal of residual cleaning agents); and
— recovery studies to validate the sampling methodology.

5.19 Before the transfer, the SU should provide information on limits for product residues, and the rationale for limit selection.

5.20 Based on the information provided by the SU, cleaning procedures should be designed at the RU, taking into account relevant characteristics of the starting materials (e.g. potency, toxicity, solubility, corrosiveness and temperature sensitivity), manufacturing equipment design and configuration, cleaning agent and products residue.

Implementation of processing, packaging and cleaning systems

5.21 Trial batch(es) ("demonstration batches") are normally produced to confirm process capability before initiating formal validation. Where trial

batches are produced, at a minimum, all critical processing parameters and finished product specifications should be assessed.

5.22 Once process capability has been established at the RU, assuring that the product, process or method at the RU meets predefined and justified specifications, process validation and cleaning validation can be carried out.

6. Quality control: analytical method transfer

6.1 Transfer of analytical methods should accommodate all the analytical testing required to demonstrate compliance of the product to be transferred with the registered specification (*15*).

6.2 Analytical methods used to test pharmaceutical products, starting materials, packaging components and cleaning (residue) samples, if applicable, should be implemented at the testing laboratory before testing of samples for process validation studies is performed by the RU. Process validation samples may be tested at the RU, the SU or a third laboratory.

6.3 A protocol defining the steps should be prepared for transfer of analytical methods. The analytical methods transfer protocol should include a description of the objective, scope and responsibilities of the SU and the RU; a specification of materials and methods; the experimental design and acceptance criteria; documentation (including information to be supplied with the results, and report forms to be used, if any); procedure for the handling of deviations; references; signed approval; and details of reference samples (starting materials, intermediates and finished products).

6.4 The SU's responsibilities for the transfer of analytical methods are to:

- provide method-specific training for analysts and other quality control staff, if required;
- assist in analysis of QC testing results;
- define all methods to be transferred for testing a given product, starting material or cleaning sample;
- define experimental design, sampling methods and acceptance criteria;
- provide any validation reports for methods under transfer and demonstrate their robustness;
- provide details of the equipment used, as necessary (part of validation report, if available) and any standard reference samples;
- provide approved procedures used in testing; and
- review and approve transfer reports.

6.5 The RU's responsibilities are to:

- review analytical methods provided by the SU, and formally agree on acceptance criteria before execution of the transfer protocol;

- ensure that the necessary equipment for QC is available and qualified at the RU site. The equipment used by the RU during the analytical transfer should meet appropriate specifications to ensure the requirements of the method or specification are met;
- ensure that adequately trained and experienced personnel are in place for analytical testing;
- provide a documentation system capable of recording receipt and testing of samples to the required specification using approved test methods, and of reporting, recording and collating data and designation of status (approved, rejected, quarantine);
- execute the transfer protocol;
- perform the appropriate level of validation to support the implementation of the methods; and
- generate and obtain approval of transfer reports.

6.6 Appropriate training should be provided and all training activities and outcomes should be documented.

6.7 Reference to compendial monographs (e.g. *The International Pharmacopoeia* (*15*), *European Pharmacopoeia*, *British Pharmacopoeia* and *United States Pharmacopeia*), where available, is expected.

6.8 Possible experimental designs and acceptance criteria for the main analytical testing methods are shown in Table 1. Note that this table represents high-level guidance to apply the general principle that method transfers should account for the variability and sensitivity of the method and the specifications for the quality parameter. Alternative procedures and acceptance criteria may be applied based on science and the characteristics of the analytical method and the analyte.

Table 1
Possible experimental designs and acceptance criteria for analytical testing

Test	Considerations for transfer	Replication of tests	Set-up	Acceptance criteria	
				Direct	Statistically derived
Identity	Transfer should focus on sample preparation, instruments, data interpretation. Acceptable to include in assay transfer where relevant	One determination usually sufficient to demonstrate equivalence			

Test	Considerations for transfer	Replication of tests	Set-up	Acceptance criteria	
				Direct	Statistically derived
Assay for potency	– *Non-specific assay should not be used for stability testing.* – Bracketing may be appropriate for multiple strengths	At each site: 2 analysts × 3 lots, in triplicate (= 18 per site)	Different sets of instruments and columns Independent solution preparation	Comparison of mean and variability	Two one-sided *t*-tests with intersite differences ≤ 2% , 95% confidence
Content uniformity	If method is equivalent to assay method, separate transfer is not usually requird	At each site: 2 analysts, × 1 lot (= 2 per site)	Different sets of instruments and columns Independent solution preparation	Mean at RU within ± 3% of mean at SU; comparison of relative st. dev.	Two one-sided *t*-tests with intersite differences ≤ 3% , 95% confidence
Dissolution	Bracketing may be appropriate for multiple strengths	6 units (12 if not routine at RU, and for extended release products)		Mean at RU within ± 5% of mean at SU	Compare profile (e.g. F^2), or Compare data at Q time points as for assay
Cleaning verification (recovery of residues from surfaces)	Confirm that same swabbing material is used at sending unit (SU) and receiving unit (RU)		Use spiked samples, with levels within 3× validated st. dev. or within ± 10% of specification (whichever is the greater)	– All samples spiked above specification should fail – 90% of samples spiked below specification should pass	
Microbiological testing (qualitative and quantitative limit tests)	– Execute common on-site validation protocol: rationale; method identity; validation parameters; data summary; acceptance criteria; methods of compiling and analysing data; handling of out-of-specification results; follow-up requirements – Use same materials, techniques, inoculum preparation	Validation in triplicate	Use different lots for each validation exercise	– Qualitative: Demonstrate recovery of microorganisms – Quantitative: Recovery levels within acceptance limits specified in protocol	

Test	Considerations for transfer	Replication of tests	Set-up	Acceptance criteria	
				Direct	Statistically derived
Impurity, degradation, residual solvents	– Confirm response factors for calculation relative to drug peak; – Confirm limit of quantitation at RU; – Compare chromatograms – Compare accuracy and precision for spiking experiments	At each site: 2 analysts × 3 lots, in duplicate (in triplicate if done together with assay)	– Different days, different sets of instruments and columns – Use samples of similar age, homogeneity, packaging, storage – Use spiked samples if necessary	(For low levels) Values at RU within ± 25% of values at SU, or Mean at RU within ± 0.05% of mean at SU (5%)	(For moderately high levels) Two one-sided *t*-tests, differences ≤ 10%, 95% confidence

st. dev., standard deviation.
Note: numbers in the table are given as examples only and should not be considered as recommendations.

The SU and the RU should execute the transfer protocol and jointly prepare a transfer report. The points to be addressed in the analytical methods transfer report are listed in these guidelines.

7. Premises and equipment

Premises

7.1 The SU should provide information to the RU on the layout, construction and finish of buildings and services (*16*,*17*) (heating, ventilation and air-conditioning (HVAC), temperature, relative humidity, water, power, and compressed air), which have an impact on the product, process or method to be transferred.

7.2 The SU should provide information on relevant health, safety and environmental issues, including:

- inherent risks of the manufacturing processes (e.g. reactive chemical hazards, exposure limits, fire and explosion risks);
- health and safety requirements to minimize operator exposure (e.g. atmospheric containment of pharmaceutical dust);
- emergency planning considerations (e.g. in case of gas or dust release, spillage, fire and firewater run-off); and
- identification of waste streams and provisions for re-use, recycling and/or disposal.

Equipment

7.3 The SU should provide a list of equipment, makes and models involved in the manufacture, filling, packing and or control of the product, process or method to be transferred, together with existing qualification and validation documentation. Relevant documentation may include:

— drawings;
— manuals;
— maintenance logs;
— calibration logs; and
— procedures (e.g. regarding equipment set-up, operation, cleaning, maintenance, calibration and storage).

7.4 The RU should review the information provided by the SU together with its own inventory list including the qualification status (IQ, OQ, PQ) of all equipment and systems, and perform a side-by-side comparison of equipment at the two sites in terms of their functionality, makes, models and qualification status.

7.5 The RU should perform a gap analysis to identify requirements for adaptation of existing equipment, or acquisition of new equipment, or a change in the process, to enable the RU to reproduce the process being transferred. GMP requirements should be satisfied and intended production volumes and batch sizes (e.g. same, scaled-up or campaign) should be considered. Factors to be compared include:

— minimum and maximum capacity;
— material of construction;
— critical operating parameters;
— critical equipment components (e.g. filters, screens, and temperature/pressure sensors);
— critical quality attribute; and
— range of intended use.

7.6 The facility- and building-specific location of all equipment at the RU should be considered at the time of drawing up process maps or flow charts of the manufacturing process to be transferred, including flows of personnel and material.

7.7 The impact of manufacturing new products on products currently manufactured with the same equipment should be determined.

7.8 Any modification of existing equipment that needs to be adapted to become capable of reproducing the process being transferred should be documented in the transfer project plan.

8. Documentation

8.1 The documentation required for the transfer project itself is wide-ranging. Examples of documentation commonly required are summarized in Table 2.

8.2 The documented evidence that the transfer of technology has been considered successful should be formalized and stated in a technology transfer summary report. That report should summarize the scope of the transfer, the critical parameters as obtained in the SU and RU (preferably in a tabulated format) and the final conclusions of the transfer. Possible discrepancies should be listed and appropriate actions, where needed, taken to resolve them.

Table 2
Examples of documentation for transfer of technology (TOT)

Key task	Documentation provided by SU	Transfer documentation
Project definition	Project plan and quality plan (where separate documents), protocol, risk assessments, gap analysis	Project implementation plan **TOT protocol**
Quality agreement		
Facility assessment	Plans and layout of facility, buildings (construction, finish) Qualification status (DQ, IQ, OQ) and reports	Side-by-side comparison with RU facility and buildings; gap analysis **Qualification protocol and report**
Health & Safety assessment	Product-specific waste management plans Contingency plans	
Skill set analysis and training	SOPs and training documentation (product-specific operations, analysis, testing)	Training protocols, assessment results
Analytical method transfer	Analytical method specifications and validation, including in-process quality control	Analytical methods transfer protocol and report
Starting material evaluation	Specifications and additional information on APIs, excipients	

Key task	Documentation provided by SU	Transfer documentation
Equipment selection and transfer	Inventory list of all equipment and systems, including makes, models, qualification status (IQ, OQ, PQ) Drawings, manuals, logs, SOPs (e.g. set-up, operation, cleaning, maintenance, calibration, storage)	Side-by-side comparison with RU equipment (makes, models, qualification status) Gap analysis **Qualification and validation protocol and report**
Process transfer: manufacturing and packaging	Reference batches (clinical, dossier, biobatches) Development report (manufacturing process rationale) History of critical analytical data Rationale for specifications Change control documentation Critical manufacturing process parameters Process validation reports Drug master file API validation status and report(s) Product stability data Current master batch manufacturing and packaging records List of all batches produced Deviation reports Investigations, complaints, recalls Annual product review	History of process development at RU Experiences at RU should be recorded for future reference Provisional batch manufacturing document (RU to develop) Provisional batch packaging document (RU to develop) Description of process at RU (narrative, process map, flow chart) **Process validation protocol and report**
Cleaning	Cleaning validation, including: Solubility information; therapeutic doses; category (toxicology); existing cleaning SOPs; validation reports — chemical and micro; agents used; recovery study	Product- and site-specific cleaning SOPs at RU **Cleaning validation protocol and report**

DQ, design qualification; IQ, installation qualification; OQ, operational qualification; API, active pharmaceutical ingredient; SOPs, standard operating procedures; RU, receiving unit.

9. Qualification and validation

General

9.1 The extent of qualification and or validation (*18*) to be performed should be determined on the basis of risk management principles.

9.2 Qualification and validation should be documented.

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Annex 8

Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services

Background

Under the World Health Organization (WHO)'s Revised Drug Strategy adopted by the World Health Assembly in 1986, WHO organized two meetings on the role of the pharmacist, in Delhi, India in 1988 and in Tokyo, Japan in 1993. This was followed by the adoption, in May 1994, of the World Health Assembly Resolution WHA47.12 on the role of the pharmacist, in support of the WHO Revised Drug Strategy.

In 1992 the International Pharmaceutical Federation (FIP) developed standards for pharmacy services under the heading "Good pharmacy practice in community and hospital pharmacy settings". The text on good pharmacy practice was also submitted to the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1994. Following the recommendations of the WHO Expert Committee and the endorsement of the FIP Council in 1997, the FIP/WHO joint document on good pharmacy practice (GPP) was published in 1999 in the thirty-fifth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 885).

Subsequently WHO organized two more meetings on the role of the pharmacist, in Vancouver, Canada in 1997 and in the Hague, the Netherlands in 1998. These meetings reinforced the need for pharmacy curricular reform and the added value of the pharmacist in self-care and self-medication.

In collaboration with WHO, the first edition of a practical handbook *Developing pharmacy practice — a focus on patient care* was launched in 2006. This handbook is designed to meet the changing needs of pharmacists, setting out a new paradigm for pharmacy practice and presenting a step-by-step approach to pharmaceutical care.

With the overall aim of improving standards and practice of distribution and use of medicines, using the FIP/WHO guidelines for GPP as the framework, FIP took the initiative to explore the possibilities for providing technical assistance to its Member Organizations in Cambodia, Moldova, Mongolia, Paraguay, Thailand, Uruguay and Viet Nam, in developing national standards for GPP in a pilot study from 2005 to 2007. In 2007 the "Bangkok declaration on good pharmacy practice in the community pharmacy settings" in the South-East Asia Region was adopted by the FIP South-East Asia Pharmaceutical Forum and set out the commitment of its Member Associations towards raising standards of pharmacy services and professional practice.

Since the adoption of the GPP guidelines in community and hospital settings, significant changes in practice, applied science and technology and pharmaceutical policy have occurred, including the relevance of more recent World Health Assembly resolutions: WHA54.11 (WHO Medicines

Strategy), WHA54.13 (Strengthening health systems in developing countries), WHA55.14 (Ensuring accessibility of essential medicines), WHA55.18 (Quality of care: patient safety), WHA57.16 (Health promotion) and WHA60.16 (Rational use of medicines).

Furthermore, in 2007 FIP established an initiative to investigate the need to update the guidelines on GPP to reflect contemporary standards of practice and thinking. An FIP working group on GPP first met on 15 October 2007 to identify key issues that needed to be considered in the revision of the guidelines.

In 2008 FIP organized an expert consultation in Basel, Switzerland during its 68th World Congress. Fifty participants attended the meeting, including the FIP Working Group (WG) on GPP, WHO staff from headquarters, representatives from the WHO Regional Office for the Eastern Mediterranean, country medicines advisers from Ghana, Nigeria and the United Republic of Tanzania, Presidents and Secretaries of the six FIP Regional Pharmaceutical Forums, FIP Member Organizations and several invited experts.

Following this consultation, the FIP WG on GPP undertook an extensive review of the existing national standards on GPP in at least 37 countries and established a time frame that would allow sufficient consultation with all of FIP's 120 national Member Associations, relevant experts and WHO. A proposal for this initiative was presented to the forty-third meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2008 and an updated report was provided to the Expert Committee at its forty-fourth meeting in October 2009.

1. Introduction

The health of the public is fundamental to the happiness and welfare of all people. Barriers to good health include poor access to quality medical products, lack of access to trained health professionals and care, an inadequate health workforce, unaffordable cost of care and poor standards of education of health-care professionals.

Medicines are an essential and critical part of health-care services in all cultures and societies. When accessed, medicines are often an essential component of many disease prevention programmes and virtually all disease treatment plans. The potential benefit of medicines is often not realized — there is a gap between the proven efficacy of medicines demonstrated in clinical trials and their actual effectiveness in practice. The reasons for this gap include problems with medicine selection and dosages, improper administration of medicines and lack of adherence by patients to prescribed treatment, medicine–medicine and medicine–food interactions, and adverse medicine events. Besides clinical problems associated with medicine-related problems, there are cost

implications. It has been estimated that the cost of problems with the use of medicines is equal to or greater than the cost of the medicines themselves.

Medicines are also increasingly expensive and their cost is compromising the affordability of health care. Managing the costs of medicines is critical to making the best use of limited resources to maximize health care for as many people as possible.

Substandard, adulterated, unlicensed and spurious/falsely-labelled/falsified/counterfeit medicines are a growing problem that compromise health. There is a need for a system of assuring the integrity of the medicine supply chain to assure the value of medicines used for the prevention of disease and the treatment of patients.

Pharmacists[1] are specifically educated and trained health professionals who are charged by their national or other appropriate (e.g. state or provincial) authorities with the management of the distribution of medicines to consumers and to engage in appropriate efforts to assure their safe and efficacious use. There is also increasing recognition that providing consumers with medicines alone is not sufficient to achieve the treatment goals. To address these medication-related needs, pharmacists are accepting greater responsibility for the outcomes of medicines use and are evolving their practices to provide patients with enhanced medicines-use services.

As health-care professionals, pharmacists play an important role in improving access to health care and in closing the gap between the potential benefit of medicines and the actual value realized and should be part of any comprehensive health system. In addition, the increasingly complex and diverse nature of pharmacists' roles in the health-care system and public health demands a continuous maintenance of the competence of pharmacists as health-care professionals who have up-to-date skills and expertise.

National pharmacy professional associations need to work together with their governing bodies and other health-care professional associations to support pharmacists in their countries through provision of continuing professional development activities, including distance-learning programmes, and establishing national standards of pharmacy services and practice objectives.

These guidelines are intended to provide a description of ways in which pharmacists can improve access to health care, health promotion and the use of medicines on behalf of the patients they serve. The role of FIP is to provide leadership for national pharmacy professional organizations,

[2] Pharmacists are health-care professionals whose professional responsibilities and accountabilities include seeking to ensure that people derive maximum therapeutic benefit from their treatments with medicines. This requires them to keep abreast of developments in pharmacy practice and the pharmaceutical sciences, professional standards and requirements, the laws governing pharmacy and medicines and advances in knowledge and technology relating to use of medicines.

which in turn provide the impetus for setting national standards.[2] The vital element is the commitment of the pharmacy profession worldwide to promoting excellence in practice for the benefit of those served. The public and other professions will judge the pharmacy profession on how its members translate that commitment into practice in all settings, especially community and hospital pharmacy settings.

It is the policy of FIP and WHO to provide guidance to national pharmacy professional organizations regarding the development of their national GPP guidelines. The conditions of practice vary widely from country to country and each national pharmacy professional organization is best able to decide what can be achieved and within what time-scale.

2. Underlying philosophy

The mission of pharmacy practice is to contribute to health improvement and to help patients with health problems to make the best use of their medicines.

There are six components to this mission:

— being readily available to patients with or without an appointment;
— identifying and managing or triaging health-related problems;
— health promotion;
— assuring effectiveness of medicines;
— preventing harm from medicines; and
— making responsible use of limited health-care resources.

In the community setting, pharmacists should be acknowledged as health-care professionals whom patients can consult for health-related problems. Because health-care products and services are available from the pharmacist, some problems can be managed at this point of care. Problems that require additional diagnostic skill or treatments not available from a pharmacist can be referred to an appropriate health-care professional or site of care, such as a hospital. This should be done in good collaboration between the health-care providers.

To improve the use of medicines, pharmacists have responsibilities for many aspects of the process of medicines use, each of which is important to achieve good outcomes from treatment. This begins with assuring the integrity of the medicine supply chain, including detecting spurious/falsely-labelled/falsified/counterfeit medicines, ensuring proper storage of medicines and quality preparation of medicines when needed. It also includes assuring the proper prescribing of medicines so that dose regimens and dosage forms

[2] Throughout this document, the term "national standards" includes laws, regulations, standards, ordinances or other requirements enacted or promulgated by an official body at any level of government, as well as guidelines, recommendations or other pronouncements of professional organizations of pharmacy.

are appropriate; instructions for use are clear; medicine–medicine and medicine–food interactions are prevented; known and predictable adverse medicine reactions, including allergies and other contraindications, are avoided; unnecessary treatments are minimized and the cost of medicines is considered.

Another important component of this mission is assisting patients and those administering medicines to understand the importance of taking medicines properly, including the correct timing of doses, foods or other medicines to avoid when taking a dose and what to expect after taking the medicine. Monitoring treatment to verify effectiveness and adverse medicine events is also an important part of the process of use of medicines.

3. Definition of good pharmacy practice

GPP is the practice of pharmacy that responds to the needs of the people who use the pharmacists' services to provide optimal, evidence-based care. To support this practice it is essential that there be an established national framework of quality standards and guidelines.

4. Requirements of good pharmacy practice

- GPP requires that a pharmacist's first concern in all settings is the welfare of patients.
- GPP requires that the core of the pharmacy activity is to help patients make the best use of medicines. Fundamental functions include the supply of medication and other health-care products of assured quality, the provision of appropriate information and advice to the patient, administration of medication, when required, and the monitoring of the effects of medication use.
- GPP requires that an integral part of the pharmacist's contribution is the promotion of rational and economic prescribing, as well as dispensing.
- GPP requires that the objective of each element of pharmacy service is relevant to the patient, is clearly defined and is effectively communicated to all those involved. Multidisciplinary collaboration among health-care professionals is the key factor for successfully improving patient safety.

