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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Forty-fourth report

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Geneva, 12–16 October 2009

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Declarations of interest

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

Professor Saleh A. Bawazir, Professor Theo G. Dekker, Ms Nilka M. Guerrero Rivas, Professor Jos Hoogmartens, Professor Jin Shaohong, Dr John H.McB. Miller, Dr Justina A. Molzon and Mr Eshetu Wondemagegnehu Biwota reported no conflict of interest.

Temporary and special advisers reported the following:

Professor Ivan Addae-Mensah, Dr Simon Mills, Ms Marie-Louise Rabouhans, Dr Birgit Schmauser, Dr Saranjit Singh and Mr Deryck Smith, reported no conflict of interest.

Mr Robert Tribe reported that he was a consultant with two commercial entities and was the owner of another one.

Mr Martin FitzGerald, attending as an observer, reported that he was Legal Adviser with the European Association of Pharmaceutical Full-Line Wholesalers; Dr Piotr Kozarewicz (representative of the European Medicines Agency) reported that he was employed by two different pharmaceutical companies in Poland from September 2003 until June 2006. Other participants reported no conflict of interest.

1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 12 to 16 October 2009. Dr Carissa F. Etienne, Assistant Director-General, Health Systems and Services (HSS), opened the meeting and, on behalf of the Director-General of the World Health Organization, welcomed all the participants to the forty-fourth meeting. She expressed her appreciation of the Expert Committee for its knowledge of and expertise in the work of WHO in the area of quality assurance of medicines. Dr Etienne welcomed the members of the Committee, temporary advisers and special advisers for prequalification; representatives of the United Nations Children's Fund, the Global Fund to Fight AIDS, Tuberculosis and Malaria, Council of Europe/European Directorate for the Quality of Medicines and HealthCare, European Medicines Agency, International Federation of Pharmaceutical Manufacturers and Associations, International Generic Pharmaceutical Alliance, International Pharmaceutical Excipients Council, International Pharmaceutical Federation, World Self-Medication Industry and an observer from the European Association of Pharmaceutical Full-line Wholesalers; representatives of the Secretariats of the Pharmacopoeias of Republic of Korea and United States of America; as well as representatives from WHO Collaborating Centres in China and South Africa.

She said the WHO Member States and the world's political and international health leaders recognized the need to strengthen health systems, renew political interest in making sustainable improvements that benefited disease areas and health programmes, and to redouble global efforts to meet the challenge of achieving the Millennium Development Goals and renew primary health care systems. Dr Etienne said that health systems had to respond better and faster to the challenges of the changing world. She stressed the single framework for action with six building blocks (governance and leadership; financing; information; medical products, vaccines and technologies; health workforce; and service delivery); health systems and health outcome programmes; obtaining results; and a more effective role for WHO at country level.

Medicines were an important component of the health system; however, unavailability, costliness and lack of quality, including counterfeit medicines, were issues of concern to countries. Developing countries with these problems were accepting policy and regulatory change as well as enforcing laws and regulations to improve availability.

The work of this Expert Committee was important to WHO Member States, United Nations and international organizations, and also in-house for all programmes dealing with medicines. One example was the Prequalification Programme (PQP) which was based entirely on the

implementation of guidelines and standards recommended by the Expert Committee on Specifications for Pharmaceutical Preparations. The work of the Expert Committee was closely linked to other organizations, for example, the European Medicines Agency, European Directorate for the Quality of Medicines and HealthCare, the Global Fund to Fight AIDS, Tuberculosis and Malaria, International Atomic Energy Agency, United Nations Children's Fund, World Intellectual Property Organization, World Bank, International Pharmaceutical Federation, International Federation of Pharmaceutical Manufacturers and Associations, World Self-Medication Industry, national and regional pharmacopoeias, other clusters, institutions, bodies, authorities, and other WHO Expert Committees.

Experts and the Secretariat were committed to this important work enabling quality medicines to reach patients. Dr Etienne raised the issue of counterfeit medicines, which should be addressed as a public health problem. Discussion during the Executive Board meeting in January 2009 regarding the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) and counterfeit medicines issues in general raised concerns regarding WHO's role in this area. (For a further update see section 2.3.)