In satisfying these requirements, the following conditions are necessary:

- the well-being of patients should be the main philosophy underlying practice, even though it is accepted that ethical and economic factors are also important;
- pharmacists should have input into decisions about the use of medicines. A system should exist that enables pharmacists to report and to obtain feedback about adverse events, medicine-related problems, medication errors, misuse or medicine abuse, defects in product quality or detection

of counterfeit products. This reporting may include information about medicine use supplied by patients or health professionals, either directly or through pharmacists;

- the relationship with other health professionals, particularly physicians, should be established as a therapeutic collaborative partnership that involves mutual trust and confidence in all matters relating to pharmacotherapy;
- the relationship between pharmacists should be one of colleagues seeking to improve pharmacy service, rather than acting as competitors;
- in reality, organizations, group practices and pharmacy managers should accept a share of responsibility for the definition, evaluation and improvement of quality;
- the pharmacist should be aware of essential medical and pharmaceutical information (i.e. diagnosis, laboratory test results and medical history) about each patient. Obtaining such information is made easier if the patient chooses to use only one pharmacy or if the patient's medication profile is available;
- the pharmacist needs evidence-based, unbiased, comprehensive, objective and current information about therapeutics, medicines and other health-care products in use, including potential environmental hazard caused by disposal of medicines' waste;
- pharmacists in each practice setting should accept personal responsibility for maintaining and assessing their own competence throughout their professional working lives. While self-monitoring is important, an element of assessment and monitoring by the national pharmacy professional organizations would also be relevant in ensuring that pharmacists maintain standards and comply with requirements for continuous professional development;
- educational programmes for entry into the profession should appropriately address both current and foreseeable changes in pharmacy practice; and
- national standards of GPP should be specified and should be adhered to by practitioners.

At the national or appropriate (e.g. state or provincial) level, it is necessary to establish:

- A legal framework that:
  — defines who can practice pharmacy;
  — defines the scope of pharmacy practice;
  — ensures the integrity of the supply chain and the quality of medicines.

- A workforce framework that:
  — ensures the competence of pharmacy staff through continuing professional development (CPD or continuing education (CE)) programmes;
  — defines the personnel resources needed to provide GPP.

- An economic framework that:
  — provides sufficient resources and incentives that are effectively used to ensure the activities undertaken in GPP.

5. Setting standards for good pharmacy practice

GPP includes standards that often exceed those laid down by national legislation. Furthermore, legislation seldom gives precise instructions about how the services should be produced to meet the requirements. Therefore, national pharmacy professional associations have a role in setting standards required for GPP, which includes a quality management framework and a strategic plan for developing services. It is also recognized that in developing national standards for GPP, attention must be paid to both the needs of the users of health-care services and the capacity of national health-care systems to support these services.

Just as pharmacy practice will vary among nations, it will also vary among practice locations. Therefore, standards should recognize the uniqueness of different pharmacy practice settings (e.g. community and hospital pharmacy). In addition, as medicines and needs change, the standards should acknowledge evolving practice settings and provide these developing services with guidance without negatively affecting the evolutionary nature of practice. At the same time, a baseline should be established for practice below which the activity cannot be considered "pharmacy practice" at all and, therefore, should not be condoned.

When establishing minimum standards on GPP, FIP emphasizes the importance of first defining the roles played by pharmacists, as expected by patients and society. Secondly, relevant functions for which pharmacists have direct responsibility and accountability need to be determined within each role. Thirdly, minimum national standards should then be established, based upon the need to demonstrate competency in a set of activities supporting each function and role.

The minimum national standards for each activity are based on processes that need to be relevant and defined appropriately according to the local needs of the pharmacy practice environment and national profession aspirations. All national pharmacy professional associations should also adapt these roles and functions in accordance to their own requirements. The activities listed below can be further defined and measured by setting indicators of good practice within a national context and can be weighted by actual practice-setting priorities.

It is recommended that national pharmacy professional associations consider the following roles, functions and activities for pharmacists, *where appropriate*:

Role 1: Prepare, obtain, store, secure, distribute, administer, dispense and dispose of medical products

- Function A: Prepare extemporaneous medicine preparations and medical products

  Minimum national standards should be established for these activities.
  - — Pharmacists should ensure that medicine preparation areas are appropriately designed to permit ease of extemporaneous preparations and are maintained in a manner that minimizes the potential for medication errors and assures the cleanliness and safety of medical products.
  - — Pharmacists should ensure that compounded medicines are consistently prepared to comply with written formulas and quality standards for raw materials, equipment and preparation processes, including sterility where appropriate.

- Function B: Obtain, store and secure medicine preparations and medical products

  Minimum national standards should be established for these activities.
  - — Pharmacists who are responsible for procurement should ensure that the procurement process is transparent, professional and ethical so as to promote equity and access and to ensure accountability to relevant governing and legal entities.
  - — Pharmacists who are responsible for procurement should ensure that procurement is supported by strong quality assurance principles to assure that substandard, adulterated, unlicensed and spurious/falsely-labelled/falsified/counterfeit medicines are not procured or allowed into the system.
  - — Pharmacists who are responsible for procurement should ensure that procurement is supported by a reliable information system which provides accurate, timely and accessible information.
  - — Pharmacists should establish contingency plans for shortages of medicines and for purchases in emergencies.
  - — Pharmacists should assure that proper storage conditions are provided for all medicines, especially for controlled substances, used in the pharmacy or health-care facility.

- Function C: Distribute medicine preparations and medical products

  Minimum national standards should be established for these activities.
  - — Pharmacists should ensure that all medical products, including medicine samples, are handled and distributed in a manner that assures reliability and safety of the medicine supply.
  - — Pharmacists should establish an effective distribution system which includes a written procedure, to recall promptly and effectively

medical products known or suspected to be defective or spurious/falsely-labelled/falsified/counterfeit, with a designated person(s) responsible for recalls.
— Pharmacists should develop with manufacturers, wholesalers and government agencies (where appropriate) an access plan for uninterrupted supply of essential medicines as part of a disaster or pandemic preparedness strategy.
— As part of a disaster or pandemic preparedness strategy, national medicines regulatory agencies may introduce new medicines which are authorized for marketing with limited safety data; pharmacists have a responsibility to be aware of the safety issues and to institute necessary mechanisms for monitoring occurrence of adverse events.

- Function D: Administration of medicines, vaccines and other injectable medications

Minimum national standards should be established for these activities.
— Pharmacists should have a role in the preparation and administration of medicines, in establishing procedures in their work settings with respect to the administration, and in monitoring the outcomes of medication administration.
— Pharmacists should have an educator, facilitator and immunizer role, thus contributing to the prevention of diseases through participation in vaccination programmes, by ensuring vaccination coverage and by also ensuring vaccine safety.
— Pharmacists should participate in directly observed therapy (DOT) programmes in areas such as the management of drug addiction, HIV/AIDS, tuberculosis and sexually transmitted diseases, where applicable.

- Function E: Dispensing of medical products

Minimum national standards should be established for these activities.
— Pharmacists should ensure that appropriate facilities, trained personnel, standard dispensing practices and documentation procedures are in place in the pharmacy for the supply and dispensing of prescribed medicines and other health-care products.
— Pharmacists should assess and evaluate all paper or electronic prescriptions received, considering the therapeutic, social, economic and legal aspects of the prescribed indication(s) before supplying medical products to the patient. Where possible, generic substitution is recommended.
— Pharmacists should ensure patient confidentiality at the point of dispensing medical products and should provide advice to ensure that the patient receives and understands sufficient written and oral information to derive maximum benefit for the treatment.

- Function F: Dispose of medicine preparations and medical products

  Minimum national standards should be established for these activities.
  — Pharmacists should ensure that regular monitoring of the medicines inventory is conducted and should always include medicines samples in the process of periodic inspection for expiration dates and removal of outdated stock.
  — Pharmacists should ensure that recalled medical products, including medicines samples, are immediately stored separately for subsequent disposal and prevented from being available for further dispensing or distribution.
  — Pharmacists should establish a safe way of medicines waste disposal at the hospital and/or community pharmacy so that patients and the public can be encouraged to return their expired or unwanted medicines and medical devices. Alternatively, pharmacists should provide appropriate information to patients on how to safely dispose of expired or unwanted medicines.

Role 2: Provide effective medication therapy management[3]

- Function A: Assess patient health status and needs

  Minimum national standards should be established for these activities.
  — Pharmacists should ensure that health management, disease prevention and healthy lifestyle behaviour are incorporated into the patient assessment and care process.
  — Pharmacists should acknowledge unique patient considerations such as education level, cultural beliefs, literacy, native language and physical and mental capacity in all individual patient assessments.

- Function B: Manage patient medication therapy

  Minimum national standards should be established for these activities.
  — Pharmacists should maintain access to an appropriate evidence base relating to the safe, rational and cost-effective use of medicines such as reference books on medicines, journals, national essential medicines lists and standard treatment guidelines.
  — Pharmacists should ensure that medicine formulary system(s) (local, regional and/or national) are linked to standard treatment guidelines, protocols and treatment pathways based on the best available evidence.
  — Pharmacists should have a key role in educating prescribers on the access to and evidence for optimal and appropriate use of medicines including the required monitoring parameters and prescribing adjustments. Where appropriate, pharmacists should provide advice

[3] Medication therapy management is a distinct service or group of services that optimize therapeutic outcomes for individual patients. Medication therapy management services are independent of, but can occur in conjunction with, the provision of a medication product.

or recommendations to the prescriber on medicine therapy, including the selection of the appropriate medication or dosage.
— Pharmacists should have access to, contribute to and use all necessary clinical and patient data to coordinate effective medication therapy management, especially when multiple health-care practitioners are involved in the patient's medication therapy, and intervene if necessary.
— Pharmacists should establish a standard operating procedure for referrals to physicians, specialists or other health-care providers, where appropriate.
— Pharmacists should provide continuity of care by transferring information on patients' medicines as patients move between sectors of care.

- Function C: Monitor patient progress and outcomes

Minimum national standards should be established for these activities.
— Pharmacists should consider patient diagnosis and patient-specific needs when assessing patient response to medicine therapy and intervene if necessary.
— Pharmacists should document necessary clinical and patient data to assess and monitor medication therapy and to track patients' therapeutic outcomes.
— Pharmacists should perform point-of-care testing for patients in order to monitor and adjust therapy, when needed.

- Function D: Provide information about medicines and health-related issues

Minimum national standards should be established for these activities.
— Pharmacists should ensure that in every pharmacy there is a suitable place for discussing confidential information with the customers and patients.
— Pharmacists should provide sufficient health, disease and medicine-specific information to patients for their participation in their decision-making process regarding a comprehensive care management plan. This information should aim at supporting adherence to treatment and empowerment of the patient.
— Pharmacists should be proactive in reducing antimicrobial resistance by providing information about the appropriate use of antimicrobials to consumers and prescribers.

Role 3: Maintain and improve professional performance

- Function A: Plan and implement continuing professional development[4] strategies to improve current and future performance

[4] The concept of continuing professional development (CPD) can be defined as "the responsibility of individual pharmacists for systematic maintenance, development and broadening of knowledge, skills and attitudes, to ensure continuing competence as a professional, throughout their careers."

Minimum national standards should be established for these activities.

— Pharmacists should perceive continuing education as being lifelong and be able to demonstrate evidence of continuing education or continuing professional development to improve clinical knowledge, skills and performance.

— Pharmacists should take steps to update their knowledge and skills about complementary and alternative therapies such as traditional Chinese medicines, health supplements, acupuncture, homeopathy and naturopathy.

— Pharmacists should take steps to update their knowledge and be engaged in implementation of new technology and automation in pharmacy practice, where feasible.

— Pharmacists should take steps to become informed and update their knowledge on changes to information on medical products.

Role 4: Contribute to improve effectiveness of the health-care system and public health

- Function A: Disseminate evaluated information about medicines and various aspects of self-care

  Minimum national standards should be established for these activities.

  — Pharmacists should ensure that the information provided to patients, other health-care professionals and the public is evidence-based, objective, understandable, non-promotional, accurate and appropriate.

  — Pharmacists should develop and/or use educational materials for health management, health promotion and disease prevention programmes that are applicable to a wide range of patient populations, age groups and health literacy levels.

  — Pharmacists should educate patients on how to evaluate and use web-based or other forms of health-care information (including medicines information) and strongly encourage them to be advised by a pharmacist regarding the information they find, particularly if obtained from the Internet.

  — Pharmacists should assist patients and their care providers to obtain and critically analyse information to meet their individual needs.

- Function B: Engage in preventive care activities and services

  Minimum national standards should be established for these activities.

  — Pharmacists should engage in preventive care activities that promote public health and prevent disease, i.e. in areas such as smoking cessation, infectious and sexually transmitted diseases.

— Pharmacists should provide point-of-care testing, where applicable, and other health screening activities for patients at higher risk of disease.

- Function C: Comply with national professional obligations, guidelines and legislations

  Minimum national standards should be established for these activities.
  — Pharmacists should take steps to ensure that they comply with the provisions of a national code of ethics for pharmacists.

- Function D: Advocate and support national policies that promote improved health outcomes

  Minimum national standards should be established for these activities.
  — Pharmacists should contribute to public and professional groups to promote, evaluate and improve health in the community
  — Pharmacists should collaborate with other health-care professionals in their efforts to improve health outcomes.

6. Conclusions

There are four main roles where pharmacists' involvement or supervision is expected by society and the individuals they serve:

1. Prepare, obtain, store, secure, distribute, administer, dispense and dispose of medical products.
2. Provide effective medication therapy management.
3. Maintain and improve professional performance.
4. Contribute to improve effectiveness of the health-care system and public health.

These roles may vary for each individual pharmacist depending on their practice responsibilities.

Specific standards of GPP can be developed only within a national pharmacy professional organization framework.

This guidance is recommended as a set of professional goals to be met in the interest of the patients and other key stakeholders in the pharmaceutical sector. Responsibility for moving the project forward will rest with each national pharmacy professional association. Achieving specific standards of GPP for each nation within these recommendations may require considerable time and effort. As health professionals, pharmacists have a duty to begin the process without delay.

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Annex 9

Model guidance for the storage and transport of time- and temperature–sensitive pharmaceutical products

Abbreviations

CAPA	corrective and preventive action (procedures)
DCVMN	Developing Countries Vaccine Manufacturers Network
EEFO	earliest-expiry-first-out. Used in this document as equivalent to FEFO (first to expire-first-out)
FIFO	first-in-first-out
GDP	good distribution practice
GMP	good manufacturing practice
GPS	global positioning system
GSP	good storage practice
HVAC	heating ventilating and air-conditioning (system)
IATA	International Air Transport Association
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IQ	installation qualification
PCCIG	Pharmaceutical Cold Chain Interest Group
PDA	Parenteral Drug Association
SKU	stock-keeping unit
SLA	service level agreement
SMS	short message service
SOP	standard operating procedure
TTSPP	time- and temperature-sensitive pharmaceutical product
UPS	uninterrupted power supply
USP	United States Pharmacopeia

Background

These guidelines set out the principal requirements for the safe storage and distribution of time- and temperature-sensitive pharmaceutical products (TTSPPs). They are based upon existing regulations and best practice guidance from a wide range of international sources (see References), while accepting that local legislation and regulations will continue to take precedence. The target audience includes regulators, logisticians and pharmaceutical professionals in industry, government and the international agencies.

The document has been prepared in close consultation with the WHO Task Force on Regulatory Oversight on Pharmaceutical Cold Chain Management which has been central to the review process. A full list of members is given at the end of this annex.

The intention is that the guidance in this document should be directly applicable in less-developed countries as well as in the industrialized world. To this end, supplementary materials will be developed to show

how the requirements can practicably be achieved, particularly in resource-constrained settings. Experience with vaccine supply chain assessments in many less-developed countries demonstrates that the mandatory standards set out in this document can be achieved, and that some countries are also capable of meeting many of the optional requirements.

The document is designed to give a balanced overview of the major aspects of good storage and distribution practice for TTSPPs. As such it deliberately includes references to requirements which can be found in general guides to good manufacturing practice (GMP), good storage practice (GSP) and good distribution practice (GDP). The purpose is not to supplant these source materials, but to ensure that the reader is aware of the relevant GMP, GSP and GDP implications when seen from the particular and specialized perspective of TTSPP management.

Key to conventions used

The following conventions are used in the requirements clauses:

- The imperative voice is used to denote a mandatory or highly desirable requirement. For example: "Ensure that…", "Provide…" and the like.
- The words "where possible" or "preferably" are used to denote an optional but desirable requirement.
- Many clauses are followed by a brief explanation setting out the underlying reason for including the clause.

Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

active systems

Actively powered systems using electricity or other fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulation (e.g. cold rooms, refrigerators, temperature-controlled trucks, refrigerated ocean and air containers).

change control

The processes and procedures to manage system changes.

common carrier

A seller of distribution services.

controlled or hazardous time- and temperature-sensitive pharmaceutical products

Time- and temperature-sensitive pharmaceutical products (TTSPPs) with high illicit value: poisons, narcotics, psychotropic products, inflammable or explosive substances and radioactive materials.

dunnage

Loose packing material used to protect TTSPPs from damage during transport.

external distribution

Transport of TTSPPs through various steps in the customer's supply chain (i.e. transport from a pharmaceutical manufacturer's distribution centre to commercial customers (including wholesalers, retailers and buying groups), to clinical facilities or direct to the patient).

installation qualification

The process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specifications and that it functions within predetermined limits when operated in accordance with the operating instructions.

internal distribution

Transport of a TTSPP within a pharmaceutical manufacturer's internal supply chain (i.e. all internal transports from manufacturing facility to packaging facility to warehouse to distribution centre).

net storage capacity

The total volume available for storing TTSPPs, taking account of the type of load support system employed (floor-standing pallets, adjustable pallet racking or shelving units), as modified by the utilization factor that can be achieved in the store.

passive systems

Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of pre-conditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

pests

Includes birds, bats, rodents and insects whose uncontrolled presence affects hygiene and cleanliness.

pharmaceutical product

Any product intended for human use or veterinary product intended for administration to food-producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. It does not, however, include medical devices.[1]

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[1] Definition from *Revision of WHO good distribution practices for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report.* Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 5.

qualification

Documented testing that demonstrates, with a high degree of assurance, that a specific process will meet its predetermined acceptance criteria.[2]

refrigeration equipment

The term "refrigeration" or "refrigeration equipment" means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

service level agreement (SLA)

A service level agreement or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees and communication mechanisms. It can either be legally binding, or an information agreement. The SLA may also specify the target and minimum level performance, operation or other service attributes.[3]

standard operating procedure (SOP)

A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness.

storage temperature

The temperature range listed on the TTSPP label, and within the regulatory documentation, for long-term storage.

storage unit temperature/humidity distribution

The range and pattern of temperatures and/or humidity within a temperature-controlled storage unit during normal operation.

suspect product

A TTSPP whose presentation and/or pharmacological formulation indicates that it has not been manufactured by the company named on the packaging. A TTSPP that shows visible or pharmacological evidence of tampering.

temperature-controlled

Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

temperature excursion

An excursion event in which a TTSPP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for

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[2] Definition from the Parenteral Drug Association (PDA) Technical Report No. 39, 2007.
[3] Definition from International Air Transport Association (IATA), Chapter 17, 9th ed., June 2009.

storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data.

temperature-modified

Includes any environment in which the temperature is predictably maintained at a level different from that of the surrounding environment, but is not actively or passively controlled within precise predefined limits.

time- and temperature-sensitive pharmaceutical product (TTSPP)

Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

transport temperature profile

Anticipated ambient temperature variation and duration to which a TTSPP may be exposed during transport.

utilization factor

The percentage of the total volume available for storing TTSPPs that can reliably be achieved in practice, taking account of the types of stock-keeping unit (SKU), the types of load support system and the stock management systems used in the store.

validation

Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria.[4]

1. Importation

1.1 Port handling and customs clearance

1.1.1 *Port of entry*

Import TTSPPs through a port of entry that is equipped to handle such products. Where this is not possible, ensure that arrangements are in place to provide the necessary level of protection and security.

Reason: To minimize the risk of damage.

1.1.2 *Offloading*

As soon as possible after arrival, remove TTSPP shipments from the wharf or airport apron to a safe and suitable temperature-controlled storage location.

[4] Definition from PDA Technical Report No. 39, 2007.

Reason: To minimize the risk of theft and to avoid exposure to adverse ambient conditions.

1.1.3 *Temporary storage at port of entry*

Store TTSPP shipments in a secure warehouse under the conditions recommended by the product manufacturer, until the shipment has been authorized for removal by customs.[5]

Reason: To avoid risk of theft or damage during temporary storage.

1.1.4 *Customs clearance*

Draw up procedures and memoranda of understanding to ensure that TTSPP shipments are cleared through customs as rapidly as possible. This can be facilitated by a pre-clearance procedure carried out by the local health agency, clearing agent or freight forwarder in collaboration with customs. Alternatively the clearance process should be conducted by customs staff, supported by personnel with suitable pharmaceutical training, especially when clearance involves the opening and resealing of temperature-controlled packaging.

Reason: To avoid delays during customs clearance that may cause temperature excursions and place TTSPPs at risk.

2. Warehousing sites

2.1 Site layout

2.1.1 *Natural hazards*

Select and/or develop storage sites to minimize risks from natural hazards such as floods, landslides and earthquakes and extreme weather conditions such as hurricanes and tornadoes.

Reason: To protect against loss of valuable pharmaceutical products, to ensure continued supply to patients in the market and to protect personnel working in the store.

2.1.2 *Site access*

Provide vehicular access to storage buildings sufficient to accommodate the largest vehicles visiting the site, including emergency vehicles.

Reason: To ensure convenient operation of the facility.

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[5] In some situations, arrangements can be made for formal customs clearance to take place away from the port of entry — for example, at a national vaccine store. In situations where the port of entry is not equipped with suitable cold storage facilities, this can reduce the risk of temperature excursions.

2.2 Site security

Provide perimeter protection to ensure security of the grounds and storage buildings against anticipated risks.

Reason: To protect against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and the value of goods stored there.

2.3 Site cleanliness

Keep the site free of accumulated dust, dirt, waste and debris. Ensure that pests are kept under control within the site area. Collect waste in designated closed containers and arrange for safe disposal at frequent intervals.

Reason: To help protect storage buildings against ingress by dust, dirt and pests.

3. Storage buildings

3.1 Construction standards

Construct or procure storage buildings that are:

— purpose-designed for the storage of TTSPPs, or well-adapted for this purpose;
— designed to suit the prevailing climate, making maximum use of passive heating, cooling and ventilation;
— designed and equipped to minimize the consumption of electricity and other fuel sources;
— constructed using materials and finishes that are robust, easy to clean and which are selected to minimize long-term maintenance;
— constructed using locally available materials and building technologies; and
— built to minimize hiding and nesting places for pests.

Reasons: Storage in unsuitable and poorly-designed buildings places TTSPPs at risk and increases storage costs. Buildings constructed using inappropriate materials and technologies are difficult to operate and maintain in resource-constrained settings.

3.2 Accommodation and layout

Ensure that the storage buildings are well laid out and contain all the necessary storage areas, goods assembly, receiving and dispatch bays and office accommodation needed for efficient operation of the TTSPP store.

3.3 Loading and receiving bays

3.3.1 *Loading bays*

Ensure that receiving and dispatch bays are designed to avoid conflict between incoming and outgoing goods and are protected from direct sunlight, dust, dirt, rain, snow and wind, and from extremes of heat, cold and solar radiation that could damage TTSPPs, and measures are taken to minimize pest activity in these areas.

Reason: Protection against damage and maintenance of product quality.

3.3.2 *Receiving bays*

Provide receiving areas with suitable equipment to clean reusable transport containers after their contents have been unloaded, and before the containers are stored for re-use.

Reason: Protection against contamination of outgoing TTSPPs.

3.4 Goods assembly and quarantine areas

3.4.1 *Goods assembly areas*

Provide sufficient space to receive, assemble and pack TTSPPs for dispatch under temperature-modified conditions. Preferably, these areas should be physically close to the temperature-controlled storage area.

Reason: Protection of TTSPPs during arrival, order assembly and dispatch.

3.4.2 *Holding area for incoming goods*

Provide a temperature-controlled holding area for incoming TTSPPs pending their acceptance into the main storage area. The holding area may be a physically separated zone, or it may be defined using a suitable stock control information system, or by a combination arrangement. Where goods are held in bond in the warehouse, awaiting customs clearance, they must be physically separated and secured.

Reason: Incoming items may need inspection and/or regulatory clearance, including laboratory testing.

3.4.3 *Quarantine area*

Provide a quarantine area for the isolation of returned, faulty, recalled and otherwise withdrawn goods pending a decision on disposal or re-stocking by the qualified person or department. Materials within quarantine areas must be clearly identified with their status.

— with temperature control, for items returned for re-stocking;

— with temperature control, for items recalled for testing;
— without temperature control, for items awaiting disposal.

The quarantine area may be a physically separated zone, or it may be defined using a suitable stock control information system, or by a combination arrangement.

Reason: Items for re-stocking, testing and disposal should be kept separate to avoid the risk of inappropriate use.

3.5 Environmental control of ancillary areas

Ensure, where possible, that ancillary areas where TTSPPs are temporarily held during arrival, order assembly or dispatch are:

— maintained within the temperature range specified for the goods being handled;
— maintained within the humidity range specified for goods that are adversely affected by high relative humidity and are not sufficiently protected by their packaging;[6]
— protected from undue exposure to direct sunlight;
— protected from the weather;
— protected against dust, dirt and waste accumulation;
— adequately ventilated;
— adequately lit to enable operations to be carried out accurately and safely;
— monitored during the times when TTSPPs are handled; and monitored during the times when TTSPPs are handled (see 4.5.1-4.5.4.

Reason: Protection of TTSPP quality during arrival, order assembly or dispatch.

3.6 Building security

3.6.1 *General building security*

Ensure that buildings used to store TTSPPs have sufficient security to prevent unauthorized access and to prevent misappropriation of goods.

Reason: To protect against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and to the value of goods stored there.

3.6.2 *Controlled and hazardous substances areas*

Ensure that all areas that are used to store controlled or hazardous TTSPPs are:

[6] Active environmental control of ancillary areas may not be needed if all TTSPPs are kept in temperature-controlled packaging and/or humidity-protective packaging when passing through these areas.

— dedicated, securely locked facilities that comply fully with all legislative and regulatory requirements applicable in the country where the store is located;
— only accessible to authorized staff;
— protected by automatic intruder and/or fire and smoke, and/or chemical and/or radiological sensor alarm systems appropriate to the type(s) of product being stored;[7]
— designed to be explosion-proof, where explosive TTSPPs are stored;[8] and
— continuously monitored by security staff.

Reason: Protection of property and life.

3.7 Fire protection

3.7.1 *Fire protection equipment*

Provide suitable fire detection and fire-fighting equipment, including fire hydrants, in all TTSPP storage areas and ensure that:

— systems and equipment are appropriate for the class of occupancy and product storage arrangements and are approved by the local fire authority; and
— equipment is regularly serviced in accordance with the equipment manufacturers' recommendations and local regulations.

Reason: Protection of property and life.

3.7.2 *Fire prevention, detection and control procedures*

Follow standard operating procedures (SOPs) for fire prevention, detection and control. Train staff and carry out regular fire drills. Prohibit smoking in all areas.

Reason: Protection of property and life.

3.8 Building hygiene

3.8.1 *Building cleanliness*

Implement a cleaning programme for all areas:

- do not allow the accumulation of dust, dirt and waste, including packaging waste;
- take precautions against spillage or breakage, and cross-contamination;

[7] Zoned sprinkler systems are recommended to control fires and to localize product damage in the event of system activation.
[8] Explosion-proof stores must have a blast roof or wall. Preferably, explosive substances should be stored in an independent building, well separated from the main store.

- collect waste in designated closed containers and arrange for safe disposal at frequent intervals;
- do not permit consumption of food or beverages other than in designated areas; and
- maintain cleaning records to demonstrate compliance.

Reason: Protection against damage and contamination of TTSPPs and to minimize the risk of pest infestation.

3.8.2 *Pest control*

Implement a programme to keep all areas free of pests. This should include enclosed receiving and loading bays. Maintain records to demonstrate compliance with a robust pest control programme.

Reason: Protection against damage and contamination of TTSPPs.

3.9 Power supply

3.9.1 *Uninterrupted power supply*

Where possible, and where necessary,[9] ensure that all temperature-controlling equipment for TTSPP storage (i.e. refrigerators, freezers, building management systems, heating, ventilation and air-conditioning (HVAC) systems, compressors, air-handling units, monitoring systems, alarms and related computer equipment) are connected to an uninterrupted power supply (UPS) system. Where a generator and associated control equipment is used it should:

— be able to manage the combined start-up load of all connected temperature-controlling and temperature-monitoring equipment;[10]
— not exceed the defined parameters of the mains power supply;
— be equipped with automatic mains failure start-up and automatic shutdown when power is restored; and
— have adequate fuel tank capacity and sufficient fuel to cover a prolonged power outage.

Regularly test and service UPS equipment and generators. Maintain records to demonstrate compliance.

Reason: Loss prevention.

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[9] UPS systems may be unnecessary in countries with a very reliable electricity supply. In smaller stores in countries where electricity is only available for a limited period each day, or is entirely absent, an alternative approach to UPS is to use refrigeration equipment with extended holdover capacity, for example, ice-lined refrigerators, or gas, kerosene or solar-powered refrigerators.

[10] The installed capacity of the UPS system can be minimized by fitting electronic controls which reduce compressor start-up loads.

3.9.2 *Power failure contingency plan*

Develop and maintain a contingency plan to protect TTSPPs in the event of power failure which places products at risk. Alternative emergency cooling systems (e.g. liquid nitrogen or dry ice) are acceptable.

Reason: Loss prevention.

3.10 Building maintenance

Implement a planned preventive maintenance programme to ensure that storage buildings and building utilities are well maintained. Keep records to demonstrate compliance with the programme.

Reason: To ensure that storage buildings continue to protect stored products against damage.

4. Temperature-controlled storage

4.1 Normative references

- EN 60068-3 parts 5, 6, 7 and 11: *Environmental testing. Guidance. Confirmation of* the performance of temperature chambers
- International Air Transport Association (IATA) *Perishable cargo regulations chapter 17.* 10th ed, July 2010
- USP <1079> *Good storage and shipping practices*
- USP <1118> *Monitoring devices — time, temperature and humidity*

4.2 Storage capacity of temperature-controlled stores

Ensure that the net storage capacity of the temperature-controlled stores is sufficient to accommodate peak TTSPP stock levels and their associated transit temperature protection components (i.e. freezer blocks, flexible ice blankets, refrigerated gel packs, phase change materials and insulated packaging, if retained), under correct temperature conditions and in a manner which enables efficient and correct stock management operations to take place.

Reason: To avoid the risks associated with overstocking and to ensure that good warehousing practices can be adopted (i.e. first in-first out (FIFO) or earliest expiry-first out (EEFO)). Overstocking makes FIFO or EEFO handling difficult or impossible and hinders accurate physical stock counts.

4.3 Temperature-controlled storage

Ensure that TTSPPs are stored in temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers which comply with the following requirements.

Temperature-controlled rooms, cold rooms and freezer rooms should be:

- capable of maintaining the temperature range defined by the system set points over the full annual ambient temperature range experienced at the store location;
- preferably equipped with an auto-defrost circuit which has a minimal effect on temperature within the unit during the defrost cycle and maintains temperature within specification for this period;
- equipped with a low temperature protection circuit in cold climates where there is a risk of breaching the low temperature set point for TTSPPs that are damaged by exposure to low temperatures;
- connected to a UPS as described in clause 3.9.1;
- equipped with a calibrated continuous temperature monitoring system with sensors located at points representing greatest temperature variability and temperature extremes;
- preferably equipped with continuous humidity monitoring devices with sensors located at points representing humidity extremes;
- equipped with alarms to indicate temperature excursions and/or refrigeration failure;
- fitted with lockable doors, or an access control system, as necessary; locks must have a safety device so that doors can be freely opened from the inside; and
- qualified as defined in clause 4.7.

Refrigerators and freezers should be:

- purpose-designed for the storage of TTSPPs; household-style units are only acceptable if they have been independently tested and found to comply with the temperature control requirements of a recognized standard for pharmaceutical refrigerators and freezers;[11]
- capable of maintaining the temperature range specified by the TTSPP manufacturer over the full annual ambient temperature range experienced at the storage site;
- equipped with calibrated temperature monitoring devices appropriate to the level of risk but preferably capable of continuous recording and with sensor(s) located at a point or points within the cabinet which most accurately represents the temperature profile of the equipment during normal operation;
- preferably equipped with alarms to indicate temperature excursions and/or refrigeration failure;
- fitted with lockable doors or lids, or access control system, as necessary; and
- qualified and/or tested as defined in clause 4.7.

[11] For example, WHO PQS standards for refrigerators and freezers are available at: http://www.who.int/immunization_standards/vaccine_quality/pqs_e03_fridges_freezers/en/index.html.

Reason: To maintain labelled TTSPP storage temperatures during long-term storage.

4.4 Temperature-controlled storage for controlled and hazardous products

Ensure that controlled and hazardous TTSPPs are securely stored:

- Provide dedicated temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers for these TTSPPs, in separate secure areas, as described in clause 3.6.2.
- Alternatively, but only if acceptable to the regulatory authority, bulk stocks of TTSPPs with high illicit-value may be stored in a securely locked section of a general temperature-controlled storage area.

Reason: To protect this category of TTSPPs against theft and misuse and to safeguard workers and general storage areas in the event of an accident involving hazardous substances.

4.5 Temperature and humidity control and monitoring in storage

4.5.1 *Temperature control*

Provide thermostatic temperature control systems for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPPs. Comply with the following minimum requirements:

- system able continuously to maintain air temperatures within the set point limits throughout the validated storage volume;
- control sensors accurate to ± 0.5 °C or better;
- control sensors calibrated as described in clause 4.10.1;
- control sensors located in areas where greatest variability in temperature is expected to occur in order to maximize available safe storage volume;
- control sensors positioned at the hot and cold spots determined by temperature mapping, even if affected by door opening, unless recommendations are being made not to store products in such areas; and
- control sensors independent of the temperature monitoring system.

4.5.2 *Temperature monitoring*

Provide air temperature monitoring systems and devices for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPPs. Comply with the following minimum requirements:

General requirements

- Monitoring sensors accurate to ± 0.5 °C or better for electronic devices and ± 1 °C or better for alcohol, bi-metal gas or vapour pressure thermometers.

- Monitoring sensors calibrated as described in clause 4.10.1.
- Monitoring sensors located in areas where greatest variability in temperature is expected to occur within the qualified and/or tested storage volume as defined in clause 4.7.
- Monitoring sensors positioned so as to be minimally affected by transient events such as door opening.
- Temperature monitoring devices, temperature traces or electronic temperature records manually checked at least twice a day, in the morning and evening, seven days a week, including public holidays.

Temperature-controlled rooms, cold rooms and freezer rooms

- Provide a temperature record with a minimum recording frequency of six times per hour for each monitoring sensor position.
- Provide documentation for each monitoring sensor position which can be stored and accessed.
- Continue to operate independently in the event of a power failure.[12]

Refrigerators and freezers

- Preferably, connect refrigerators and freezers to a multipoint monitoring system with a minimum recording frequency of six times per hour for each sensor position which can operate independently in the event of a power failure.
- Alternatively use battery-powered portable temperature monitoring devices with a minimum recording frequency of six times per hour.
- The least preferred option is a thermometer or maximum/minimum thermometer.
- Provide documentation for each appliance which can be stored and accessed.

Reasons: To maintain labelled TTSPP temperatures during long-term storage. Thermometers provide only limited and discontinuous temperature information. For this reason, continuous recording devices are preferable.

4.5.3 *Humidity control*

Provide humidity control in temperature-controlled rooms that are used to store TTSPPs which are adversely affected by high relative humidity and are not sufficiently protected by their packaging. Such products are typically labelled "store in a dry place", or carry similar wording and require a humidity-controlled environment.

[12] Where there is no UPS, the autonomy period for the device should be matched to the maximum length of anticipated power outages.

4.5.4 *Humidity monitoring*

Provide humidity monitoring systems and devices in temperature-controlled rooms that are used to store TTSPPs which require a humidity-controlled environment. Comply with the following minimum requirements:

- sensors accurate to ± 5% RH;
- sensors calibrated as per clause 4.10.2;
- sensors located to monitor worst-case humidity levels within the qualified storage volume defined in clause 4.7;
- sensors positioned so as to be minimally affected by transient events such as door opening;
- provides a humidity record with a minimum recording frequency of six times per hour for each sensor position;
- provides documentation for each sensor position which can be stored and accessed; and
- continues to operate independently in the event of a power failure.[13]

Reason: To maintain labelled TTSPP humidity conditions during long-term storage.

4.6 Alarm systems

4.6.1 *Temperature alarms*

Provide temperature alarm systems for temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPPs. Comply with the following minimum requirements:

General requirements

- Sensors accurate to ± 0.5 °C.
- Sensors calibrated as described in clause 4.10.1.
- Sensors located to monitor worst-case temperatures within the validated storage volume defined in clause 4.7; where the alarm system is not integrated with the temperature monitoring system, sensors should be located close to the temperature monitoring sensors.
- Sensors positioned so as to be minimally affected by transient events such as door opening.

Temperature-controlled rooms, cold rooms and freezer rooms

- High/low alarms set points to trigger appropriately located visual alarm(s).
- Preferably there should also be appropriately located audible alarm(s) in addition to the visual alarm(s).

[13] Where there is no UPS the autonomy period for the device should be matched to the maximum length of anticipated power outages.

- Preferably there should be an automatic telephone dial-up or SMS text warning system to alert on-call personnel when an alarm is triggered outside working hours.

Refrigerators and freezers

- Preferably there should be a visual and/or audible alarm system; this may be integrated with a portable continuous temperature monitoring device.

Reason: Loss prevention.

4.6.2 *Humidity alarms*

Provide humidity alarm systems for temperature-controlled rooms used to store TTSPPs that require a humidity-controlled environment. Comply with the following minimum requirements:

- sensors accurate to ± 5% relative humidity (RH);
- sensors calibrated as described in clause 4.10.2;
- sensors located to monitor worst-case humidity levels within the validated storage volume defined in clause 4.7; where the alarm system is not integrated with the humidity monitoring system, sensors should be located close to the humidity monitoring sensors;
- sensors positioned so as to be minimally affected by transient events such as door opening;
- high/low alarms set points to trigger appropriately located visual alarm(s);
- preferably there should also be appropriately located audible alarm(s) in addition to the visual alarm(s); and
- preferably there should be an automatic telephone dial-up or SMS text warning system to alert on-call personnel when an alarm is triggered outside working hours.

Reason: Loss prevention.

4.7 Qualification of temperature-controlled stores

Qualify new temperature-controlled storage areas and new refrigeration equipment before it becomes operational. The qualification procedure should:

- demonstrate the air temperature profile throughout the storage area or equipment cabinet, when empty and in a normal loaded condition;
- define zones which should not be used for storage of TTSPPs (for example areas in close proximity to cooling coils, cold air streams or heat sources); and
- demonstrate the time taken for temperatures to exceed the designated limits in the event of power failure.

Fully document the initial qualification. Carry out additional qualification exercises whenever modifications are made to the storage area that may

increase loading or affect air circulation, or when changes are made to the refrigeration equipment, such as a change in the set point. Consider the need for requalification whenever temperature and/or humidity monitoring shows unexplained variability that is greater than normal.

Qualification may not be required for equipment which requires little or no site assembly or commissioning, such as vaccine refrigerators and freezers that have been independently tested and found suitable for the storage of TTSPPs. Independent testing must be carried out between the chosen set points and under the ambient temperature conditions to which the equipment will be exposed during operation. Prequalified equipment of this type must be correctly installed in each location in accordance with written guidance.

Reason: To ensure that labelled TTSPP temperatures can be maintained during long-term storage and that the facility can demonstrate to the regulatory authorities and other interested parties that due diligence has been observed.

4.8 Cleanliness of temperature-controlled stores

Implement a cleaning and decontamination programme for all temperature-controlled rooms:

- Ensure that floor areas are fully accessible for cleaning. Do not store goods directly on the floor.
- Do not permit storage of any non-pharmaceutical products except transport-related items such as icepacks, gel packs and the like.
- Do not allow the accumulation of dust, dirt and waste, including packaging waste.
- Take precautions against spillage or breakage, and cross-contamination.
- Do not allow accumulation of frost and ice, particularly ice contaminated by spillages.
- Collect waste in designated closed containers and arrange for safe disposal at frequent intervals.

Maintain cleaning records to demonstrate compliance.

Reason: Protection against damage and contamination of TTSPPs and hazards to workers, arising from spillage or breakage.

4.9 Refrigeration equipment maintenance

Implement a maintenance programme for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers:

- Carry out regular planned preventive maintenance on all temperature-controlling equipment.

- Make arrangements to ensure that emergency maintenance is carried out within a time period that does not place TTSPPs at risk of damage.
- Ensure that there is a contingency plan to move products stored in non-functioning equipment to a safe location before damage to the product occurs in the event that equipment cannot be repaired in a timely manner.

Maintain records to demonstrate compliance.

Reason: Loss prevention.

4.10 Calibration and verification of control and monitoring devices

4.10.1 *Calibration of temperature control and monitoring devices*

Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified. Calibration should demonstrate the accuracy of the unit across the entire temperature range over which the device is designed to be used. Single-use devices that are supplied with a manufacturer's calibration certificate do not need to be re-calibrated.

4.10.2 *Calibration of humidity control and monitoring devices*

Calibrate devices against a certified, traceable reference standard at least once a year unless otherwise justified. Single-use devices that are supplied with a manufacturer's calibration certificate do not need to be re-calibrated.

4.10.3 *Alarm equipment verification*

Check functionality of temperature and humidity alarms at least once every six months at the designated set points.

Maintain records to demonstrate compliance.

Reason: To ensure that labelled TTSPP storage temperatures and humidity control can be maintained during long-term storage and that the store can demonstrate to the regulatory authorities and other interested parties that due diligence has been observed.

5. Materials handling

5.1 Materials handling equipment

Where powered materials handling equipment is used in temperature-controlled rooms, cold rooms or freezer rooms, select equipment which is certified for safe use in confined spaces.

Reason: Protection of the workforce.

6. Transport and delivery

6.1 Normative references

- Directive 94/62/EC. *European Parliament and Council Directive of 20 December 1994 on packaging and packaging waste.*1994.
- EN 13428:2004. *Packaging. Requirements specific to manufacturing and composition. Prevention by source reduction.*
- EN 13430:2004. *Packaging. Requirements for packaging recoverable by material recycling.*
- EN 13431:2004. *Packaging. Requirements for packaging recoverable in the form of energy recovery, including specification of minimum inferior calorific value.*
- EN 13432:2000. *Packaging. Requirements for packaging recoverable through composting and biodegradation. Test scheme and evaluation criteria for the final acceptance of packaging.*
- IATA *Perishable Cargo Regulations Chapter 17,* 9th Edition, July 2009.
- *Isothermal and refrigerating containers for health products — Thermal performance qualification method.*
- ISTA — 5B: *Focused Simulation Guide for Thermal Performance Testing of Temperature Controlled Transport Packaging.*
- ISTA — 7D: *Thermal Controlled Transport Packaging for Parcel Delivery System Shipment. Basic Requirements: atmospheric conditioning, vibration and shock testing.*
- WHO Technical Report Series, No. 937, 2006. Annex 5: *Good distribution practices for pharmaceutical products.*

6.2 Product stability profiles

Transport TTSPPs in such a manner that transport temperatures meet local regulatory requirements at the sending and receiving sites and/or so that temperature excursions above or below the manufacturer's labelled storage temperature range do not adversely affect product quality. Product stability data must demonstrate the acceptable temperature excursion time during transport.

Reason: Protection of TTSPPs against degradation.

6.3 Transport route profiling and qualification

Profile and qualify transport routes:

- Select the most suitable methods for protecting TTSPPs against anticipated ambient temperature and humidity conditions throughout the year.
- Use suitable methods, including published standards, weather data, laboratory tests and field tests to select suitable transport equipment and shipping containers.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.4 Temperature-controlled transport

6.4.1 *Air and sea transport*

Ensure that any carrier contracted to transport TTSPPs by air or by sea operates under the terms of a formal service level agreement (SLA) drawn up between the parties. The carrier is to be made responsible for maintaining load temperatures within the transport temperature profile defined for each product.