Dr Gilles Forte, speaking on behalf of the Director, Essential Medicines and Pharmaceutical Policies (EMP), expressed the importance of the Committee's work on standard-setting for the functionality of good manufacturing practices (GMP); he also emphasized that the improvement of quality assurance, updating of quality guidelines and laboratory testing were key functions of the Committee. Dr Forte also acknowledged that the agenda was very impressive and thanked the Expert Committee for its support in helping define and address future challenges. He emphasized that WHO valued the work carried out by this Expert Committee.

Dr Lembit Rägo, Coordinator of the Quality Assurance and Safety: Medicines team, said that nowadays funding for the team mainly originated from external donors in order to sustain its activities, comprising those of this Expert Committee. The team, including the Medicines Quality Assurance Programme, must continue to attract donors and to date it had been relatively successful in obtaining donor funding.

A current challenge was related to the fact that a WHO Collaborating Centre had closed due to restructuring in Sweden, but the Programme was very hopeful that it could obtain a replacement institute quickly.

Dr Rägo informed the Committee that the Medicines Strategy was in print following the usual consultative process. It would be put on the web site for the next biennium with a link to the Millennium Development Goals.

Dr Rägo thanked the members of the Expert Committee for their dedication and contribution to the work of WHO, and also for the help and time given.

The Secretary of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, Dr Sabine Kopp, explained the administrative process of appointment of experts and the working procedures related to the Expert Committee meeting.

The Secretary explained that the Expert Committee was an official advisory body to the Director-General of WHO and was governed through rules and procedures. The report of the WHO Expert Committee consisted of a summary of the discussions, recommendations to WHO and its Member States and included newly adopted guidelines. The report was presented to the WHO Governing Bodies for final comments, endorsement and implementation by Member States and constituted WHO technical guidance.

The Expert Committee consultation process involves several steps, i.e. preliminary consultation and drafting, circulation of the first draft for comments, revision of the draft, discussion of the draft by the WHO Expert Committee and finally, once adopted, publication in the Expert Committee report as an annex, submission to the WHO Governing Bodies and recommendation to Member States for implementation.

2. General policy

2.1 International collaboration

2.1.1 *International organizations, agencies and nongovernmental organizations*

The Expert Committee welcomed the collaboration of international organizations and agencies with the work of this Committee. The following presented their work in more detail.

European Directorate for the Quality of Medicines and HealthCare

The European Directorate for the Quality of Medicines and HealthCare (EDQM) is responsible for a number of activities in collaboration with the European Union, related to surveillance of pharmaceutical products marketed and distributed in Europe. EDQM is at the centre of the European regulatory framework for medicines and one of its tasks since 2008 has been to protect patients in Europe from counterfeit medicines. Another activity transferred to EDQM in 2008 is the legal classification of medicines as regards their supply with or without medical prescription. Since 2009 EDQM activities have expanded to include newer areas, e.g. cosmetics and food contact materials, packaging and containers. EDQM collaborates in

various WHO activities, including the joint EDQM/WHO External Quality Assurance Assessment Scheme.

European Medicines Agency

The European Medicines Agency (EMA) works under the European Union (EU) regulatory system and protects and promotes public and animal health, facilitates access for patients to new and better medicines, coordinates the safety of medicines (pharmacovigilance), procures the same product information for professionals and for patients, promotes the European pharmaceutical industry and is a platform for public health issues at the European level.

The role of EMA in the regulation of human and veterinarian medicines covers: designation of orphan medicines; paediatric investigation plans; scientific advice; initial application; post-authorization; referrals from national authorization systems; inspection (coordination and guidelines); information; parallel import and certificate; guidelines; advice and support to EU commissions, the EU parliament and Member States.

The Global Fund to Fight AIDS, Tuberculosis and Malaria

In November 2007, during the sixteenth Board Meeting of the Global Fund, the Board requested the Secretariat to carry out a review of the quality assurance (QA) Policy for Pharmaceutical Products under oversight of the Portfolio Committee. In November 2008 the Board approved a revised QA policy.

As a general rule the Global Fund will only fund the purchase of finished pharmaceutical products (FPPs) that are either WHO-prequalified or stringent regulatory authority (SRA)-authorized. This would provide an improved economic incentive for the manufacturers of FPPs to conform to these standards. It should also limit opportunistic strategies adopted by suppliers who might initiate a process of prequalification but who do not take the necessary steps to effectively pursue it until its end.

Groupement International de la Répartition Pharmaceutique — European Association of Pharmaceutical Full-line Wholesalers

The representative of the European Association of Pharmaceutical Full-line Wholesalers gave a brief update on the Association's activities and involvement in the development of good distribution practices for pharmaceutical products (see section 8.2). He also gave the view and feedback from the Healthcare Distribution Management Association (HDMA) especially regarding good distribution practices. The representative indicated that there was a need to clearly identify and define the activities of all participants in the supply chain, including those of the holders of a marketing authorization and the holders of a distribution authorization, as

well as for those parties involved in the supply to the public that did not physically handle medicines. It was important to allocate responsibilities to all participants, to license and inspect all actors in accordance with the relevant good practices, such as GMP, good distribution practices, good trade practices and good brokerage practice.

International Federation of Pharmaceutical Manufacturers and Associations

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) had official observer status with the United Nations in Geneva, including WHO. IFPMA represents the research-based pharmaceutical, biotechnological and vaccine industry, and global intergovernmental agencies. It advocates policies that encourage discovery of new life-saving and life-enhancing medicines.

IFPMA supports high standards of manufacturing and quality assurance in two areas:

— vaccines and biotechnology products, working in collaboration with WHO/EMP and the WHO Expert Committee on Biological Standardization; and
— medicines, including medicines for children, in collaboration with this Expert Committee and the WHO Expert Committee on the Selection and Use of Essential Medicines.

International Generic Pharmaceutical Alliance

The International Generic Pharmaceutical Alliance (IGPA) has member generic trade associations from Canada, Europe, India, Japan and the USA. Observer status had been granted within the last year to generic associations from Brazil, the People's Republic of China, Jordan and South Africa; observer status for Malaysia and Mexico was currently under consideration. The General Policy Initiatives of IGPA comprise cross-cutting quality assurance issues, collaboration with the WHO Expert Committee on Biological Standardization and International Collaboration (ICH Expert Working Groups on Quality and Safety). Other activities supported by IGPA are:

— nomenclature, terminology and databases — IGPA and the European Generic Medicines Association (EGA) have been involved in the discussion of international nonproprietary names (INN) for biologicals and biosimilars;
— prequalification of priority essential medicines — EGA works with WHO on an accelerated prequalification procedure for generics approved by SRAs;
— bioequivalence — although not on the WHO Expert Committee's agenda, IGPA was working on a proposal for international harmonization of bioequivalence requirements; and

— stability — IGPA was working with certain national associations regarding implementation of the latest WHO stability guidelines.

International Pharmaceutical Federation

The International Pharmaceutical Federation (FIP) reported that over the past year FIP and WHO had established work plans to support their involvement in key strategic collaborative areas of work. FIP's main priority was medicines and strengthening the pharmaceutical workforce. Other areas of importance included the roles and added value of pharmacists in patient safety, primary health care, noncommunicable diseases and maternal, newborn and child health. FIP continued to collaborate on these projects related to medicines in WHO.

In particular the issue of good distribution practices (GDP) is an important element in securing the legitimate supply and distribution chain, and also in preventing the infiltration of counterfeit medical products (see section 8.2). FIP played an active role in the final revision and drafting of the WHO GDP guidelines in September 2009. FIP had produced a WHO/FIP Handbook on Developing Pharmacy Practice and is currently working towards a revision of the FIP/WHO guidelines on good pharmacy practice (GPP). FIP also assisted IMPACT in improving the information available to the public regarding counterfeit medicines and the work of IMPACT.

United Nations Children's Fund

The United Nations Children's Fund (UNICEF) promotes and protects children's rights, especially those of the most vulnerable in the poorest countries. UNICEF core commitments are health and nutrition, education, water and sanitation, child protection and HIV/AIDS.

One of the main activities of UNICEF is the supply of quality medicines to countries and communities in need; the supply headquarters is located in Copenhagen. The Supply Division oversees UNICEF's global supply procurement and logistics operations on behalf of UNICEF and its procurement services partners. It ensures that supplies of high quality and good value reach children and their families quickly.

Prequalification of suppliers of pharmaceuticals in UNICEF involves the review of submitted documentation and/or GMP inspections to ensure compliance with WHO GMP guidelines using a technical questionnaire developed by WHO. The technical questionnaire covers manufacturing sites, dosage forms and products of interest, export experience and licence to manufacture pharmaceuticals. Local authorities are invited to participate in GMP inspections. There are also joint inspections with WHO and other partners.