Reason: To ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product and that compliance can be demonstrated to the contracting organization, the regulatory authorities and other interested parties.

Temperature-controlled road vehicles operated by common carriers

Temperature control in vehicles operated by a common carrier must be qualified and the details and responsibilities for this process should be set out in a formal SLA drawn up between the parties.

Reason: To ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product and that compliance can be demonstrated to the contracting organization, the regulatory authorities and other interested parties.

6.4.2 *Temperature-controlled road vehicles generally*

Ensure that temperature-controlled road vehicles used for the transport of TTSPPs are:

- capable of maintaining the temperature range defined by the system set points over the full annual ambient temperature range experienced over known distribution routes and when the vehicle is in motion, or parked with the main engine stopped;
- equipped with a low temperature protection circuit in cold climates where there is a risk of breaching the low temperature set point for TTSPPs that are damaged by exposure to low temperatures;
- equipped with calibrated temperature monitoring devices with sensors located at points representing temperature extremes;
- equipped with alarms to alert the driver in the event of temperature excursions and/or refrigeration unit failure;
- fitted with doors with security seals and/or security locks that protect against unauthorized access during transit;

- qualified as defined in clause 6.6; and
- regularly calibrated and maintained and records kept to demonstrate compliance.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.4.3 *Transport of controlled TTSPPs and TTSPPs with high illicit value*

Ensure that controlled TTSPPs and TTSPPs with high illicit value are transported in the following manner:

- Transport practices comply with all relevant local legislation and regulations.
- Vehicles are equipped with lockable doors and an intruder alarm.
- Vehicles use unique seal lock indicating devices such as cable seal locks with unique identifiers that are tamper-resistant to protect against unauthorized access during transit.[14]
- Security-cleared delivery drivers are employed.
- All deliveries are documented and tracked.
- Signed dispatch and arrival records are kept.
- Shipments are fitted with security equipment appropriate to the product being transported and the assessed security risk, such as global positioning system (GPS) devices located in the vehicle and/or hidden in the product.
- Drivers are informed about the perishability of the product and the maximum acceptable transport time.

Reason: To prevent theft and misappropriation of this category of TTSPP and to ensure the security and safety of the driver.

6.5 Temperature and humidity control and monitoring during transit

6.5.1 *Temperature control in temperature-controlled road vehicles*

Provide thermostatic temperature control systems for all temperature-controlled vehicles used to transport TTSPPs. Comply with the following minimum requirements:

- system able continuously to maintain air temperatures within the set point limits throughout the validated storage volume defined in clause 6.6;
- control sensors accurate to ± 0.5 °C;
- control sensors calibrated as described in clause 6.7.1;

[14] Refer to ISO/PAS 17712: *Freight containers — Mechanical seals.*

- control sensors located to control worst-case temperatures in order to maximize available safe storage volume;
- control sensors positioned in the return air stream; and
- control sensors independent of the temperature monitoring system.

6.5.2 *Temperature monitoring in temperature-controlled road vehicles*

Provide air temperature monitoring systems and devices for vehicles used to transport TTSPPs. Comply with the following minimum requirements:

- monitoring sensors accurate to ± 0.5 °C;
- monitoring sensors calibrated as described in clause 6.7.2;
- monitoring sensors located to monitor worst-case temperatures within the qualified storage zone defined in clause 6.6;
- monitoring sensors positioned so as to monitor worst-case positions;
- provide a temperature record with a minimum recording frequency of six times per hour for each sensor position;[15] and
- provide documentation which can be stored and accessed.

Establish transit temperature specifications and document transit temperatures for every internal and external shipment.

6.5.3 *Humidity monitoring in temperature-controlled road vehicles*

Preferably provide humidity monitoring systems and devices for temperature-controlled vehicles which are used to transport TTSPPs that require a humidity-controlled environment. Systems and devices should comply with the following minimum requirements:

- sensors accurate to ± 5% RH;
- sensors calibrated as described in clause 6.7.3;
- sensors located to monitor worst-case humidity levels within the qualified storage zone defined in clause 6.6;
- sensors positioned so as to be minimally affected by transient events such as door opening;
- provide a humidity record with a minimum recording frequency of six times per hour for each sensor position; and
- provide documentation which can be stored and accessed.

Establish transit humidity specifications and document transit humidity conditions for internal and external shipments where required.

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[15] Recording frequency should take account of the storage capacity of the data logger and the expected transport period.

6.5.4 *Temperature monitoring in passive and active shipping containers*

Use chemical or electronic freeze indicators, electronic loggers (with or without alarms) and/or other suitable indicators to monitor temperature and/or humidity exposure during internal distribution. Preferably use these devices for external distribution. Monitor and document indicator status upon arrival.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.6 Qualification of temperature-controlled road vehicles

Where temperature-controlled vehicles are directly owned and/or operated, qualify each vehicle before it becomes operational, wherever possible. The qualification procedure should:

- demonstrate that the air temperature distribution is maintained within the limits specified throughout the temperature-controlled compartment for both air and product temperatures for commonly used load layouts and at the ambient temperature extremes anticipated during normal operation over known routes;
- demonstrate the humidity distribution throughout the temperature-controlled compartment for commonly used load layouts, where products are being transported that require a humidity-controlled environment;
- define zones within the vehicle's payload area which should not be packed with TTSPPs (for example areas in close proximity to cooling coils or cold air streams);
- demonstrate the time taken for temperatures to exceed the designated maximum in the event that the temperature-controlling unit fails; and
- document the qualification exercise.

An alternative approach is to perform an initial full qualification on each trailer/refrigeration unit type combined with an installation qualification (IQ) for each example when a new vehicle becomes operational.

Carry out additional qualification exercises whenever significant modifications are made to the vehicle. Consider the need for requalification whenever temperature and/or humidity monitoring shows unexplained variability that is greater than normal.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.7 Calibration and verification of transport monitoring devices

6.7.1 *Calibration of transport temperature control devices*

Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified.

6.7.2 *Calibration of transport temperature monitoring devices*

Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified.

6.7.3 *Calibration of transport humidity monitoring devices*

Calibrate devices against a certified, traceable, reference standard at least once a year, unless otherwise justified.

6.7.4 *Verification of transport alarm equipment*

Check functionality of temperature and humidity alarms at the designated set points. Check functionality of security alarm systems. Carry out these checks at least once a year, unless otherwise justified.

Maintain records to demonstrate compliance.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.8 Shipping containers

6.8.1 *Container selection generally*

Select shipping containers that:

- comply with applicable national and international standards relevant to the product type and the chosen transport route and mode(s);
- protect personnel and the general public from hazards arising from spillage, leakage or excessive internal pressure;
- protect the product being transported against mechanical damage and the anticipated ambient temperature range that will be encountered in transit; and
- can be closed in a manner that allows the recipient of the consignment to establish that the product has not been tampered with during transport.

Reason: Quality assurance and safety.

6.8.2 *Uninsulated containers*

Ensure that uninsulated containers are correctly used, in a manner which protects their contents:

- transport uninsulated containers in a qualified temperature-controlled environment such as an actively or passively temperature-controlled vehicle;
- ensure that the transport system is able to maintain the temperature of the TTSPP within the product's stability profile as stated by the product manufacturer and/or to maintain the TTSPP within the transit temperature specification requirements specified by the regulatory authorities at both the sending and receiving locations.

Reason: Quality assurance and safety.

6.8.3 *Qualification of insulated passive containers*

Qualify insulated passive containers, including any and all necessary ancillary packaging such as temperature stabilizing medium, dry ice, ice or gel packs, cool water packs or warm packs, phase change materials, partitions, bubble wrap and dunnage:

- ensure that the qualified packaging system is capable of maintaining the TTSPP within the temperature range needed to meet the product stability profile as stated by the product manufacturer. Container qualification should include full details of the packaging assembly, the thermal conditioning regime and the minimum and maximum shipping volume, weight and thermal mass that can safely be accommodated in the container. Qualification should also include the correct placement of temperature monitors where these are used;
- take account of the transport route and of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of arrival in the recipient's temperature-controlled store.

Reason: To ensure that TTSPPs can safely be transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.8.4 *Qualification of active containers*

Qualify active containers:

- ensure that the container is capable of maintaining the TTSPP within the temperature range needed to meet the product stability profile as stated by the product manufacturer;
- take account of the transport route and of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of arrival in the recipient's temperature-controlled store.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.9 Shipping container packing

Pack TTSPP shipping containers to:

- the exact specified configuration to ensure that the correct TTSPP temperature range is maintained;
- minimize the risk of theft and fraud and assure the recipient that the goods have not been tampered with while in transit, for example by using locked containers or shrink-wrapped pallets;
- minimize the risk of mechanical damage during transport;
- protect freeze-sensitive products against temperatures below 0 °C when frozen packs are used;
- protect products against light, moisture and contamination or attack by microorganisms and pests;
- protect products against adverse effects when dry ice is used as a coolant;
- clearly label containers to identify the correct transport temperature range and to show correct orientation for handling; and
- ensure that packages containing dangerous goods (including dry ice) are labelled in compliance with relevant transport regulations and requirements.

Reason: To ensure that shipping containers are systematically used in the manner defined during the container qualification process and that this can be demonstrated to the regulatory authorities and other interested parties.

6.10 Product handling during packing and transport

Handle TTSPPs correctly during packing and transport:

- pack TTSPPs in an area set aside for the assembly and packaging of these products as specified in clause 3.3.1;
- take precautions against spillage or breakage, contamination and cross-contamination;
- deliver TTSPPs to outside recipients by the most suitable mode(s) of transport available in order to minimize delivery time; and
- ensure that patients receiving TTSPP deliveries are given clear advice on correct storage of the product before use.

Reason: To maintain TTSPP quality during transport.

6.11 Cleaning road vehicles and transport containers

Implement a cleaning and decontamination programme for all road vehicles and reusable shipping containers used to transport TTSPPs:

- ensure that all internal surfaces of load compartments are regularly cleaned;

- do not allow the accumulation of dust, dirt and waste, including packaging waste in load compartments, or in reusable shipping containers;
- take precautions against spillage or breakage, and cross-contamination;
- do not allow accumulation of frost and ice in refrigerated vehicles, particularly ice contaminated by spillages; and
- collect waste in designated closed containers and arrange for safe disposal at frequent intervals.

Maintain cleaning records for vehicles and reusable shipping containers to demonstrate compliance.

Reason: Protection against damage and contamination of TTSPPs and hazards to workers arising from spillage or breakage.

6.12 Transport of returned and recalled TTSPPs

6.12.1 *Transport of returned TTSPPs*

Ensure that that returned TTSPPs are transported under the same conditions as those used for the initial delivery:

- the sender and recipient must work together so that that the product is maintained within the temperature range needed to meet the manufacturer's stated product stability profile;
- take account of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of return; and
- quarantine returned TTSPPs in temperature-controlled storage pending a decision by the quality control department or qualified person to dispose of the product or to return it to stock.

Reason: To ensure that returned and recalled TTSPPs are maintained within the correct transport temperature profile so that they can safely be re-stocked if a decision to do so is made.

6.12.2 *Transport of recalled TTSPPs*

Ensure that recalled TTSPPs are:

- marked for disposal as either "recalled" or "withdrawn";
- transported back from the recipient and quarantined under secure conditions pending a final decision on disposal as described in clause 8.6.3.

7. Labelling

7.1 Normative references

- *IATA Perishable Cargo Regulations Chapter 179th Edition, July 2009. Clauses 17.10.5 and 17.10.6.*

7.2 Labelling

7.2.1 *Labelling generally*

Label internal shipping and external distribution containers containing TTSPPs as follows:

- identify the product in accordance with all national and international labelling requirements relevant to the container content, transport route and mode(s);
- identify hazardous products in accordance with relevant national and international labelling conventions; and
- indicate the appropriate temperature and humidity ranges within which the product is to be transported and/or stored.

7.2.2 *Labelling air-freighted shipments*

In cases where TTSPPs are to be air-freighted, the package(s) should be labelled using the standard International Air Transport Association (IATA) time and temperature-sensitive symbol, in accordance with the conditions outlined in Chapter 17 of the IATA Perishable Cargo Regulations. Apply the label to the outer surface of individual shipping packages, overpacks or bulk containers.

Reason: To ensure that products are correctly and safely handled at all points in the supply chain.

8. Stock management

8.1 Stock control systems

8.1.1 *General stock control systems and procedures*

TTSPP stock control systems and procedures meet the following minimum requirements:

— allow access only to authorized persons;
— record all receipts and dispatches;
— record batch numbers and expiry dates;
— record short-dated and expired products;
— record product status (i.e. released, quarantined, hold, reject);
— record all product returns, recalls, withdrawals, damage and disposals;
— manage the issue of products in EEFO order; and
— take regular physical inventories and reconcile stock records with the actual physical count. Investigate and report on stock discrepancies in accordance with agreed procedures. Preferably physical counts should be made at least twice a year.

Reason: To ensure that accurate and complete stock records are kept at all times.

8.1.2 *Stock control procedures for controlled and hazardous TTSPPs*

In addition to the requirements set out in clause 8.1.1, implement the following procedures:

- Institute a customer verification process to ensure that all recipients of these products are authorized to receive them.
- Maintain stock records which specifically identify products in these categories.
- Carry out regular audits and make audit reports available to the responsible authorities.
- Comply with all record-keeping procedures specified in local legislation and regulations. Retain product transaction and delivery records for at least the minimum time period required by local regulations.

Reason: To ensure that accurate and complete stock records are kept at all times and to satisfy the requirements of the regulatory authorities.

8.2 Incoming goods

8.2.1 *Product arrival checks*

Check and record the following for all incoming TTSPPs:

— product name, item code (identifier), strength, and batch/lot number;
— quantity received against order;
— name and address of the supplying site;
— examine containers for tampering, damage or contamination;
— examine expiry dates — accept short-dated products only if prior agreement has been reached with the supplier; do not accept products that have expired or which are so close to their expiry date that this date is likely to occur before use by the consumer;
— delays encountered during transport;
— status of any attached temperature recording device(s) and/or time/temperature indicators; and
— verify that required storage and transport conditions have been maintained.

8.2.2 *Actions following arrival checks*

- Enter product details, including product name/number, strength, batch numbers, quantities received, expiry dates and acceptance status into the stock recording system.
- Store checked goods under the correct temperature and security regime immediately upon receipt.
- Quarantine defective or potentially defective products, products with incomplete or missing paperwork, products that experienced unacceptable temperature excursions during transport, or products suspected to be counterfeit. Do not release until checks have been completed satisfactorily.

All unacceptable temperature excursions should be evaluated to determine their effect on the product.
- Report any defects to the supplying store or holder of the marketing authorization.
- Do not transfer to saleable stock until all relevant disposition procedures have been completed.

Reason: To ensure that incoming TTSPPs are in acceptable condition, accurately recorded and correctly stored and that defective and/or incorrect shipments are followed up with the supplier.

8.3 Outgoing goods (external deliveries)

8.3.1 *Management of outgoing goods*

Implement outgoing goods procedures to ensure that:

- Transport vehicle conformity, including conformity with SLA or quality assurance (QA) agreements, is checked before loading goods.
- Expired products are never issued.
- Products with short expiry dates are not issued unless the recipient accepts that they can be consumed before the expiry date is reached.
- Products are distributed in strict EEFO order unless a product-based time-temperature exposure indicator, such as a vaccine vial monitor, demonstrates that a batch should be distributed ahead of its EEFO order.
- Details of any temperature monitoring devices packed with the external distributions are recorded.
- Details of outgoing products, including product name/number, strength, batch numbers, expiry dates and quantities distributed, are entered into the stock recording system.

8.3.2 *Actions following dispatch*

Monitor TTSPPs following dispatch in order to:

- trace products to their intended destination;
- record and retain records to provide assurance of goods arrival status. A suitable delivery report from the carrier is an acceptable alternative; and
- take appropriate action in the event of returns, recalls or complaints.

Reason: To ensure that outgoing TTSPPs are in acceptable condition, that short-dated stock does not accumulate in the store and that evidence is kept to demonstrate that correct quantities are distributed and received in good condition.

8.4 Product complaint procedures

Manage product complaints as follows:

- If a product defect is discovered or suspected in a batch of TTSPPs, cooperate with the regulatory authority to determine whether other batches are affected and recall products if required to do so by the regulatory authority.
- Where complaints or defects relate to a product or its packaging, immediately notify the holder of the marketing authorization for the product.
- Where complaints or defects arise as a result of errors or omissions within the organization, immediately evaluate the causes and take remedial measures to prevent a recurrence.
- Record all complaints and the remedial actions taken. Monitor and analyse trends in the complaint records.

Reason: Protection of the public and of the reputation of the supplying organization.

8.5 Suspect product procedures

8.5.1 *Suspect products*

Implement systems for identifying and managing suspect products found in the supply chain as follows:

- Physically segregate any suspect TTSPPs found in the supply chain and store securely until legal investigations are complete.
- Label them clearly as "Not for use" or other similar phrase;
- Immediately notify the regulatory authority or authorities and any other relevant authorities, as well as the holder of the marketing authorization of the product.
- Cooperate with regulatory authorities to assist with investigating the source of suspect products and implement appropriate remedial action(s).
- Document the decision-making process for disposal or return of condemned or defective TTSPPs and make these records available to the relevant authorities.

Reason: Protection of the public, protection of legitimate suppliers and manufacturers and conformity with regulatory requirements.

8.6 Product return, recall, withdrawal and disposal procedures

8.6.1 *Return procedures*

Manage product returns as follows:

- Quarantine returned TTSPPs in a suitable temperature-controlled area and under the security conditions applicable to the product type.
- Do not return to saleable stock unless storage and transport temperature conditions after dispatch from the distribution site have been fully verified and documented, including the return leg to the distribution site.

- Where appropriate, obtain written advice from the holder of the marketing authorization regarding handling and/or disposal of the returned TTSPP.
- If returned stock is re-issued, distribute in EEFO order or in accordance with the exposure status of any product-mounted time-temperature indicator device.
- Quarantine returned TTSPPs that have been exposed to unacceptable storage and/or transport temperatures and mark for disposal.
- Maintain records of all returned TTSPPs.

Reason: Protection of the public.

8.6.2 *Recall procedures*

Manage product recalls as follows:

- Conduct urgent and non-urgent TTSPP recalls in accordance with an agreed emergency plan.
- Notify the local regulatory authority or authorities.
- Notify overseas regulatory counterparts where the product has been exported.
- Notify all affected customers as applicable.
- Quarantine any remaining inventory of recalled TTSPPs and mark for further investigation before disposal.
- Maintain records of all TTSPP recalls, including reconciliation of quantity sold, quantity returned, quantity remaining or quantity consumed.

Reason: Protection of the public and conformity with regulatory requirements.

8.6.3 *Disposal procedures*

Manage product awaiting board of survey or disposal as follows:

- Ensure that rejected and/or recalled or withdrawn TTSPPs cannot be used, released or cause contamination to other products. Store separately from other products, in accordance with local regulations, to await destruction or return to the supplier.
- Safely dispose of rejected and/or recalled/withdrawn products in accordance with local regulations, including where relevant, regulations covering the disposal of hazardous and controlled drugs.
- Maintain disposal records.

Reason: Protection of the public and the environment.

8.7 T*raceability or stock tracking*

Ensure that stock and distribution records enable traceability, or stock tracking, of TTSPPs from the point of supply to the end-user or patient.

Traceability should include records of the temperature exposure of the product during internal shipping and storage. These records should include:

- for incoming goods: status of shipping indicators used (if any), status of product-based time-temperature indicators (if any) and physical condition of goods and time of receipt;
- for outgoing goods: type of shipping indicators used (if any), status of product-based time-temperature indicators (if any) and physical condition of goods and time of dispatch.

Monitor, record, and investigate discrepancies.

Reason: To demonstrate that TTSPPs have been correctly distributed and to facilitate product recalls and detect theft and fraud.

9. General procedures and record-keeping

9.1 Emergencies and contingency planning

Make contingency arrangements for the safe storage of TTSPPs in the event of emergencies, including, but not confined to:

— extended power supply outages;
— equipment failure; and
— vehicle breakdown during transport of TTSPPs.

Prepare action plans to deal with products subjected to temperature excursions.

Ensure that the responsible staff know, and have rehearsed, the appropriate actions to be taken in the event of the identified emergency scenarios.

Reason: Loss prevention.

9.2 General record-keeping

9.2.1 *Record-keeping*

Maintain comprehensive records and ensure that they are laid out in an orderly fashion and are easy to check.

Paper records must be:

— stored and maintained so that they are accessible and easily retrievable;
— labelled, dated and filed for easy identification;
— protected against deterioration and loss due to fire, flood or other hazards;
— kept secure and protected against unauthorized access; and
— signed and dated by authorized persons and not changed without due authorization.

Computer records must be:

— logically filed for easy identification and retrieval;
— kept secure and protected against unauthorized access;
— where feasible, manually signed, dated and scanned or when electronically archived dated, encrypted and with check-sum;[16]
— regularly backed-up and archived on media that are independent of the record-keeping computer system(s). Back-up media may be a separate secure server, a separate hard disc, a flash drive or other digital media appropriate to the scale of the operation.

9.2.2 *Content of records*

Ensure that the following traceability data is recorded for each TTSPP batch number, as applicable:

— status of product on arrival;
— temperature and humidity records including records of excursions outside labelled storage and/or transit temperature specification conditions;
— general TTSPP stock transactions, including purchase and sale records;
— controlled drug audits;
— audits for products with high illicit value;
— audits for hazardous products;
— stock tracking;
— return, recall, withdrawal and disposal reports, where relevant;
— product complaint reports, where relevant; and
— counterfeit product reports, where relevant.

Maintain all records in accordance with local legislation and regulations.

9.2.3 *Record review and retention*

Ensure that records are reviewed and approved on a regular basis by a designated member of the quality management team. Ensure that records are accessible for review by end-users, the regulatory authority and other interested parties. Retain records for the minimum period required under local legislation, but for not less than three years.

Reason: Internal quality control, transparency and external inspection by the regulatory authorities and other interested parties.

[16] Electronic records from data loggers are usually encrypted and protected by check-sums. This ensures compliance with FDA Title 21 CFR Part 11:Electronic Records; Electronic Signatures; Final Rule (1997).

9.3 Temperature and humidity records

9.3.1 *Temperature records*

Monitor and record storage temperatures in all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, as follows:

- Check and record temperatures at least twice daily — in the morning and evening — and preferably continuously.
- Review temperature records monthly and take action to rectify systematic excursions.
- Systematically file temperature records for each storage environment or piece of equipment to ensure traceability. Keep records for at least one year after the end of the shelf-life of the stored material or product, or as long as required by national legislation.

9.3.2 *Humidity records*

When storing products which are adversely affected by high relative humidity (see clause 4.5.3), monitor and record humidity levels in all temperature-controlled rooms as follows:

- Record humidity at least twice every 24 hours or preferably continuously.
- Check humidity records daily.
- Review humidity records monthly and take action to rectify systematic excursions.
- Systematically file humidity records for each temperature-controlled room to ensure traceability. Keep records for at least one year after the end of the shelf-life of the stored material or product, or as long as required by national legislation.

Reason: Internal quality assurance and availability of records for review by the regulatory authorities and other interested parties.

10. Environmental management

10.1 Normative references

- ISO 14001: 2004. *Environmental management systems — Requirements with guidance for use.*
- *The Montreal Protocol on Substances that Deplete the Ozone Layer.* UNEP, 2000.

10.2 Environmental management of refrigeration equipment

Ensure that all new refrigeration equipment for temperature-controlled storage and transport is specified to:

- use refrigerants that comply with the Montreal Protocol;
- minimize or eliminate the use of refrigerants with high global warming potential (GWP); and
- minimize CO_2 emissions during operation.

Select equipment to minimize whole-life environmental impact and employ best practice to eliminate leakage of refrigerant into the environment during installation, maintenance and decommissioning of refrigeration equipment.

Reason: Compliance with international protocols and accords on climate change and environmental protection.

11. Quality management

11.1 Normative references

- ICH, 2005: *ICH Harmonized Tripartite Guideline: Quality risk management Q9*
- ISO 9000:2005. *Quality management systems — Fundamentals and vocabulary*
- ISO 9001:2008. *Quality management systems — Requirements*
- ISO 9004:2000. *Quality management systems — Guidelines for performance improvements*
- ISO 10005:2005. *Quality management systems — Guidelines for quality plans*
- ISO 19011:2002. *Guidelines for quality and/or environmental management systems auditing*

11.2 Organizational structure

Establish, document and maintain an organizational structure for the TTSPP storage and shipping and distribution operations which clearly identifies all key management responsibilities, and the personnel who are accountable.

Reason: Quality management.

11.3 Quality systems

11.3.1 *Quality system*

Establish, document and maintain a quality system for the management of TTSPPs including, the following, as applicable:

— standard quality system(s) and associated auditing procedures;
— written procedures and specifications;
— record storage, record retention and record destruction programme;
— risk management;

— calibration programme;
— stability programme;
— qualification and validation programme;
— deviation and root cause investigation programme;
— corrective and preventive action (CAPA) procedures;
— training programme;
— periodic temperature-controlled process assessment;
— change control programme;
— maintenance programme;
— management controls;
— product return and recall/withdrawal policies, including emergency recalls;
— product complaint policies;
— material destruction programme;
— warehouse and storage programme;
— shipping and distribution programme;
— notification systems for regulatory agencies; boards of health and ministries of health; and
— self-inspection programme and continuous quality improvement.

Carry out annual reviews of the quality management system to ensure that it remains appropriate, relevant, and effective.

Reason: Quality assurance.

11.3.2 *Self inspections*

Conduct regular self-inspections to ensure continuing compliance with quality management standards GSP and GDP; record results, follow-up with the corrective actions needed to rectify areas of non-compliance and document the changes made.

11.3.3 *Contractors subject to service level agreements*

Ensure that every contractor with whom there is an SLA provides periodic evidence of compliance with the GSP and/or GDP standards incorporated into the SLA.

Reason: To demonstrate compliance with applicable quality management standards.

11.4 Management of documents and standard operating procedures

11.4.1 *Standard operating procedures*

Develop and maintain SOPs covering correct storage, internal shipping and external distribution of TTSPPs, including, but not limited to, the following topics:

— security, including management of controlled and hazardous TTSPPs;
— safe handling of TTSPPs;
— temperature monitoring;
— calibration of temperature and humidity monitoring devices and alarm systems;
— qualification and validation procedures, including temperature mapping;
— maintenance of controlled-temperature equipment;
— facility cleaning and pest control;
— facility maintenance;
— product arrival (receiving) procedures and records;
— stock storage and warehousing procedures (put away, replenishment, order fulfilment, packing);
— stock control procedures and records;
— distribution procedures and records;
— management of temperature excursions;
— product return and recall/withdrawal procedures and records;
— product complaint procedures and records;
— safe disposal of damaged, expired and quarantined products and records which are no longer required;
— temperature-controlled packaging and route qualification;
— temperature-controlled vehicle operation, including management of security locks and seals;
— emergency response procedures; and
— environmental management.

Ensure that all documents are clear and unambiguous and that document change control procedures are in place as specified in clause 11.5.

Reason: Quality management and staff training.

11.5 Document control

Ensure that all quality manuals, SOPs and similar documents are:

— authorized by an appropriate person;
— recorded in a document register;
— regularly reviewed and kept up to date, with all changes recorded and authorized;
— version controlled;
— issued to all relevant personnel; and
— withdrawn when superseded.

Withdraw superseded documents and retain record copies for document history files and for the minimum period(s) required by the regulatory authorities and for duty-of-care purposes.

Reason: Good quality management practice.

12. Personnel/training

12.1 Training

12.1.1 *General training*

Provide regular and systematic training for all relevant personnel responsible for storage, loading and unloading areas used for non-hazardous TTSPPs, covering the following:

— applicable pharmaceutical legislation and regulations;
— SOPs and safety issues; and
— response to emergencies.

Ensure that each employee understands his or her specific responsibilities. Provide similar training for drivers who are responsible for transporting these substances. Maintain individual training records to demonstrate compliance and regularly evaluate the effectiveness of training programmes.

Reason: To ensure that all relevant personnel are competent to carry out their duties.

12.1.2 *Specialist training*

In addition to the training described in clause 12.1.1, provide regular and systematic additional training for relevant personnel responsible for storage, loading and unloadinorof controlled or hazardous TTSPPs. Training should cover the following:

— applicable legislation and regulations;
— security and safety risks; and
— response to emergencies.

Ensure that each employee understands his or her specific responsibilities. Maintain training records to demonstrate compliance and perform effectiveness checks on training. Provide similar training for drivers who are responsible for transporting these substancese.

Reason: To ensure that all relevant personnel are competent to handle controlled or hazardous TTSPPs.

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Annex 10

Procedure for prequalification of pharmaceutical products

1. Introduction

The World Health Organization (WHO) provides United Nations agencies with advice on the acceptability, in principle, of pharmaceutical products for procurement by such agencies.

This activity of WHO aims to facilitate access to priority essential medicines that meet WHO-recommended norms and standards of acceptable quality. WHO undertakes a comprehensive evaluation of the quality of pharmaceutical products, based on information submitted by the manufacturers of such products or other applicants, and on an inspection of the corresponding manufacturing facilities and clinical sites. This is done through a standardized procedure which is based on WHO-recommended quality standards. The quality of pharmaceutical products is obviously crucial for the safety and efficacy of such products.

The pharmaceutical products found to meet the WHO-recommended quality standards are included in the list of medicines, as manufactured at the specified manufacturing sites, which are considered to be acceptable, in principle, for procurement by United Nations agencies. The list of prequalified pharmaceutical products is principally intended for use by United Nations agencies — including the Joint United Nations Programme on HIV/AIDS (UNAIDS), United Nations Children's Fund (UNICEF) and United Nations Population Fund (UNFPA) — to guide their procurement decisions. The growing list of pharmaceutical products that have been found to meet WHO-recommended standards may, however, also be of interest to other organizations and countries wishing to engage in the bulk procurement of pharmaceutical products.

Inclusion in the list does not imply any approval by WHO of the pharmaceutical products and manufacturing sites in question (which is the sole prerogative of national authorities). Moreover, inclusion in the list does not constitute an endorsement or warranty by WHO of the fitness of any product for a particular purpose, including its safety and/or efficacy in the treatment of specific diseases.

2. Glossary

The definitions given below apply to the terms used in this procedure. They may have different meanings in other contexts.

active pharmaceutical ingredient (API)

A substance used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have

direct effect in restoring, correcting or modifying physiological functions in human beings.

applicant

The person or entity who, by the deadline mentioned in the invitation, submits an expression of interest (EOI) to participate in this procedure in respect of the product(s) listed in the invitation, together with the required documentation on such product(s).

contract research organization (CRO)

An organization (commercial, academic or other) to which an applicant may have transferred some of its tasks and obligations in relation to the conduct of clinical studies with the product submitted to WHO for assessment under the current procedure.

finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling.

invitation for expressions of interest (EOIs) or invitation

Invitation calling upon interested parties (e.g. manufacturers or other applicants) to submit an expression of interest (EOI) to WHO by a specified deadline for the purpose of participating in the WHO prequalification procedure in respect of the product(s) listed in the invitation. Such an EOI should be accompanied by the required documentation on the product(s) in question.

manufacturer

A company that produces, packages, repackages, labels and/or relabels pharmaceutical products.

pharmaceutical product

Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.

prequalification

Standardized quality assessment procedure of WHO to evaluate the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies. Agencies using information resulting from the prequalification procedure should perform additional steps of qualification prior to purchasing, such as ensuring financial stability and standing of the supplier, ability to supply the required quantities, security of the supply chain, preshipment quality control and other related aspects.

stringent regulatory authority (SRA)

For the purpose of this procedure, a stringent regulatory authority (SRA) is:

— the medicines regulatory authority in a country which is: (a) a member of the International Conference on Harmonisation (ICH) (European Union (EU) Japan and the United States of America); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by SwissMedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time); and
— only in relation to good manufacturing practices (GMP) inspections: a medicine regulatory authority that is a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) as specified at http://www.picscheme.org.

3. Purpose and principles

The purpose of this WHO procedure is to evaluate whether certain pharmaceutical products (considered by WHO to be vital for the prevention and treatment of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis, malaria and other diseases, or for reproductive health) meet the requirements recommended by WHO and are manufactured in compliance with current good manufacturing practices (hereinafter referred to as GMP).

This procedure established by WHO is based on the following principles:

— the medicines eligible for prequalification are listed in invitations for EOI published on the WHO web site (http://who.int/prequal/info_applicants/info_for_applicants_EOIs.htm);
— a general understanding of the production and quality control activities of the manufacturer;
— assessment of pharmaceutical product data and information on safety, efficacy and quality submitted by the manufacturer, including product formulation, manufacture and test data and results;
— inspection of finished pharmaceutical product (FPP) and active pharmaceutical ingredient (API) manufacturing site(s) for compliance with GMP;
— inspection of clinical testing units or contract research organizations (CROs) performing clinical trials for compliance with current good clinical practices (hereinafter referred to as GCP) and current good laboratory practices (hereinafter referred to as GLP);
— reliance on the information supplied by stringent national medicines regulatory authorities;

— random sampling and testing of pharmaceutical products supplied;
— handling of complaints and recalls reported to WHO; and
— monitoring of complaints from agencies and countries.

WHO may collaborate with national medicines regulatory authorities (NMRAs) regarding dossier assessments and inspections. Subject to the terms of section 4 below, the prequalification of a product may also be based on approval by a stringent regulatory authority (SRA).

WHO recommends that applicants expressing interest in participation in the prequalification procedure inform the NMRAs in the country of manufacture of their intention and request them to collaborate with WHO in the quality assessment process. It is recommended that applicants provide the NMRAs with the necessary authorization to discuss the relevant product files with WHO representatives during dossier assessment and site inspections (subject to appropriate confidentiality provisions, if necessary).

4. Steps of the procedure

WHO undertakes a comprehensive evaluation of the quality of pharmaceutical products, based on information submitted by the applicants, and inspection of the relevant manufacturing and clinical sites. (A flowchart showing the prequalification process is provided in Appendix 1.)

At regular intervals, and also taking into consideration pertinent input received from relevant United Nations agencies, WHO will publish an invitation to interested parties, requesting them to voluntarily participate in this procedure in respect of the products mentioned in the invitation.

By submitting an EOI, the applicant undertakes to share information with WHO on all relevant aspects of manufacture and control of the specified products along with changes made and/or planned. Interested applicants provide the necessary information to WHO by submitting a product dossier in the prescribed format, and other information as requested.

The procedure will normally include:

— assessment of product dossiers, which must include product data and information as specified in the guidelines for submission, available on the WHO web site (http://apps.who.int/prequal/);
— inspection of manufacturing sites of FPPs and active pharmaceutical ingredients (APIs), to assess compliance with GMP;
— inspection of clinical sites (if applicable), to assess compliance with GCP and GLP as appropriate.

If the evaluation above demonstrates that a product and its corresponding manufacturing (and clinical) site(s) meet WHO-recommended standards,

the product will be included in the list of pharmaceutical products that are considered to be acceptable, in principle, for procurement by United Nations agencies.

WHO reserves the right to terminate the evaluation of a specific product if the applicant is not able to provide the required information, and/or is unable to implement any corrective actions which WHO may require within a specified time period, or when the information supplied is inadequate to complete this procedure.

WHO recognizes the evaluation of relevant products by SRAs which apply standards for quality equivalent to those recommended by WHO. Provided that the NMRA is willing to share certain information with WHO on the products in question, WHO will consider such products for inclusion in the list of WHO-prequalified products. It will do so as and when information about such products becomes available to WHO and when the holders of the regulatory approval of such products express their interest in having these products prequalified by WHO. These products will be added to the list of products prequalified by WHO, on the basis of the scientific assessment and inspections conducted by the regulatory authority concerned, and the exchange of relevant information between the regulatory authority and WHO.

An inspection of a manufacturer or CRO may not be required if:

1. There has been an inspection by an SRA; and
2. The inspection was conducted within the last three years; and
3. Information on the inspection (including inspection report and responses to any deficiencies) is available for review by WHO; and
4. Based on this and other available information, it is determined[1] that the site(s) in question meet(s) the applicable WHO-recommended standards.

With a view to coordinating inspection activities, avoiding duplication and promoting information sharing without prejudice to the protection of any confidential and or proprietary information of the applicants and manufacturers in accordance with the terms of this procedure, WHO may disclose inspection related information to regulatory authorities of WHO Member States as well as to regulatory authorities that are members of the PIC/S.

5. Invitation for expressions of interest

The pharmaceutical products listed in an invitation for EOIs are considered by WHO to be vital for the effective treatment and prevention of the

[1] Taking into account any known specific risk(s) associated with the product(s), the results of previous inspections conducted by WHO or an SRA, any complaints (if known), the scope and detail of the inspection report, the number and type of any GMP deficiencies reported, the comprehensiveness of the manufacturer›s response and the timelines for implementation of corrective action(s).

specified diseases (including HIV/AIDS, malaria and tuberculosis) or for reproductive health. These products are normally included in either the WHO Model List of Essential Medicines or the relevant WHO treatment guidelines and recommendations (or both).

The products included in the WHO Model List of Essential Medicines are those that satisfy the priority health-care needs of a population. They are selected, among other criteria, on the basis of disease prevalence, evidence on efficacy and safety, and analysis of comparative cost-effectiveness. Products included in WHO treatment guidelines are selected on the basis of an assessment of the evidence for benefits, risks, costs and appropriateness for use in a variety of situations, taking into account the needs of special populations and the values and preferences of the groups (professional and patient) using them.

Each invitation will be open and transparent, inviting all relevant parties to submit an EOI for the pharmaceutical products listed. Such an invitation will normally be published on the WHO web site and possibly also through other media, such as the international press.

In situations of high public health concern as determined by WHO, the Organization may also directly invite relevant parties to submit specified product dossiers for evaluation by WHO under this procedure without publication of an invitation for EOI.

6. Data and information to be submitted

Interested parties are expected to submit documentation on the pharmaceutical products as called for in the invitation for EOIs. Applicants should submit their product dossiers with the required information to the WHO focal point, before the deadline specified in the invitation. Guidance and instructions developed for the submission of the dossiers are made available on the WHO web site.

Normally the applicants who participate in the WHO prequalification scheme for pharmaceutical products are the manufacturers of the FPPs, as specified in the invitations for EOIs. In the case that an applicant is not the manufacturer of the FPP, all relevant documentation, including (but not limited to) contract manufacturing documentation, should be submitted, demonstrating that the applicant is in full control of the manufacturing process for, and quality assurance of, the products submitted for prequalification.

In submitting an EOI for product evaluation, the applicant should send the following to the WHO focal point:

— a covering letter, expressing interest in participating in the WHO prequalification procedure and confirming that the information submitted in the product dossier is complete and correct;

— a product dossier, in the format specified in the WHO guidance documents on submitting product data and information;
— product samples, to enable visual examination and chemical and pharmaceutical analysis;
— a site master file (SMF) for each manufacturing site listed in the product dossier, in the format specified in the WHO guidance documents for submitting an SMF; and
— a contract research organization master file (CROMF) for each clinical site listed in the dossier, in the format specified in the WHO guidance documents for submitting a CROMF.

All documentation should be submitted in English.

For the purposes of this procedure, different requirements for documentation to be submitted apply to the following categories of products:

— multisource (generic) FPPs to be assessed by WHO;
— innovator FPPs approved by SRAs; and
— multisource (generic) FPPs approved by SRAs.

The documentation requirements for each of the above categories can be found on the WHO web site at: http://who.int/prequal/info_applicants/info_for_applicants_guidelines.htm. These requirements may be revised from time to time.

Multisource generic products must be shown, either directly or indirectly, to be therapeutically equivalent to the comparator product if they are to be considered interchangeable. WHO will maintain and make public the list of comparator products for this purpose. The WHO web site provides guidance on the evidence needed for a product to be considered equivalent without the need for in vivo equivalence studies (i.e. application of biowaiver).

If considered necessary or desirable by either party, and before the actual evaluation process starts, a discussion may be held between the manufacturer and WHO. This meeting should be scheduled as early as possible with a predefined agenda to address questions sent in advance to WHO by the manufacturer.

7. Screening of dossiers submitted

Each product dossier submitted by an applicant will be screened for completeness before being evaluated. Dossiers submitted for products which are not listed in an invitation for EOIs or have not otherwise been invited by WHO will not be accepted for assessment.

Similarly WHO will not consider dossiers that are incomplete. The applicant will be informed that an incomplete dossier has been received

and will be requested to complete the dossier within a specified time period. In the event of non-compliance, the dossier may be rejected on grounds of incompleteness and returned to the applicant. Dossiers that are considered complete as the result of the screening will be retained by WHO for assessment.

After screening, if the dossier is accepted for assessment the applicant will be informed of this, including the dossier reference number, by letter. This letter will serve as an agreement between WHO and the applicant for the participation in prequalification and a commitment to comply with the provisions of the prequalification procedure.

8. Dossier assessment

The product information submitted in the dossiers will be assessed by teams of experts (assessors) appointed by WHO. The assessors involved in dossier assessment must have the relevant qualifications and experience in the fields of pharmaceutical development, quality assessment of pharmaceutical products, quality assurance, biopharmaceutics and other relevant fields. The assessors will be appointed in accordance with a standard operating procedure (SOP) established by WHO. The assessors should preferably be from NMRAs and they will act as temporary advisers to WHO. The assessors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure.

The assessment of product dossiers will be done in accordance with SOPs established by WHO for that purpose so as to ensure uniformity in evaluation and timeliness of assessment activities. If needed, WHO may provide training to these experts.

Following the assessment of each part of the dossier, a report will be provided to the applicant. Applicants are expected to submit responses to comments and any additional information that may be requested as soon as possible. Within one month, the applicant should inform WHO of the estimated time frame required to address and respond to all queries. The procedure is usually suspended (i.e. WHO will not undertake any further action) until all required responses and any additional information is received by WHO.

Each applicant may request a hearing or meeting with the WHO experts involved in the assessment of this applicant's dossier to clarify issues identified by the WHO experts. WHO may provide technical assistance to applicants regarding appropriate product information to be submitted as well as production and control requirements.

9. Site inspection

WHO will plan and coordinate, in accordance with SOPs established by WHO and based on quality risk management (QRM) principles, the performance of inspections of the site(s) of manufacture of the API(s) and the FPP, and of the clinical testing units or CROs.

The following factors will be taken into account when planning inspections:

— the results of previous inspection(s) by WHO or an SRA, and history of compliance of the company or facility with GMP, GCP and or GLP as appropriate;
— the outcome of the assessment of data submitted to WHO;
— complexity of the site, processes and product;
— number and significance of known quality defects (e.g. complaints, recalls);
— major changes to, e.g. buildings, equipment, processes, key personnel;
— site experience with manufacturing and testing of a product; and
— test results of official control laboratories.

The inspections of the manufacturing site(s) are conducted to assess compliance with GMP as recommended by WHO and include data verification. SMFs submitted by the applicant will be reviewed before an inspection is performed.

The inspections of clinical testing units or CROs are carried out to assess compliance with GCP and GLP, and to perform data verification.

The WHO norms and standards applicable to inspections of APIs and FPPs, and of clinical testing units or CROs, can be found on the WHO web site at http://who.int/prequal/assessment_inspect/info_inspection.htm#2. These requirements may be revised from time to time.

The inspections will be performed by a team of inspectors usually including experts appointed by WHO, preferably from NMRA inspectorates, who will act as temporary advisers to WHO. The inspectors must have the relevant qualifications and experience to perform such inspections, be competent in areas such as production and quality control of pharmaceuticals, and have appropriate experience in GMP and GCP or GLP. The inspectors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure. If needed, WHO may provide training to these experts.