Decisions are based on the regulatory environment in the country of origin and prior experience of UNICEF, GMP inspection by UNICEF or by 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 2003–2009, 145 GMP inspections carried out in 47 companies failed (32%). In case of failure a detailed GMP inspection report is forwarded to the company with a request to respond within one month.

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

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

2.1.2 *Pharmacopoeial Discussion Group*

The Pharmacopoeial Discussion Group (PDG), which consists of the European Pharmacopoeia, Japanese Pharmacopoeia and United States Pharmacopeia, met in association with the Expert Working Groups of the International Conference on Harmonisation (ICH) from 8 to 12 June 2009 in Yokohama, Japan. The Secretary of this Expert Committee participated as an observer for WHO.

The experts recommended reviews of the following general methods against existing related *International Pharmacopoeia* (Ph.Int.) texts and adding those not yet included in the Ph.Int. for future adoption:

- Test for extractable volume of parenteral preparations (General Chapter);
- Test for particulate contamination: sub-visible particles (General Chapter);
- Disintegration test;
- Dissolution test (General Chapter) (pending availability of final text);
- Sterility test (General Chapter);
- Microbiological examination of non-sterile products; and
- Acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use (General Chapter).

The Committee recommended that the following should be considered for adoption:

- Microbiological examination of non-sterile products:
  — Microbial enumeration tests (General Chapter);
  — Tests for specified microorganisms (General Chapter); and
- Tablet friability (General Chapter).

The Secretariat informed the experts that preliminary discussions had already been held with the PDG members, based on previous recommendations

of the Expert Committee. The PDG parties indicated that, in the event of these methods being of interest to *The International Pharmacopoeia*, WHO should contact the respective PDG Lead Pharmacopoeias regarding their final acceptance to use the texts within the Ph.Int.

2.1.3 *International Conference on Harmonisation*

The International Conference on Harmonisation (ICH) Expert Working Groups met from 8 to 12 June 2009 in Yokohama, Japan.

The Secretary of this Expert Committee also attended, as an observer for WHO, the ICH Q4B Working Group meetings (consisting of members from the six ICH partners and observers). An update of the current activities in the quality area was given by the co-chair of the meeting.

2.1.4 *International Conference of Drug Regulatory Authorities*

The International Conference of Drug Regulatory Authorities (ICDRA) provide medicines regulatory authorities (MRAs) of WHO Member States with a forum to meet and discuss ways to strengthen collaboration. The conferences have been held since 1980 with the aim of promoting exchange of information and collaborative approaches to issues of common concern. As a platform established to develop international consensus, the ICDRA continues to be an important tool for WHO and MRAs in their efforts to harmonize regulation and improve the safety, efficacy and quality of medicines. The ICDRA programme is developed by a planning committee of representative medicines regulators. Discussions during the four days of the ICDRA usually include topics relating to quality issues, herbal medicines, homeopathy, regulatory reform, medicines safety, counterfeiting, access, regulation of clinical trials, harmonization, new technologies and e-commerce. Recommendations are proposed for action among agencies, WHO and related institutions.

The recommendations formulated by the 13th International Conference of Drug Regulatory Authorities held in Berne, Switzerland, from 16 to 19 September 2008 are available on the WHO web site (http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra).

The 14th ICDRA would take place in Singapore from 30 November to 3 December 2010. A pre-ICDRA meeting on “Effective Collaboration: The Future for Medicines Regulation” would take place on 28–29 November.

Registration, details and programme are available on the ICDRA web site: http://www.icdra2010.sg/.

2.2 Cross-cutting issues in pharmaceuticals — quality assurance issues

2.2.1 *Herbal medicines*

The Committee received a report on WHO's policy and activities in the field of traditional medicine.

The representative of the Traditional Medicine (TRM) team reported on the activities of International Regulatory Cooperation for Herbal Medicines (IRCH) — membership had increased to 22, consisting of 19 Member Countries and three Member Regional Bodies. The third annual meeting was held in Montreal, Canada in February 2009, at which a strategic plan of action for IRCH was discussed and agreed upon. Based on the review of current issues relating to herbal medicines, eight working groups addressing the priority issues identified had been established.

TRM also reported on the publication of Volume 4, *WHO monographs on selected medicinal plants*, which contained 28 monographs. TRM thanked the Expert Committee and the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations for their technical contribution and support in the development of the monographs.

A major outcome of the WHO Congress on Traditional Medicine was the adoption of the "Beijing Declaration". The World Health Assembly in May 2009 adopted a new resolution on traditional medicine (resolution WHA 62.13), referring to the "Beijing Declaration" and requested the Director-General to update the WHO Traditional Medicine Strategy. It also requested WHO to support the efforts of Member States in integrating traditional medicine into national health systems.

In the context of primary health care, the report of the WHO interregional workshop on the use of traditional medicine in primary health care, held in Ulaanbaatar, Mongolia in August 2007, was printed in May 2009 and was widely disseminated.

The Committee was informed of WHO's new project on the development of international classification of traditional medicine, towards the integration of traditional medicine into general health information systems, and standardization of clinical terms used by providers of traditional medicine. This project also aimed at responding to the need expressed by national pharmacovigilance centres for an appropriate coding system accommodating the reporting of adverse events to herbal medicines.

The Committee was also informed about the progress of implementation of the Global Strategy and Plan of Action on public health, innovation and intellectual property (GSPOA) in the field of traditional medicine.

The Expert Committee encouraged countries to make use of the materials available from this Programme and took note of the role of traditional medicines within the concept of primary health care.

2.2.2 *Biologicals and vaccines*

WHO Expert Committee on Biological Standardization

The role of the Expert Committee on Biological Standardization was to develop international recommendations for the production and control of biological medicines and the establishment of associated international biological reference materials. The Committee would next meet on 19–23 October 2009 and a key agenda item that might be of interest to the Expert Committee on Specifications for Pharmaceutical Preparations was the proposed guidelines on evaluation of similar biotherapeutic products. These guidelines, if established, would set international expectations for the regulatory evaluation of this increasingly important and relatively new class of biological medicines. It would, however, be only a first stage in providing equity of access to this type of product and WHO recognized that much would need to be done to assist Member States to develop the capacity to ensure effective use of such products.

A second topic was the issue of transition of some drugs from biologicals to chemicals. The Expert Committee on Biological Standardization had initiated a process whereby all proposals for new or replacement reference materials were first submitted to the Committee for review. Proposals were being received for certain reference materials to be calibrated in SI units instead of the International Unit of biological activity. Where this was the case, consultation with the Expert Committee on Specifications for Pharmaceutical Preparations was also sought prior to the initiation of the study.

Two other topics for more detailed discussion by the Expert Committee on Specifications for Pharmaceutical Preparations were examples of cross-cutting initiatives between the two Committees. The first was the guidelines that were under development to establish GMP for blood establishments and the second, the guidelines for regulatory oversight of temperature-controlled distribution of pharmaceuticals.

A joint concern of both Committees was to ensure effective implementation of guidelines and recommendations. Implementation workshops had been set up by the secretariat to promote the understanding and use of guidelines and recommendations established by the Expert Committee on Biological Standardization. New guidelines on regulatory expectations for stability evaluation of vaccines had been used as a case study and positive feedback had been obtained from all stakeholders on the value of such an approach.

Finally, a review of the roles and responsibilities of the Expert Committee on Biological Standardization was proposed. It was approximately 10 years since the last such review and thus it was important to have such an external validation of the direction and output of the Committee. As part of the process comments from the Expert Committee on Specifications for Pharmaceutical Preparations would be invited.

2.2.3 *Blood products*

The Committee was informed about WHO's work in the area of blood products and related biologicals. More details on the GMP for blood establishments can be found in section 6.6.

2.2.4 *Essential medicines*

Further to the WHO-led initiative "make medicines child size" launched in December 2007, WHO received a grant from the Bill & Melinda Gates Foundation in October 2008 to work in collaboration with UNICEF in order to conduct crucial research in the area of children's medicines. The aim of the project was to increase the number of child-size medicines designed and formulated specifically for children. The grant provided support for essential research to:

— determine the optimum dosage forms for paediatric medicines (e.g. small tablets, dispersible tablets, powders);
— develop dosing guides (e.g. a review of existing priority medicines and the identification of the appropriate doses for new medicines for children); and
— develop guidelines for testing of medicines and treatment of use of medicines in children, including guidelines on conducting clinical trials in children.