A WHO staff member will coordinate the team and will normally lead the inspection team. Each team will perform the inspections and report its findings to WHO in accordance with SOPs established by WHO for that purpose so as to ensure a standard harmonized approach. A representative

of the NMRA of the country of manufacture would normally be expected to accompany the team to the manufacturing and testing facilities to assess the compliance with GMP and GCP or GLP.

In accordance with SOPs established by WHO and based on QRM principles, an on-site inspection by a WHO inspection team may be waived provided that the site in question is found to meet the applicable WHO-recommended standards following a desk review of requested inspection reports, the manufacturers response(s) to the relevant inspectorate describing corrective actions to any deficiencies identified in the inspection reports and an acceptable product quality review report for the identified product(s).

10. Reporting and communication of the results of the evaluation

Each assessment and inspection team will finalize its reports according to the established WHO SOP and format, describing the findings and including recommendations to the applicant, manufacturer(s) and/or CROs where relevant.

The findings from the dossier assessment including, but not limited to, deficiencies of the documentation and data submitted, shall be communicated in writing to the applicant requesting submission of the missing data and information, as appropriate.

The inspection report will be communicated to the manufacturer or CRO as applicable. With the written agreement of the manufacturer or CRO, a copy of the inspection report may also be provided to the applicant (if other than the manufacturer or CRO). If any additional information is required, or corrective action has to be taken by the manufacturer or CRO, WHO will postpone its decision on the acceptability of the site(s) concerned until such information has been evaluated or the corrective action has been taken and found satisfactory in light of the specified standards.

WHO reserves the right to terminate this procedure for a specific product if the applicant is not able to provide the required information or implement the corrective actions within a specified time period, or if the information supplied is inadequate to complete this procedure.

In the event of any disagreement between an applicant and WHO, an SOP established by WHO for the handling of such disagreements will be followed to discuss and resolve the issue.

As WHO is responsible for the prequalification procedure, the ownership of the reports lies with WHO. Thus, WHO shall be entitled to use and publish such reports subject always, however, to the protection of any commercially

sensitive confidential information of the applicant, manufacturer(s) and/or testing organization(s). "Confidential information" in this context means:

— confidential intellectual property, know-how and trade secrets (including, e.g. formulas, processes or information contained or embodied in a product, unpublished aspects of trade marks, patents, etc.); and
— commercial confidences (e.g. structures and development plans of a company).

Provisions of confidentiality will be contained in the exchange of letters, to be concluded before the assessment of the product dossier or inspection of the manufacturing and clinical sites, between WHO and each applicant, manufacturer or CRO.

Notwithstanding the foregoing, WHO reserves the right to share the full assessment and inspection reports with the relevant authorities of any interested Member State of the Organization and interested United Nations agencies.

11. Outcome of the prequalification procedure

Once WHO is satisfied that this procedure is complete for the relevant product, and that the WHO-recommended standards are met, the product, as manufactured at the specified manufacturing site(s), will be included in the list of prequalified pharmaceutical products. The list of prequalified pharmaceutical products will be compiled in accordance with an SOP established by WHO for final decision-making on inclusion in the list. The list will be published on the WHO web site and will specify the characteristics of the prequalified pharmaceutical products, as described in Appendix 2 to this procedure.

Each applicant will receive a letter of prequalification from WHO informing it of the outcome of the quality assessment process in regard of the submitted product(s). Once the product(s) are included in the list of prequalified pharmaceutical products, the applicant shall be responsible for keeping WHO continuously updated on all relevant aspects of the manufacture and control of such product(s) and to meet any requirements, as agreed with WHO.

In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, WHO will — subject to the protection of any commercially sensitive confidential information — publish WHO Public Assessment Reports (WHOPAR(s)) on the product dossier assessments and WHO Public Inspection Reports (WHOPIR(s)) on the manufacturers and CROs, that were found to be in compliance with WHO-recommended guidelines and standards. These reports will be published on the WHO web site. Subject always to the protection of commercially sensitive confidential

information, WHO shall also be entitled to publish negative evaluation outcomes in accordance with SOPs established by WHO. These include notices of concern as well as notices of suspension.

The decision to list a pharmaceutical product is made based upon information available to WHO at that time, i.e. information in the submitted dossier and on the status of GMP, GLP and GCP at the facilities used in the manufacture and testing of the product at the time of the site inspection(s) conducted by WHO or at the time of the site inspection(s) conducted by an SRA, the outcome of which has been determined by WHO to meet the applicable WHO-recommended standards, in accordance with the terms of this procedure. This decision is subject to change on the basis of new information that may become available to WHO. If serious safety and/or quality concerns arise in relation to a prequalified product, WHO may delist the product after evaluation of the new evidence and a risk–benefit assessment, or may suspend the product until results of further investigations become available and are evaluated by WHO.

12. Maintenance of prequalification status

Applicants are required to communicate details to WHO of any changes (variations) in manufacture and control that may have an impact on the safety, efficacy and quality of the product.

Guidance on variations to prequalified dossiers as can be found on the WHO web site at http://who.int/prequal/info_applicants/info_for_applicants_guidelines.htm. These requirements may be revised from time to time.

It is the applicant's responsibility to provide WHO with the appropriate documentation (referring to relevant parts of the dossier) to prove that any intended or implemented variation will not have a negative impact on the quality of the product that has been prequalified. WHO will undertake an evaluation of variations according to the established WHO guidelines and SOPs and communicate the outcome to the applicant within the prescribed time lines. Adherence to the reporting requirements will be verified during the inspections carried out by WHO.

Random samples of prequalified products supplied by listed manufacturers or applicants will be taken for independent testing of final product characteristics. Certificates of analysis of final products released by the manufacturer and specifications for test methods should be provided by the manufacturer or applicant to WHO for review upon request. In the event of failure to meet the established criteria for testing, WHO will investigate the problem and communicate the outcome of this investigation to the manufacturer and applicant, if other than the manufacturer.

Complaints concerning prequalified pharmaceutical products communicated to WHO will be investigated in accordance with an SOP established by WHO for that purpose. After investigation, WHO will provide a written report of the problem and include recommendations for action where relevant. WHO will make the report available to the applicant/manufacturer, and to the NMRA of the country where the manufacturing site is located. Subject always to the protection of commercially sensitive information as referred to above, WHO shall be entitled to make such reports public. In addition, WHO reserves the right to share the full report with the relevant authorities of interested Member States of the Organization and interested United Nations agencies.

Manufacturers of prequalified pharmaceutical products and associated API manufacturers will be re-inspected at regular intervals as determined by WHO, but normally at least once every three years. Re-inspections are conducted to verify compliance with GMP as recommended by WHO and include data verification.

Furthermore, in order to maintain their prequalification status, WHO will arrange for prequalified pharmaceutical products to be requalified at regular intervals.

Every five years from the date of prequalification, or when requested to do so by the WHO Prequalification of Medicines Programme, the holder of a prequalified product is required to submit data and information in relation to the product to WHO for assessment. The purpose of this assessment is to verify that the product conforms to information and data submitted in relation to prequalification, conforms to current norms and standards, and to verify the consistency of the quality of the product and its manufacturing process(es) over the identified period.

The procedure and guidelines on the requalification of prequalified products can be found on the WHO web site at http://who.int/prequal/info_applicants/info_for_applicants_guidelines.htm. These requirements may be revised from time to time. Re-inspection and/or requalification may also be performed:

— if any fraud or omissions by the applicant, manufacturer(s) of an FPP or API, or CROs in the initial assessment procedure or during the follow-up activities, become evident; and
— if WHO or any United Nations agency considers that a batch or batches of supplied prequalified pharmaceutical products are not in compliance with the specifications which were found to be applicable upon prequalification

If, as a result of re-inspection or requalification, it is found that a product and/or specified manufacturing site no longer complies with the WHO-

recommended standards, such products and manufacturing sites may be suspended or removed from the list of prequalified pharmaceutical products. Failure of a manufacturer or applicant to participate in re-inspection or requalification (as applicable) may also lead to suspension or removal from this list.

13. Cost recovery

WHO reserves the right to charge for this procedure on a cost-recovery basis.

14. Confidentiality undertaking

The assessors and inspectors will treat all information to which they will gain access during the assessments and inspections, or otherwise in connection with the discharge of their responsibilities in regard to the above-mentioned project, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below.

Assessors and inspectors will take all reasonable measures to ensure that confidential information:

— is not used for any purpose other than the assessment/inspection activities described in this document; and
— is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Assessors and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

— was known to them prior to any disclosure by or on behalf of WHO (including by manufacturers); or
— was in the public domain at the time of disclosure by or on behalf of WHO (including by manufacturers); or
— has become part of the public domain through no fault of theirs; or
— has become available to them from a third party not in breach of any legal obligations of confidentiality.

15. Conflict of interest

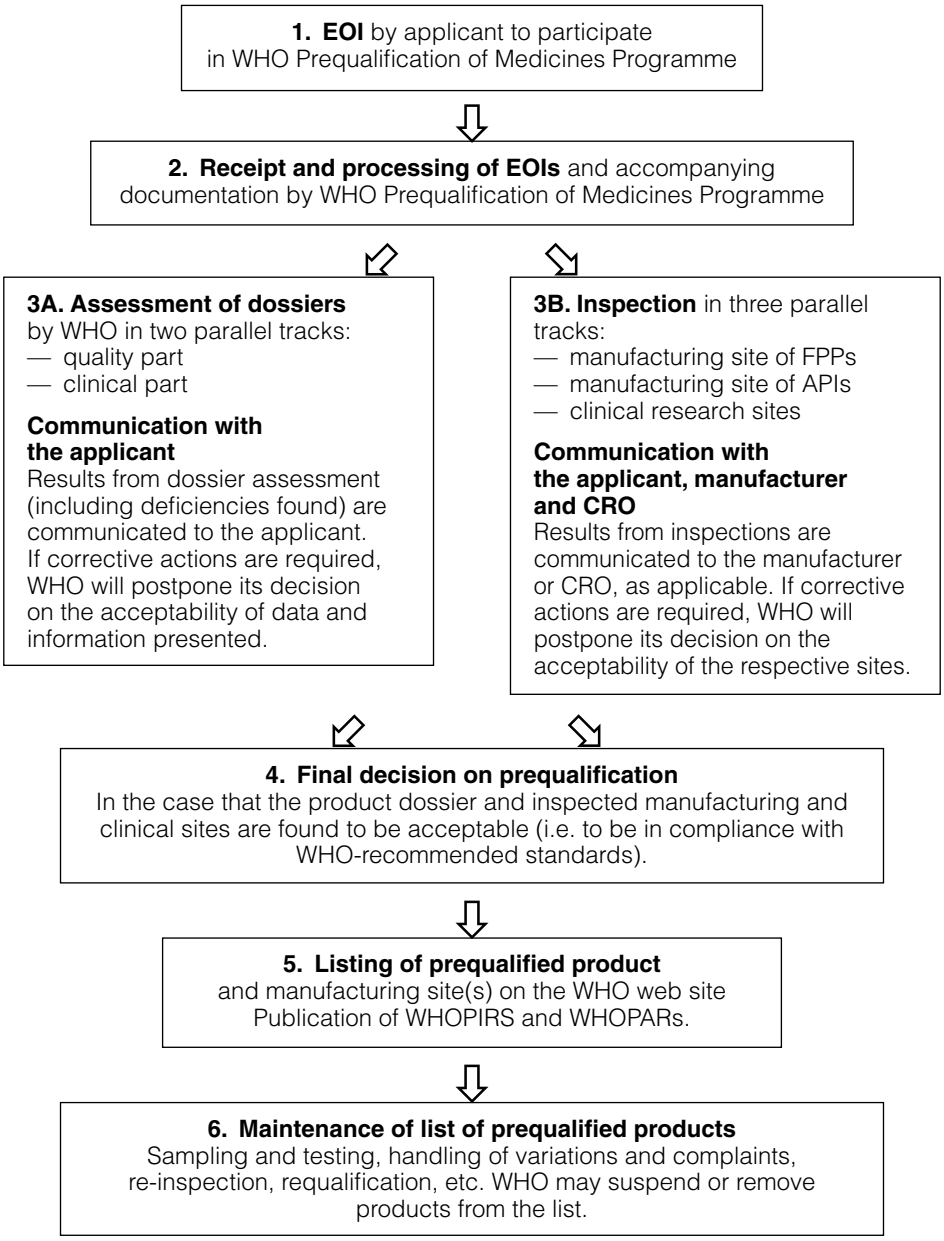
Before undertaking the work, each assessor and inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest. If, based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is

felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the assessor or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify WHO of any change in this information.

All inspectors furthermore agree that, at the manufacturer's or CRO's request, WHO will advise the manufacturer or CRO, in advance, of the identity of each inspector and the composition of the team performing the site inspection, and provide curricula vitae of the inspectors. The manufacturer or CRO then has the opportunity to express possible concerns regarding any of the inspectors to WHO before the visit. If such concerns cannot be resolved in consultation with WHO, the manufacturer or CRO may object to a team member's participation in the site visit. Such an objection must be made known to WHO by the manufacturer or CRO within 10 days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

Appendix 1

Flowchart of WHO prequalification of pharmaceutical products



EOI, expression of interest; FPP, finished pharmaceutical product; API, active pharmaceutical ingredient; CRO, contract research organization; WHOPIR, public inspection report; WHOPAR, public assessment report.

Appendix 2

Characteristics of the prequalified pharmaceutical product to be made available for public access on the WHO web site

— WHO product reference number
— International Nonproprietary Name (INN) of active pharmaceutical ingredient(s) (API(s))
— dosage form and strength
— trade name(s) of the product (if applicable)
— name of applicant and official address
— name of manufacturer of finished pharmaceutical product (FPP)
— physical address of manufacturing site(s) (and unit, if applicable)
— name of API manufacturer, physical address of manufacturing site(s) (and unit, if applicable)
— product description (as in FPP specifications, i.e. coated, scored, etc.)
— pack size(s), primary and secondary packaging material(s)
— storage conditions
— shelf-life (provisional, if applicable)
— summary of product characteristics
— package leaflet
— labelling

WHO Technical Report Series, No. 961, 2011

Annex 11

Guidelines on submission of documentation for prequalification of innovator[1] finished pharmaceutical products approved by stringent regulatory authorities[2]

The World Health Organization (WHO) recognizes the scientific evaluation of innovator finished pharmaceutical products (FPPs) by regulatory authorities, which apply similarly stringent standards for quality, safety and efficacy to those recommended by WHO. Where an applicant and a stringent regulatory authority (SRA) can agree to share the following information on an innovator FPP with WHO, WHO will consider such an FPP for inclusion in the list of WHO prequalified products, as and when information about such a product becomes available to WHO and when the applicant in question expresses his or her interest in the product being prequalified by WHO.

The following should be submitted:

1. A covering letter, which should include:
   — a statement indicating that the information submitted is true and correct;
   — a statement confirming that, for WHO prequalification, the product, including composition, formulation, strength, specifications, packaging will at the time of submission be the same in all respects as the product registered with the relevant SRA; and
   — the name of the person responsible for communication with WHO on any issues related to the product.

2. An original or certified copy of the current WHO-type Certificate of a Pharmaceutical Product issued and fully completed, including answers to each question, by the relevant SRA, together with the latest approved summary of product characteristics (SmPC), or an equivalent thereof, as well as the patient information leaflet (PIL) and the labelling.

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[1] Generally, the innovator pharmaceutical product is that which was first authorized for marketing, on the basis of documentation of quality, safety and efficacy (WHO Technical Report Series, No. 937, Annex 7, 2006).

[2] Stringent regulatory authority (SRA): a regulatory authority which is: (a) a member of the International Conference on Harmonisation (ICH) (as specified on www.ich.org); or (b) an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

3. An assessment report issued by the relevant SRA: a publicly available scientific assessment report, such as the Scientific Discussion of the European Public Assessment Report (EPAR), issued by the relevant SRA is also acceptable.
4. A certified copy of the marketing authorization issued by the relevant SRA. If applicable a certified copy of the latest renewal of the marketing authorization should also be provided.
5. A list of the SRA-approved manufacturer(s) of the FPP, with the physical address of the manufacturing site(s) (and unit if applicable).
6. A list of the SRA-approved manufacturer(s) of the active pharmaceutical ingredient(s) (API(s)) used in the manufacture of the FPP, with the physical address of the manufacturing site(s) (and unit if applicable).
7. A sample(s) of the product in market packaging(s) should be provided with the submission to enable a visual inspection to be made. The respective certificate of analysis should be attached.

Please note that the submission must be in English, which includes certified English translations of the SmPC and other documents. These documents should be made available both as hard copies and electronically. The SmPC and PIL should be submitted as Word files.

Variations to and renewal of the marketing authorization of a product that has been prequalified by WHO based on the approval by an SRA, remain the responsibility of the relevant SRA.

Once the product has been prequalified, WHO should be provided with a copy of the regulatory acceptance letter of any changes to the main characteristics of the product — such as the labelling for storage, the nature and contents of the container, the shelf-life, manufacturing site(s) of the FPP or API, or any other relevant change to the product information — immediately after the variation has been approved by the relevant SRA. The main characteristics of the product will be listed in the Letter of Prequalification.

The preferred storage condition for WHO prequalified products is "do not store above 30 ºC". If this is not indicated on the SmPC, PIL and labels of the innovator product, applicants are encouraged to apply for a variation in this respect with the relevant SRA. This could also be done after prequalification of the product.

Products that received tentative approval from the United States Food and Drug Administration (FDA) or positive opinions under Article 58 of European Union Regulation (EC) No. 726/2004 or the Canada S.C. 2004, c. 23 (Bill C-9) procedure are not within the scope of this guideline. Such products can be co-listed on the WHO List of Prequalified Products in accordance with mutual agreements between WHO and these regulatory authorities.[3]

[3] Information and the full text of the relevant WHO documents can be found on the web site http://apps.who.int/prequal/.

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Annex 12

Prequalification of quality control laboratories. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies

Introduction

The World Health Organization (WHO) provides United Nations agencies, on request, with advice on the acceptability, in principle, of quality control laboratories that are found to meet WHO recommended quality standards for such laboratories, i.e. *Good practices for pharmaceutical quality control laboratories* (GPCL) (*1*) and the relevant parts of good manufacturing practices (GMP) (*2*). This is done through a standardized quality assessment procedure. The purpose of the quality assessment procedure is to evaluate whether the quality control laboratories to be used for the quality control of pharmaceutical products meet the requirements recommended by WHO for such laboratories.

Participation in the prequalification procedure is voluntary and any pharmaceutical quality control laboratory (governmental or private) could participate. Certification such as ISO (in terms of ISO/IEC17025) is encouraged and will also be considered in the prequalification procedure. It is recommended that laboratories should work towards obtaining certification.

The quality assessment procedure established by WHO is based on the following principles:

— commitment of the laboratory to providing services of testing of pharmaceutical products to United Nations agencies;
— a general understanding of the quality assurance management and quality control testing activities of the laboratory;
— evaluation of information submitted by the laboratory;
— assessment of compliance with WHO recommended quality standards for quality control laboratories, i.e. GPCL (*1*) and the relevant parts of GMP (*2*); and
— monitoring of performance of prequalified laboratories.

WHO invites the national medicines regulatory authority (NMRA) having regulatory oversight over a laboratory participating in the prequalification procedure, to join as an observer in the inspection of the laboratory's compliance with WHO recommended standards for quality control laboratories. WHO recommends that laboratories expressing an interest in participating in the prequalification procedure, inform the regulatory authority of the country in which they are established as well as relevant networks (e.g. the Official Medicines Control Laboratories (OMCL) network) of their submission for prequalification.

This procedure is to be followed for prequalification of quality control laboratories for use by the United Nations agencies.

1. Steps of the procedure

WHO requires information related to the activities of, and quality control of pharmaceutical products in, laboratories interested in being assessed under this procedure. Interested quality control laboratories should submit the information about their activities as requested by WHO (see point 1.2 below). In addition to the evaluation of the information submitted, a site inspection (or inspections) may be performed.

If, due to insufficient resources and time constraints, WHO has to set priorities in the assessment of interested laboratories, then priority will be given to quality control laboratories in areas where United Nations agencies identify the need for testing of the quality of pharmaceutical products, and to national quality control laboratories and laboratories providing testing services to governments.

WHO reserves the right to terminate the quality assessment of a laboratory when the laboratory is not able to provide, or fails to provide, the required information, when the information supplied is inadequate to complete the quality assessment effectively, the laboratory fails to collaborate in inspections required by WHO and/or is unable to implement corrective actions which WHO may require within a specified time period.

1.1 Publication of invitation for Expressions of Interest

WHO will publish an invitation to quality control laboratories to submit an Expression of Interest (EOI) to participate in the prequalification procedure. Such an invitation will specify the scope of quality control testing which is subject to prequalification and will be published widely, i.e. on the WHO web site and possibly also through other media, such as the international press. The invitation will be open and transparent, inviting all interested quality control laboratories to submit the EOI for prequalification.

1.2 Submission of Expressions of Interest and laboratory information

Each interested laboratory should provide the WHO focal point indicated in the invitation for EOIs with:

— a letter expressing interest in participating in the prequalification procedure; and
— the relevant laboratory information.

WHO will record the receipt of the EOI from each laboratory in a register.

Guidelines for the submission of EOIs and for the preparation and submission of the relevant information are available on the WHO web site

at http://apps.who.int/prequal/ and will be sent to interested laboratories upon request.

If the laboratory has documented its quality system as a quality manual, this can be submitted, provided that it is supplemented with the information required for the laboratory information file (LIF, see below) that is not provided in the quality manual.

If there is no quality manual, the information should be submitted as described in the document *Guidelines for preparing a laboratory information file* (*3*) and contain information on the areas listed below:

— general information on the laboratory, including activities proposed for prequalification;
— quality management system implemented, and inspections and external audits performed in the laboratory;
— participation in proficiency testing schemes and/or collaborative trials;
— internal audits;
— control of documentation and records;
— personnel;
— premises;
— equipment;
— reagents, reference substances and reference materials;
— subcontracting of testing (where applicable);
— handling of samples;
— validation of analytical procedures;
— investigation of out-of-specification (OOS) results;
— stability testing (where applicable); and
— microbiological testing (where applicable).

1.3 Screening of submitted laboratory information

The information submitted by the laboratory will be screened for completeness against the *Guidelines for preparing a laboratory information file* (*3*). Incomplete information will not be considered for evaluation. The laboratory will be informed that incomplete information has been received, and be requested to complete it within a specified time period. In the event of noncompliance with this request, the laboratory information will in principle be rejected on grounds of incompleteness and returned to the laboratory.

1.4 Evaluation of the laboratory information

Laboratory information that complies with the requirements set out in section 1.2 above will be evaluated in accordance with a standard operating

procedure (SOP) established by WHO to ensure uniformity in evaluation of the information. The information will be evaluated against the WHO recommended quality standards for quality control laboratories, i.e. GPCL (*1*) and the relevant parts of GMP (*2*), and the laboratory will be considered for a possible site inspection.

A laboratory may submit the report of the inspection or audit performed by a regulatory authority applying standards at least equivalent to WHO recommended quality standards for quality control laboratories, i.e. GPCL (*1*) and the relevant parts of GMP (*2*), and the response of the laboratory to the observations made by the authority during inspection or audit. Based on WHO's assessment of the report and response, if the laboratory is considered to be operating at an acceptable level of compliance with WHO recommended standards, WHO may decide that it is not necessary to conduct a site inspection.

1.5 Site inspection

Depending on the outcome of the evaluation of the laboratory information, WHO may plan and coordinate inspections of the laboratory to assess compliance with WHO recommended quality standards for such laboratories, i.e. GPCL (*1*) and the relevant parts of GMP (*2*).[1] The inspection will be performed by an inspector, or a team of inspectors, having the relevant qualifications and experience in the field of quality control of medicines. External inspectors will be appointed in accordance with a SOP established by WHO and will act as temporary advisers to WHO. The external inspectors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure. A WHO staff member will coordinate the team. The inspector or inspection team will perform the inspections and report on the findings in accordance with SOPs established by WHO to ensure a standard harmonized approach.

A representative or representatives of the NMRA having regulatory oversight over a laboratory participating in the prequalification procedure, is invited to accompany the team as an observer.

With a view to coordinating inspection activities, avoiding duplication and promoting information sharing without prejudice to the protection of any confidential and proprietary information of the laboratory in accordance with the terms of this procedure, WHO may disclose inspection-related information to regulatory authorities of WHO Member States, United Nations agencies and to the European Directorate for the Quality of Medicines & HealthCare (EDQM).

[1] Training modules can be found on the Prequalification web site (http://apps.who.int/prequal/).

1.6 Report and outcome of inspection

The inspector or inspection team will finalize a report describing the findings according to the established WHO SOP and format. The report will be communicated by WHO to the laboratory and a copy will be sent to the NMRA having regulatory oversight over the laboratory.

If any additional information is required, or if a corrective action has to be taken by the laboratory, WHO will postpone its decision on the acceptability of the laboratory concerned until the additional information has been evaluated, or the corrective action has been taken, and found satisfactory. If the decision cannot be made based on the information received, a follow-up inspection will be performed.

In the event of any disagreement between a laboratory and WHO, an SOP for the handling of such disagreements will be followed to discuss and resolve the issue.

As WHO is responsible for the quality assessment procedure, the ownership of the reports lies with WHO (without prejudice, however, to any confidential and proprietary information of the laboratory contained in this report). Thus, WHO shall be entitled to use and publish such reports subject always, however, to the protection of any confidential and proprietary information of the laboratory. "Confidential information" in this context means:

— confidential intellectual property, "know-how" and trade secrets (including, e.g. programs, processes or methods, unpublished aspects of trade marks, patents, etc.); and
— commercial confidences (e.g. structures and development plans).

Provisions of confidentiality will be contained in the letters exchanged between WHO and the laboratory, to be agreed upon before the evaluation of the information and site inspection.

Notwithstanding the foregoing, WHO reserves the right to share the full reports with the relevant authorities of any interested Member State of the Organization and interested United Nations agencies.

1.7 Results of assessment

Once WHO is satisfied that the quality assessment process for the laboratory is complete, and that the laboratory is acceptable in principle for use by United Nations agencies (i.e. it has been found to meet the WHO recommended quality standards for quality control laboratories), the laboratory at the specified site will be included in a list referred to as "List of prequalified quality control laboratories".

Laboratories on the list will be considered to be able to test products in compliance with WHO recommended quality standards for quality control laboratories. Inclusion in the list does not, however, imply any approval by WHO of the laboratories (which is the sole prerogative of national authorities).

Each laboratory will receive a letter from WHO informing it of the outcome of the quality assessment process for that particular laboratory.

A copy of this letter will be sent to the NMRA of the country where the laboratory is located. The list of prequalified laboratories will be published on the WHO web site and will specify the areas of expertise assessed and considered prequalified. The list will be updated whenever new relevant information is obtained.

In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, WHO will — subject to the protection of any confidential and proprietary information — publish WHO Public Inspection Reports (WHOPIR(s)) on the laboratories considered to meet WHO recommended quality standards for quality control laboratories. These reports will be published on the WHO web site.

1.8 Monitoring of prequalified quality control laboratories

Once the laboratory is included in the list of prequalified quality control laboratories, it should inform WHO without delay about any implemented changes which may have an impact on the prequalification of the laboratory (such as changes to facility, equipment or key personnel) and should submit an updated LIF.

Each prequalified quality control laboratory will be re-evaluated on a routine basis at regular intervals (annually) or earlier, when information requiring re-evaluation is obtained by WHO.

To enable WHO to carry out re-evaluation, all prequalified laboratories are requested to submit a brief annual report on their activities. The report should cover all activities related to quality control of medicines within the preceding calendar year and should be submitted by the end of March of the subsequent year. The following items should be included in the report:

— a summary of services provided to United Nations agencies, other public health organizations procuring medicines and other customers;
— a summary of number of samples analysed, differentiating between compliant and non-compliant samples;
— a list of analytical methods used;
— a summary of complaints concerning results of analyses performed by the laboratory received from customers;

— brief details of participation in proficiency testing schemes (organizing party, methods involved, outcomes and, if appropriate, adopted corrective measures);
— listing of inspections and audits performed by external parties, identifying the party and scope of the inspection and audit; and
— in the case that changes have been implemented, which have an impact on the content of the LIF, a summary of these changes should be included in the report and an updated LIF should be attached.

WHO will conduct re-inspections of prequalified laboratories in accordance with SOPs established by WHO. The frequency of such re-inspections depends on WHO's assessment of the quality risk management factors described below. Normally, however, such re-inspections will take place at least once every three years. The following factors will be taken into account when planning inspections:

— major changes to e.g. premises, equipment, key personnel;
— the results of previous inspection(s)/audit(s) by WHO or another external party, and history of compliance of the laboratory with WHO recommended quality standards;
— the outcomes of participation of the laboratory in proficiency testing schemes;
— number and significance of known complaints by customers;
— laboratory experience with testing of medicines; and
— WHO experience with testing services provided by the laboratory.

WHO reserves the right to proceed with the re-inspection of a prequalified laboratory at any time, when considered necessary based on information or complaints received by WHO. The NMRA which has regulatory oversight over the laboratory will be invited to participate in the re-inspection as an observer.

WHO may suspend or withdraw a prequalified quality control laboratory from the List of prequalified quality control laboratories when there is evidence of non-compliance with the WHO recommended quality standards for such laboratories and/or this procedure.

1.9 Monitoring of complaint(s)

Complaint(s) concerning the results of analysis of pharmaceutical product(s) performed by the prequalified laboratory or concerning the service provided by the prequalified laboratory, which are communicated to WHO, will be investigated in accordance with an SOP established by WHO. The NMRA which has regulatory oversight over the laboratory will be invited to participate in the investigation of the complaint.

After conducting its investigation, WHO will provide a written report of the problem, which may, where appropriate, include recommendations for action to the laboratory under investigation and to the NMRA having the regulatory oversight over the laboratory.

1.10 Cost recovery

WHO reserves the right to charge for the quality assessment procedure on a cost-recovery basis.

1.11 Confidentiality undertaking

WHO will require any external inspectors (acting as temporary advisers to WHO) to treat all information to which they gain access during the inspections of the laboratory, or otherwise in connection with the discharge of their responsibilities in regard to the prequalification procedure, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set out below.

Such inspectors will be required to take all reasonable measures to ensure that confidential information:

— is not used for any purpose other than the activities described in this document; and
— is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

External inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

— was known to them prior to any disclosure by or on behalf of WHO (including by laboratories); or
— was in the public domain at the time of disclosure by or on behalf of WHO (including by laboratories); or
— has become part of the public domain through no fault of theirs; or
— has become available to them from a third party not in breach of any legal obligations of confidentiality.

1.12 Conflict of interest

Before undertaking the work, each external inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest. If, based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and

it is thus deemed appropriate for the inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify WHO of any change in this information.

All external inspectors furthermore agree that, at the laboratory's request, WHO will advise the laboratory in advance of the identity of each such inspector and the composition of the team performing the site inspection and provide curricula vitae of the external inspectors. The laboratory then has the opportunity to express possible concerns regarding any of the external inspectors to WHO prior to the visit. If such concerns cannot be resolved in consultation with WHO, the laboratory may object to an external inspector's participation in the site visit. Such an objection must be made known to WHO by the laboratory within 10 days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel its agreement with the inspector in question and the activities to be undertaken by that inspector, in whole or in part.

References

1. Good practices for pharmaceutical quality control laboratories. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report.* Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 1.
2. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2, Second updated edition. Good manufacturing practices and inspection.* Geneva, World Health Organization, 2007; *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. World Health Organization, 2010* (CD-ROM) (http://apps.who.int/medicinedocs/en/q/).
3. WHO guidelines for preparing a laboratory information file. Revision. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report.* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 13.

WHO Technical Report Series, No. 961, 2011

Annex 13

WHO guidelines for preparing a laboratory information file

Background

The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted in its thirty-eighth report in 2003 the *Guidelines for preparing a laboratory information file* (WHO Technical Report Series, No. 917, 2003, Annex 5).

The content of these guidelines is closely related to *WHO guidelines on good practices for pharmaceutical quality control laboratories*, which have recently been revised (the revised version was adopted by the WHO Expert Committee at its forty-fourth meeting in 2009).

The WHO Expert Committee on Specifications for Pharmaceutical Preparations discussed the need for a revision of both sets of guidelines at its forty-third meeting in 2008 and recommended that if the *Guidelines for good practices for national pharmaceutical control laboratories* were revised, the *Guidelines for preparing a laboratory information file* should be revised accordingly.

On the basis of the above and following the usual consultation process, the following text will replace the previously published guidelines.

1. General information on the laboratory
2. Quality management system
3. Control of documentation and records
4. Personnel
5. Premises
6. Equipment
7. Materials
8. Subcontracting of testing
9. Handling of samples
10. Validation of analytical procedures
11. Investigation of out-of-specification results
12. Stability testing (where applicable)
13. Microbiological testing (where applicable)

A laboratory information file (LIF) is a document prepared by the laboratory. It contains specific and factual information about the operations carried out at the named site and any closely integrated operations of the laboratory. If only some of the operations are carried out on the site, the LIF needs to describe only those operations, e.g. sampling, chemical analysis or stability testing.

An LIF should be written in English, succinct and, if possible, should not exceed 30 A4 pages, excluding appendices.

The laboratory should give a short description of its activities under each of the following headings. Policy or essential steps for each activity should be described and reference to a standard operating procedure (SOP) or other supporting documents should be given, where applicable. Where appropriate, supportive documentation should be appended.

1. General information on the laboratory

1.1 Brief information on the laboratory (including name, physical (location) and mailing address, contact details and brief history). If the laboratory is part of an organization or company, provide details of its position within the organization or company, including reporting lines (e.g. organizational chart).

1.2 Summary of all laboratory activities, including objectives of the laboratory, categories of customers, types of sample tested. In addition, state the relation (if any) to a manufacturing site.

1.3 Areas of expertise proposed for prequalification (list methods and tests, for examples see the List of Prequalified Quality Control Laboratories).[1]

Type of analysis	Finished products	Active pharmaceutical ingredients
Physical/chemical analysis		
Identification		
Assay, impurities and related substances		
Microbiological tests		
Bacterial endotoxin testing (BET)		
Stability testing		

1.4 Brief description of a policy for participation in proficiency testing schemes and collaborative trials and for the evaluation of the performance. Attach the list of tests in which the laboratory has participated in the last three years, including the organizer and results.

[1] http://www.who.int/prequal/lists/PQ_QCLabsList.pdf.

2. Quality management system

2.1 Short description of the quality management system implemented in the laboratory, including reference to the standard used (such as *WHO good practices for pharmaceutical quality control laboratories*, ISO 17025, good manufacturing practices) and existence of a quality manual.

2.2 Information on inspections carried out by national or regional authorities and external audits performed in the laboratory in the last three years, including reference to valid accreditation, certificate, authorization or licence.

2.3 Brief description of the procedures for internal audits, implementation of corrective and preventive actions and complaints.

3. Control of documentation and records

3.1 Brief description of the procedures for the control of and changes to documents that form a part of the quality documentation. Attach a list of valid SOPs.

3.2 Brief description of the procedures for the preparation, revision and distribution of necessary documentation for specifications, standard test procedures, analyst workbooks or worksheets.

3.3 Brief description of any other documentation related to product testing, including reports, records, arrangements for the handling of results (including laboratory information management systems (LIMS), where used).

3.4 Brief description of the procedures for release of certificates and analytical reports.

4. Personnel

4.1 Number of employees engaged in the following activities:

Activity	Number
Supervisors	
Chemical sector	
analysts	
technicians	
Microbiological sector	
microbiologists	
technicians	
Quality assurance staff	
Staff trained for sampling	
Other	
Total number of employees in the laboratory:	

4.2 Organization chart showing the arrangements, responsibilities and reporting lines in the laboratory.

4.3 Qualifications, experience and responsibilities of key personnel.

4.4 Outline of arrangements for initial and ongoing training and its recording.

5. Premises

5.1 Simple plan or description of the layout of the laboratory areas with an indication of scale (architectural or engineering drawings not required, but photographs may be submitted if available).

5.2 Nature of construction and finishing.

5.3 Brief description of ventilation systems including those for microbiological testing areas, storage areas, etc. (Include reference to air circulation and control of temperature and relative humidity.)

5.4 Brief description of special areas for the handling and storage of hazardous materials such as highly toxic (including genotoxic), poisonous and flammable materials.

5.5 Description of planned programmes for preventive maintenance of the premises and the system for recording maintenance activities.

5.6 Brief description of the procedures for cleaning of areas and equipment.

5.7 Short description of the storage areas (size, location) including arrangements for the storage of materials and retention samples.

6. Equipment

6.1 Brief description of the main equipment used in the laboratory. Attach a list of equipment in use, in tabular form, indicating the equipment and its brand model and date of installation.

6.2 Brief description of the planned programme for the preventive maintenance of equipment and the system for recording the maintenance activities.

6.3 Brief description of arrangements and status for qualification of equipment (installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)) as well as calibration of measuring equipment, including the recording system.

6.4 Brief description of computer system and its validation and data integrity management, including access to data and frequency of back-up.

7. Materials

7.1 Brief description of general policy for purchasing and handling of materials (including chemicals and reagents and availability of safety data sheets) and for handling of waste. Brief description of the procedure for selection and evaluation of suppliers.

7.2 Brief description of the water system in the laboratory, its qualification and arrangements for the sampling and testing of the water.

7.3 Brief description of the system for purchasing, preparation, handling and storage of reference substances and reference materials.

8. Subcontracting of testing

8.1 List of activities contracted out to other laboratories, including names and addresses of subcontractors of subcontractors. Description of the way in which the compliance with standards for activities contracted out is assessed.

9. Handling of samples

9.1 Brief description of general policy for sampling. If the laboratory is responsible for sampling describe briefly the procedures used and standards applied.

9.2 Brief description of the procedures for handling of samples from their receipt to storage after completion of testing. Where possible, flow charts describing important steps and work allocation in the laboratory should be supplied.

10. Validation of analytical procedures

10.1 Brief description of general policy for validation of analytical methods, including verification of pharmacopoeial methods or analytical procedures validated by manufacturers

11. Investigation of out-of-specification results

11.1 Brief description of the procedure for recording and investigation of out-of-specification results.

12. Stability testing (where applicable)

12.1 Brief description of the stability testing procedure.

12.2 Brief description of the conditions under which samples are kept, the arrangements for monitoring and the equipment used.

13. Microbiological testing (where applicable)

13.1 Brief description of the activities for microbiological testing.

13.2 Brief description of preparation and control of media and types of media used.

13.3 Brief description of the procedure in place for positive and negative controls.

13.4 Brief description of validation policy.

13.5 Brief description of arrangements for waste disposal.

WHO Technical Report Series, No.961, 2011

Annex 14

WHO guidelines for drafting a site master file[1]

[1] Based on the *Explanatory notes for pharmaceutical manufacturers on the preparation of a site master file* of the Pharmaceutical Inspection Convention.

1. Introduction

1.1 The site master file (SMF) is prepared by the pharmaceutical manufacturer and should contain specific information about the quality management policies and activities of the site, the production and/or quality control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a pharmaceutical operation is carried out on the site, an SMF need only describe those operations, e.g. analysis, packaging, etc.

1.2 When submitted to a regulatory authority, the SMF should provide clear information on the manufacturer's good manufacturing practices (GMP)-related activities that can be useful in general supervision and in the efficient planning and undertaking of GMP inspections.

1.3 An SMF should contain adequate information but, as far as possible, not exceed 25–30 pages plus appendices. Simple plans, outline drawings or schematic layouts are preferred instead of narratives. The SMF, including appendices, should be readable when printed on A4 paper sheets.

1.4 The SMF should be a part of documentation belonging to the quality management system of the manufacturer and kept updated accordingly. The SMF should have an edition number, the date it becomes effective and the date by which it has to be reviewed. It should be subject to regular review to ensure that it is up to date and representative of current activities. Each annex can have an individual effective date, allowing for independent updating.

2. Purpose

The aim of these explanatory notes is to guide the manufacturer of medicinal products in the preparation of an SMF that is useful to the regulatory authority in planning and conducting GMP inspections.

3. Scope

These explanatory notes apply to the preparation and content of the SMF. Manufacturers should refer to regional and or national regulatory requirements to establish whether it is mandatory for manufacturers of medicinal products to prepare an SMF.

These explanatory notes apply for all kinds of manufacturing operations such as production, packaging and labelling, testing, relabelling and repackaging of all types of medicinal products. The outlines of this guide could also be used in the preparation of an SMF or corresponding document by blood and tissue establishments and manufacturers of active pharmaceutical ingredients (APIs).

4. Content of site master file

Refer to the Appendix for the format to be used.

Appendix

Content of a site master file

1. General information on the manufacturer

1.1 Contact information on the manufacturer

— name and official address of the manufacturer;
— names and street addresses of the site, buildings and production units located on the site;
— contact information of the manufacturer including 24-hour telephone number of the contact personnel in the case of product defects or recalls; and
— identification number of the site as e.g. global positioning system (GPS) details, D-U-N-S (Data Universal Numbering System) number (a unique identification number provided by Dun & Bradstreet) of the site or any other geographical location system.

1.2 Authorized pharmaceutical manufacturing activities of the site

— copy of the valid manufacturing authorization issued by the relevant competent authority in Annex 1; or when applicable, reference to the EudraGMP database. If the competent authority does not issue manufacturing authorizations, this should be stated;
— brief description of manufacture, import, export, distribution and other activities as authorized by the relevant competent authorities including foreign authorities with authorized dosage forms/activities, respectively; where not covered by the manufacturing authorization;
— type of products currently manufactured on-site (list in Annex 2) where not covered by Annex 1 or the EudraGMP database; and
— list of GMP inspections of the site within the last five years; including dates and name/country of the competent authority having performed the inspection. A copy of the current GMP certificate (Annex 3) or reference to the EudraGMP database should be included, if available.

1.3 Any other manufacturing activities carried out on the site

— description of nonpharmaceutical activities on site, if any.

2. Quality management

2.1 The quality management system of the manufacturer

— brief description of the quality management systems run by the company and reference to the standards used;

— responsibilities related to the maintaining of the quality system including senior management; and
— information on activities for which the site is accredited and certified, including dates and contents of accreditations, and names of accrediting bodies.

2.2 Release procedure of finished products

— detailed description of qualification requirements (education and work experience) of the authorized person(s)/qualified person(s) responsible for batch certification and releasing procedures;
— general description of batch certification and releasing procedure;
— role of authorized person/qualified person in quarantine and release of finished products and in assessment of compliance with the marketing authorization;
— the arrangements between authorized persons/qualified persons when several authorized persons/qualified persons are involved; and
— statement on whether the control strategy employs process analytical technology (PAT) and/or real-time release or parametric release.

2.3 Management of suppliers and contractors

— a brief summary of the establishment/knowledge of supply chain and the external audit programme;
— a brief description of the qualification system of contractors, manufacturers of APIs and other critical materials suppliers;
— measures taken to ensure that products manufactured are compliant with transmitting animal spongiform encephalopathy (TSE) guidance;[2]
— measures adopted where substandard/spurious/falsely-labelled/falsified/counterfeit medical products, bulk products (i.e. unpacked tablets), APIs or excipients are suspected or identified;
— use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;
— list of contract manufacturers and laboratories including the addresses and contact information and flowcharts of supply chains for outsourced manufacturing and QC activities, e.g. sterilization of primary packaging material for aseptic processes, testing of starting raw materials, etc., should be presented in Annex 4; and
— brief overview of the responsibility sharing between the contract giver and acceptor with respect to compliance with the marketing authorization (where not included under 2.2).