In December 2008 a group of paediatricians, pharmacists, clinical pharmacologists and representatives of the European Medicines Agency (EMA), International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), Medicines for Malaria Venture (MMV), National Institutes of Health (NIH), United Nations Children's Fund (UNICEF) and the Bill & Melinda Gates Foundation attended a meeting hosted by WHO to discuss the preferred dosage form of medicines for children. As a result of this consultation the dosage forms of medicines most suitable for children were identified, with particular attention paid to conditions prevailing in developing countries and future areas of research required in this area (http://www.who.int/childmedicines/progress/Dosage_form_reportDEC2008.pdf).

The report of the WHO Subcommittee for the Selection and Use of Medicines, including the second Essential Medicines List for Children (EMLc), was reviewed and endorsed by the Expert Committee on Selection

and Use of Essential Medicines at its seventeenth meeting in March 2009. New additions to the EMLc included sections on palliative care medicines; ear, nose and throat medicines and medicines for neonates, and also the inclusion of liposomal amphotericin B, a dispersible formulation of artemether + lumefantrine (20 mg + 120 mg) and enalapril tablets (2.5 mg and 5 mg). The Expert Committee agreed that the Subcommittee had fulfilled the terms of reference regarding the development and revision of the WHO EMLc and made the recommendation to the Executive Board and the Director-General that the Subcommittee should now be dissolved. However, it was recommended that future Expert Committees should include adequate expertise to consider medicines for children and maintain the EMLc.

The Expert Committee for the Selection and Use of Essential Medicines also reviewed simulation studies proposing potential new strengths for fixed-dose combinations (FDCs) of antituberculosis medicines for children: isoniazid 150 mg + pyrazinamide 400 mg + rifampicin 250 mg and ethambutol 250 mg + isoniazid 150 mg + pyrazinamide 400 mg + rifampicin 250 mg.

However, it was noted that at this time there were no FDCs that delivered the ideal doses of first-line medicines for tuberculosis treatment in children with weights between 5 and 30 kg. It was also highlighted that there was a need for a two-drug FDC for use in the continuation phase of treatment and the Expert Committee for the Selection and Use of Essential Medicines recommended that the following combination (for continuation treatment only) would be reasonable based on the analyses presented: isoniazid 150 mg + rifampicin 250 mg.

The Expert Committee for the Selection and Use of Essential Medicines reviewed and agreed a proposal by the Medicines Quality Assurance Programme for a revision to the listing of pharmaceutical products in the Model Lists of Essential Medicines. As a result, the medicines listed in the left-hand column would in future be named as the active moieties, using INN and, where applicable, entries in the right-hand column would provide information on the dosage forms and strengths of products available in WHO Member States. The explanatory notes in the Model List of Essential Medicines and the EMLc had also been expanded to provide more information and guidance to users with regard to dosage form terminology and medicine strength (see section 11.1).

Future activities in relation to the Better Medicines for Children project would include a summit in Amsterdam in October 2009 to discuss scientific standards required for undertaking clinical research in children. As part of this meeting WHO would host a discussion day with a group of experts from developing countries to identify what might need to be done to

adapt current guidance documents for promoting appropriate research on medicines for children in resource-poor settings. In February 2010 WHO would host a meeting of regulatory authorities to facilitate the development of a Paediatric Medicines Regulators Network.

2.2.5 *Regulatory support*

The Expert Committee was updated on the area of medicines regulatory support. The mission of QSM in medicines regulatory support was to enhance the capacity of national and regional medicines regulatory systems to contribute to universal access to medicines of assured safety, quality and efficacy. Core functions included developing evidence on the situation and needs of medicines regulatory systems worldwide; providing direct support to countries and regions for strengthening medicines regulation; developing and continuously improving tools to assist regulatory activities (e.g. guidelines, manuals and other information materials); facilitating communication and promoting harmonization among MRAs; developing and continuously improving internal capacities; and developing and maintaining comprehensive databases on MRAs.

The scope of regulatory support activities involved assessing medicines regulatory systems to identify needs, assisting in the development of institutional plans and supporting capacity building. So far, 50 assessments had been performed on 46 regulatory systems with the involvement of the respective WHO regional offices.

In close collaboration with the capacity building teams of the WHO Prequalification Programme and the WHO Immunization, Vaccines and Biologicals Department, the Medicines Regulatory Support Programme had organized various training activities to strengthen capacity of national MRAs.

Regional support involved provision of technical assistance to Regional Economic Communities in Africa, within the framework of the African Medicines Registration Harmonization Initiative.