[1] For further information please see: http://www.who.int/bloodproducts/tse.

2.4 Quality risk management

— brief description of quality risk management (QRM) methodologies used by the manufacturer; and
— scope and focus of QRM including brief description of any activities which are performed at corporate level, and those which are performed locally. Any application of the QRM system to assess continuity of supply should be mentioned.

2.5 Product quality reviews

— brief description of methodologies used.

3. Personnel

— organization chart showing the arrangements for quality management, production and quality control positions/titles in Annex 5, including senior management and authorized person(s)/qualified person(s); and
— number of employees engaged in the quality management, production, quality control, storage and distribution, respectively.

4. Premises and equipment

4.1 Premises

— short description of plant: size of the site and list of buildings. If the production for different markets, i.e. for local country or regional economic areas, takes place in different buildings on the site, the buildings should be listed with destined markets identified (if not identified under 1.1);
— simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings are not required);
— layouts and flowcharts of the production areas (in Annex 6) showing the room classification and pressure differentials between adjoining areas and indicating the production activities (i.e. compounding, filling, storage, packaging, etc.) in the rooms;
— layouts of warehouses and storage areas, with special areas for the storage and handling of highly toxic, hazardous and sensitizing materials indicated, if applicable; and
— brief description of specific storage conditions if applicable, but not indicated on the layouts.

4.1.1 *Brief description of heating, ventilation and air-conditioning (HVAC) systems*

— principles for defining the air supply, temperature, humidity, pressure differentials and air-change rates, policy of air recirculation (%).

4.1.2 ***Brief description of water systems***

— quality references of water produced; and
— schematic drawings of the systems in Annex 7.

4.1.3 ***Brief description of other relevant utilities such as steam, compressed air, nitrogen, etc.***

4.2 Equipment

4.2.1 Listing of major production and control laboratory equipment with critical pieces of equipment identified should be provided in Annex 8.

4.2.2 ***Cleaning and sanitation***

— brief description of cleaning and sanitation methods of product contact surfaces (i.e. manual cleaning, automatic clean-in-place, etc.).

4.2.3 ***Good manufacturing practices critical computerized systems***

— description of GMP critical computerized systems (excluding equipment-specific programmable logic controllers (PLCs)).

5. Documentation

— description of documentation system (i.e. electronic, manual); and
— when documents and records are stored or archived off-site (including pharmacovigilance data, when applicable): list of types of documents/records; name and address of storage site; and an estimate of time required to retrieve documents from the off-site archive.

6. Production

1.1 Type of products

References to Annex 1 or 2 can be made.

— type of products manufactured including:
  • list of dosage forms of both human and veterinary products which are manufactured on the site
  • list of dosage forms of investigational medicinal products (IMP) manufactured for any clinical trials on the site, and when different from the commercial manufacturing, information on production areas and personnel;
— toxic or hazardous substances handled (e.g. with high pharmacological activity and/or with sensitizing properties);

— product types manufactured in a dedicated facility or on a campaign basis, if applicable; and
— PAT applications, if applicable: general statement of the relevant technology; and associated computerized systems.

6.2 Process validation

— brief description of general policy for process validation; and
— policy for reprocessing or reworking.

6.3 Material management and warehousing

— arrangements for the handling of starting materials, packaging materials, bulk and finished products including sampling, quarantine, release and storage; and
— arrangements for the handling of rejected materials and products.

7. Quality control

— description of the QC activities carried out on the site in terms of physical, chemical and microbiological and biological testing.

8. Distribution, complaints, product defects and recalls

8.1 Distribution (to the part under the responsibility of the manufacturer)

— types (wholesale licence holders, manufacturing licence holders, etc.) and locations (countries or regional economic areas) of the companies to which the products are shipped from the site;
— description of the system used to verify that each customer/recipient is legally entitled to receive medicinal products from the manufacturer;
— brief description of the system to ensure appropriate environmental conditions during transit, e.g. temperature monitoring/control;
— arrangements for product distribution and methods by which product traceability is maintained; and
— measures taken to prevent manufacturers' products tentering into the illegal supply chain.

8.2 Complaints, product defects and recalls

— brief description of the system for handling complaints, product defects and recalls.

9. Self-inspections

— short description of the self-inspection system with focus on criteria used for selection of the areas to be covered during planned inspections, practical arrangements and follow-up activities.

Annexes to a submission of a site master file

Annex 1 Copy of valid manufacturing authorization

Annex 2 List of dosage forms manufactured including the International Nonproprietary Names (INN) or common name (as available) of APIs used

Annex 3 Copy of valid GMP certificate

Annex 4 List of contract manufacturers and laboratories including the addresses and contact information, and flowcharts of the supply chains for these outsourced activities

Annex 5 Organizational charts

Annex 6 Layouts of production areas including material and personnel flows, general flowcharts of manufacturing processes of each product type (dosage form)

Annex 7 Schematic drawings of water systems

Annex 8 List of major production and laboratory equipment

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Annex 15

Guidelines on submission of documentation for a multisource (generic) finished product. General format: preparation of product dossiers in common technical document format

1. Introduction

1.1 Background

In its forty-fifth report, the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations published the *Procedure for prequalification of pharmaceutical products* (*1*) which outlines the procedure and considerations for the process undertaken by WHO in providing United Nations agencies with advice on the acceptability in principle of pharmaceutical products for procurement by such agencies. The above-mentioned report states:

> *"This activity of WHO aims to facilitate access to priority essential medicines that meet WHO-recommended norms and standards of acceptable quality".*

As mentioned in this report, when submitting an Expression of Interest (EOI) for product evaluation, the applicant should send to the WHO focal point (together with the other data requirements) a *product dossier* (PD), in the format specified in the WHO guidance documents on submitting product data and information.

Through the International Conference on Harmonisation (ICH) process, considerable harmonization has been achieved in the organization of the registration documents with the issuance of the common technical document (CTD) guideline *(2-5)*. This recommended format in the CTD guideline for registration applications has become widely accepted by regulatory authorities both within and beyond the ICH Regions.

This document provides recommendations on the format and presentation for these types of PDs.

1.2 Objectives

These guidelines are intended to:

- assist applicants in the preparation of PDs for multisource products by providing clear general guidance on the format of these dossiers;
- fully adopt the modular format of the CTD as developed by ICH; and
- provide guidance on the location of regional information (Module 1) and other general data requirements.

These measures are intended to promote effective and efficient processes for the development of these PDs and the subsequent assessment procedures.

1.3 Scope

These guidelines apply to PDs for multisource pharmaceutical products containing existing active pharmaceutical ingredients (APIs) of synthetic

or semi-synthetic origin and their corresponding finished pharmaceutical products (FPPs). For the purposes of these guidelines, an existing API is one that has been previously authorized through a finished product by a stringent regulatory authority (SRA).[1] APIs from fermentation, biological, biotechnological or herbal origin are covered by other guidelines.

These guidelines primarily addresses the organization of the information to be presented in PDs for multisource products. They are not intended to indicate what studies are required. They merely indicate an appropriate format for the data that have been acquired. Applicants should not modify the overall organization of the CTD as outlined in the guidelines.

1.4 General principles

These guidelines present the agreed-upon common format for the preparation of a well-structured CTD for PDs that will be submitted to WHO. A common format for the technical documentation will significantly reduce the time and resources needed to compile PDs for the prequalification of multisource pharmaceutical products and will ease the preparation of electronic submissions. Assessments and communication with the applicant will be facilitated by a standard document containing common elements. In addition, exchange of regulatory information between national medicine regulatory authorities (NMRAs) and with WHO will be simplified.

Ultimately, this is intended to support the objectives of the WHO-managed Prequalification of Medicines Programme in listing pharmaceutical products of acceptable safety, efficacy and quality in the interest of public health.

These *general filing guidelines* should be read in conjunction with other applicable WHO and ICH reference documents and guidelines that provide further guidance and recommendations on the topic-specific content requirements for multisource products, notably:

- *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (6)*;
- *Bioequivalence trial information form (BTIF) (7);*
- *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part (8)*;
- *Quality overall summary — product dossier (QOS–PD) (9).*

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[1] Stringent regulatory authority (SRA): a regulatory authority which is:
— a member of the International Conference on Harmonisation (ICH) (as specified on www.ich.org); or
— an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic, Health Canada and World Health Organization (WHO), and may be updated from time to time); or
— a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (may be updated from time to time).

Together, these guidelines, templates and reference documents mentioned within them are intended to assist applicants and WHO by harmonizing with international approaches and facilitating the preparation and subsequent assessment procedures for PDs through the integration of the internationally accepted CTD format and, where possible, terminology.

Once implemented these guidelines will supersede the following guidelines and template which were in use previously:

- *Guideline on submission of documentation for prequalification of multisource (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis*;
  — Supplement 1 — Dissolution testing;
  — Supplement 2 — Extension of the WHO List of Stable (not easily degradable ARV) APIs;
- *Pharmaceutical Quality Information Form (PQIF)*.

2. Glossary

active pharmaceutical ingredient (API)

Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings (*1*).

applicant

The person or entity who, by the deadline mentioned in the invitation, submits an expression of interest (EOI) to participate in this procedure in respect of the product(s) listed in the invitation, together with the required documentation on such product(s) (*1*).

finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling (*1*).

manufacturer

A company that produces, packages, repackages, labels and/or relabels pharmaceutical products (*1*).

multisource (generic) pharmaceutical products

Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable (*6*).

3. Organization of a product dossier for a multisource product in common technical document format

The CTD is organized into five *modules*. Module 1 is region-specific. Modules 2, 3, 4 and 5 are intended to be common for all regions. Conformance with these guidelines should ensure that Modules 2, 3, 4 and 5 are provided in a format acceptable to WHO and to regulatory authorities.

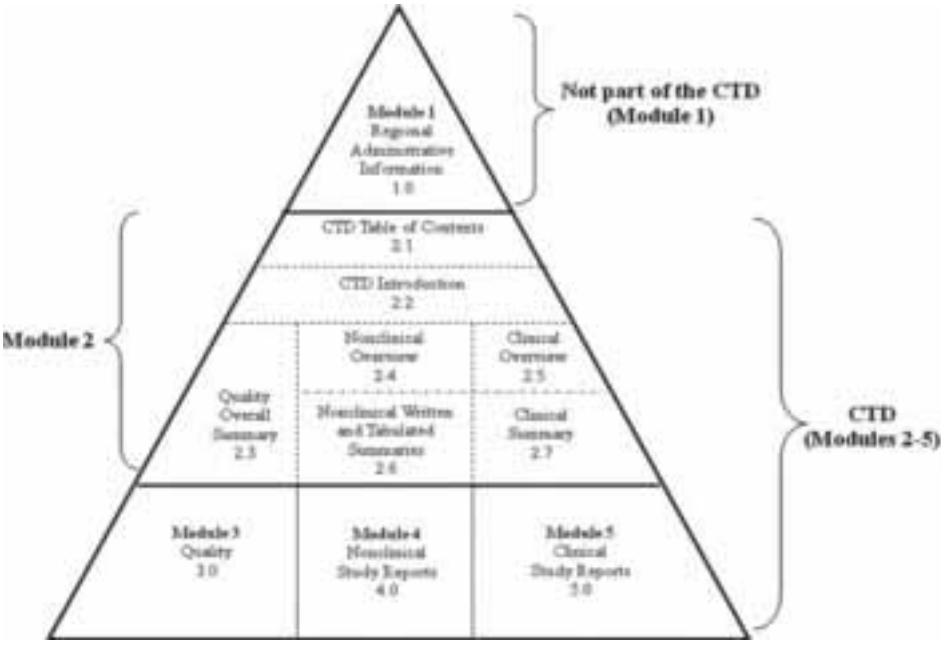
This section provides an overview of module contents for a multisource product in greater detail.

- Module 1: Administrative information and prescribing information
  - This module should contain documents specific to WHO and each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by WHO and the relevant regulatory authorities.
  - A summary of the bioequivalence/bioavailability information should be provided according to WHO's *Bioequivalence Trial Information Form (BTIF) (7)*.
  - Quality information summary (QIS): see WHO's *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part* for instructions *(8)*.
- Module 2: CTD summaries
  - This Module should begin with a general introduction to the pharmaceutical, including its pharmacological class, mode of action and proposed clinical use. In general, the Introduction should not exceed one page.
  - A summary of the quality information should be provided according to WHO's *Quality overall summary — product dossier (QOS–PD)* template *(9)*.
  - The organization of these summaries is described in Guidelines for ICH M4, M4Q and M4S *(3-5)*.
- Module 3: Quality
  - Information on quality should be presented in the structured format described in ICH M4Q and WHO's *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part (8)*.
- Module 4: Nonclinical study reports
  - Generally not applicable for multisource products (some exceptions may apply).
- Module 5: Clinical study reports
  - The human study reports and related information should be presented in the order described in ICH M4E *(3)* and WHO's *Multisource (generic)*

pharmaceutical products: guidelines on registration requirements to establish interchangeability (6).

The overall organization of the CTD is presented in Figure 1.

Figure 1
Organization of the CTD



This figure is reproduced with the kind permission of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

In preparing PDs for multisource products, it is acknowledged that certain modules or sections of the CTD would generally *not be applicable* (e.g. Module 4 — nonclinical study reports, although some exceptions may apply) and should be marked as such.

4. Modules (including Module 1) of a product dossier for a multisource pharmaceutical product

This section outlines filing considerations for PDs in the CTD format. Table 1 provides an overview of the presentation of the PD, including modular structure and main headings.

Table 1

Modular format of PDs for multisource products in CTD format

Module 1 — Administrative information and prescribing information
1.0 Cover letter
1.1 Table of contents of the application including Module 1 (Modules 1–5)
1.2 Application information:
1.2.1 Copy of the expression of interest (EOI)
1.2.2 Manufacturing and marketing authorization(s)/international registration status and/or the WHO certificate of pharmaceutical product (CPP)
1.2.3 Copy of certificate(s) of suitability of the *European Pharmacopoeia* (CEP) (including any annexes)
1.2.4 Letters of access for active pharmaceutical ingredient master files (APIMFs)
1.2.5 Good manufacturing practices (GMP) information
1.2.6 Biowaiver requests in relation to conducting a comparative bioavailability study
1.3 Product information:
1.3.1 Summary of product characteristics (SmPC)
1.3.2 Labelling (outer and inner labels)
1.3.3 Package leaflet (also known as patient information leaflet or PIL)
1.4 Regional summaries:
1.4.1 Bioequivalence trial information form (BTIF)
1.4.2 Quality information summary (QIS)
1.5 Electronic review documents (e.g. product information, BTIF, QIS, QOS–PD)
1.6 Samples (e.g. FPP, device(s), certificates of analysis)
Module 2 — Common technical document (CTD) summaries
2.1 CTD Table of contents (Modules 2–5)
2.2 CTD Introduction
2.3 Quality overall summary — product dossier (QOS–PD)
2.4 Nonclinical overview — generally not applicable for multisource products (some exceptions may apply)
2.5 Clinical overview
2.6 Nonclinical written and tabulated summaries — generally not applicable for multisource products (some exceptions may apply)
2.7 Clinical summary
Module 3 — Quality
3.1 Table of contents of Module 3
3.2 Body of data
3.3 Literature references

Module 4 — Nonclinical study reports — generally not applicable for multisource products (some exceptions may apply)
4.1 Table of contents of Module 4
4.2 Study reports
4.3 Literature references
Module 5 — Clinical study reports
5.1 Table of contents of Module 5
5.2 Tabular listing of all clinical studies
5.3 Clinical study reports
5.3.1 Reports of biopharmaceutical studies
5.3.7 Case-report forms and individual patient listings
5.4 Literature references

Additional guidance for some of the sections to be included in Module 1 is provided below:

1.0 Cover letter

The cover letter submitted with the PD should include a clear statement by the responsible person submitting the PD, indicating that the information submitted is true and correct.

1.2.2 ***Manufacturing and marketing authorization(s)/international registration status***

List the countries in which:

— the FPP (or set of FPPs) has been granted a marketing authorization;
— the FPP (or one or more of the set of FPPs) has been withdrawn from the market; and
— an application for the marketing of the FPP (or one or more of the set of FPPs) has been rejected, deferred or withdrawn.

For further guidance see section 3.2.P.3.1 of the *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part (8)*.

1.4 Regional summaries

The regional summaries should be prepared in accordance with the available WHO templates, which are available on the WHO Prequalification web site.

1.5 Electronic review documents

Electronic submission of documentation (CD or DVD) should be submitted in Microsoft Word (required for templates/summaries, e.g. QOS–PD, QIS, BTIF) or text-selectable PDF format (other documentation).

1.6 Samples (e.g. FPP, device(s))

A sample and certificate of analysis of the FPP(s) and devices(s) should be provided to enable visual inspection of the pharmaceutical product, the packaging materials and the label as well as comparison of the data with those in the SmPC, labelling and the package leaflet.

Draft labelling may be submitted at the time of dossier submission when labelling for marketing has not been finalized. For guidance regarding labelling, refer to the information on WHO public assessment reports (WHOPARs) available on the Prequalification web site under Information for Applicants (Prequalification Guidelines).

5. Module 3 — quality

For Module 3.2.S Drug substance (or active pharmaceutical ingredient (API)), there are three options to satisfy the information requirements for APIs within the Prequalification Programme. In brief these are:

- Option 1: certificate of suitability of the *European Pharmacopoeia* (CEP) procedure;
- Option 2: active pharmaceutical ingredient master file (APIMF) procedure; or
- Option 3: full details in the PD.

All options require the submission of information in CTD format (3.2.S), although the content may differ in places. The *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part (8)* provides detailed guidance on this issue and on the preparation of the FPP information by the applicant.

6. Module 5 of a product dossier for a multisource pharmaceutical product

The majority of PDs for multisource products are supported by one or more pivotal comparative bioavailability studies. When filing a PD in the CTD format, it is anticipated that only the following relevant sections of Module 5 will normally be required.

Module 5: Clinical study reports

- 5.1 Table of contents for Module 5
- 5.2 Tabular listing of all clinical studies
- 5.3 Clinical study reports
  - 5.3.1 Reports of biopharmaceutical studies
    - 5.3.1.2 Comparative bioavailability and bioequivalence study reports

- 5.3.1.3 In vitro–in vivo correlation study reports if available
- 5.3.1.4 Reports of bioanalytical and analytical method for human studies[2]

— 5.3.7 Case-report forms (CRFs) and individual patient listings: only CRFs for subjects who experienced serious adverse events should be included. All CRFs should be available upon request.

• 5.4 Literature references

For guidance regarding biowaivers, refer to the biowaiver implementation documents available on the Prequalification web site. For guidance regarding comparator products, refer to the information available under Guidance on bioequivalence studies on the Prequalification web site.

7. Guidance on format and presentation of a product dossier in common technical document format

7.1 Guidance on format

Throughout the CTD, the information should be displayed in an unambiguous and transparent manner. Text and tables should be prepared using margins that allow the document to be printed on both A4-sized paper (European Union and Japan) and 8.5 × 11-inch paper (US). The left-hand margin should be sufficiently large that information is not obscured whatever the method of binding. Fonts for text and tables should be of a style and size large enough to be easily legible, even after photocopying. Times New Roman, 12-point font is recommended for narrative text.

Acronyms and abbreviations should be defined the first time they are used in each module.

References should be cited in accordance with the current edition of the *Uniform requirements for manuscripts submitted to biomedical journals*, International Committee of Medical Journal Editors (ICMJE).[3] Copies of relevant pages of references should be provided, with a copy of the full article in the case of a publication. English translations should be provided as necessary.

7.2 Guidance on presentation

The paper copies of the application should be bound for easy access to information.

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[2] Bioanalytical or analytical methods for BA/BE or in vitro dissolution studies should ordinarily be provided in the individual clinical study reports. However, where a method is used in multiple studies, the method and its validation should only be included once in section 5.3.1.4 and referenced in the appropriate individual clinical study reports.

[3] The first edition of the *Uniform requirements for manuscripts submitted to biomedical journals* was conceived by the Vancouver Group and was published in 1979.

Each binder should be labelled with the proprietary name (if applicable) and the non-proprietary name of the FPP (e.g. "Name ABC" Abacavir (as sulfate) 300 mg tablets) and the company name of the applicant. For ease of reference, the following information could also be included on the label of each binder (space permitting): the volume number for that binder (out of the total number of volumes *for that module*), the section(s) contained within each volume and the date of the application (month and year), e.g.:

FPP "Name ABC"
Nonproprietary name
Applicant "XYZ"
Module 3 — Quality
Volume 1 of 3
Module 3.1 — 3.2.S.3
Month/year

8. Variations

All variation applications should be submitted using the CTD format, regardless of the original PD format.

In the case of the filing of a variation, applicants would normally provide only the relevant modules or sections affected by the change. For example, if the variation was for a change in the shelf-life of the FPP, only those sections affected by the change would need to be submitted *(10)*.

An updated and annotated QIS should be provided with each variation application.

References

1. Procedure for prequalification of pharmaceutical products. Revision. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report.* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 10.
2. Common Technical Document for the Registration of Pharmaceuticals for Human Use: Efficacy (ICH M4E) together with the complementary ICH Questions and Answers documents for the above mentioned guidelines.
3. Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use (ICH M4) (2003): Efficacy.
4. Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality (ICH M4Q) (2003): Quality.
5. Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety (ICH M4S) (2003): Safety.
6. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability In: *WHO Expert Committee on*

Specifications for Pharmaceutical Preparations. Fortieth report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 7.

7. Bioequivalence trial information form (BTIF) on: http://apps.who.int/prequal/.
8. Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part: on: http://apps.who.int/prequal/.
9. Quality overall summary - product dossier (QOS-PD): on: http://apps.who.int/prequal/.
10. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report.* Geneva, World Health Organization, 2009 (WHO Technical Report Series, No. 953), Annex 2.