The Medicines Regulatory Support Programme had been particularly active in promoting the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce; in facilitating harmonization of regulatory requirements with subregional economic blocs; and improving communication among MRAs through networking, sharing of information and regulatory decisions.

The Programme had also been active in providing feedback on the implementation of existing WHO guidelines, developing training materials, developing internal procedures, developing and maintaining technical competence of regulatory staff and enhancing technical cooperation with partners both within and outside the Organization.

Future work would include improving feedback and identification of needs for guidance, establishing a pool of regulatory experts and conducting the assessment of medicines regulatory systems in a more systematic way and for training purposes. The programme intends to establish a network of centres of excellence in the regulatory affairs area to serve as training centres, design new intervention mechanisms for supporting activities and new concepts for conducting day-to-day work.

2.2.6 *HIV-related activities*

The representative of the HIV Department, Strategic Information and Research Unit, gave a short update on how the work of this Expert Committee was useful to the HIV Department's activities. The Department published an annual report entitled "Towards universal access" on progress made in the health sector to address the HIV epidemic. In the section on access to treatment, it reported on the progress made on prequalification of antiretrovirals by QSM. A QSM quality assessment survey was also included in the 2008 report.

2.3 Counterfeit medicines

The Committee was provided with an update by the Programme Manager of the newly created EMP/QSM Anti-Counterfeiting Programme (ACM), who was also Executive Secretary ad interim of the IMPACT Secretariat.

Discussion took place during the Executive Board meeting in January 2009 on IMPACT and counterfeit medicines in general. 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 (one on the activities of IMPACT and the second on WHO's activities in the area of counterfeit (http://apps.who.int/gb/e/e_wha62.html, WHA62: **A62/13** Counterfeit medical products, and **A62/14** Counterfeit medical products: International Medical Products Anti-Counterfeiting Taskforce). Additional information on IMPACT could be found on the web site (http://www.who.int/impact). The Assembly agenda item on counterfeits was subsequently postponed to 2010.

The Secretariat and Chair for IMPACT continued to be based in WHO.

The Director-General of WHO reconfirmed that counterfeit medicines were an important issue for the Organization and that WHO would continue to collaborate with partners in this field. The WHO Secretariat would work on the basis that there were no changes to this current situation at least until the World Health Assembly in May 2010, during which WHO's role should be clarified by its Member States.

ACM would complete the following activities in 2009:

- Revise and update the WHO and IMPACT web sites.

- Proceed with the joint WHO Expert Committee on Specifications for Pharmaceutical Preparations/IMPACT review of the *WHO Good distribution practices (GDP) for pharmaceutical products*, which was proposed by IMPACT in 2007.
- Start the review process of the draft document on Model Legislation developed by IMPACT in 2008, including a revision of the current definition of counterfeit medicines, possibly through the Expert Committee.
- Plan and implement advocacy, training, country support and enforcement activities with interested governments in Africa, as far as specified donor funds were available (mostly from the European Union for African, Caribbean and Pacific countries).
- Recruit one technical expert on regulatory matters and pursue the possibility of FIP arranging the secondment of a communication expert.
- Prepare a fund-raising plan for future staff and activities to combat counterfeit medicines and approach interested donors.

In addition to WHO's work on counterfeit medicines described above, the Assistant Director-General, HSS would continue her two-year mandate as elected Chair of IMPACT and WHO would continue to fulfil the functions of the IMPACT Secretariat. As such WHO would continue to work with IMPACT, drawing on its technical input and the involvement of a large number of stakeholders, whilst clearly distinguishing between documents prepared by IMPACT and those issued by WHO.

Technical documents prepared by IMPACT working groups would be posted on the IMPACT web site, without the WHO logo. These could be reviewed, adapted and ultimately approved as appropriate, through the normal WHO consultative procedures.

The IMPACT web site would be revised and updated. It would include the proposal for the *Draft principles and elements for national legislation against counterfeit medical products*, inviting comments thereon. A Circular Letter would be prepared to draw Member States' attention to this draft document and the new proposal for the definition of counterfeit medical products contained therein.

A direct link to the above-mentioned document was available in the news section of the IMPACT web site (http://www.who.int/impact/news/BonnMeetingDraftPrinciples.pdf).

A proposed revision of the *WHO Good Distribution Practices (GDP) for pharmaceutical products* was discussed by this Expert Committee with a view to its adoption. The document could be found on the WHO web site at: http://www.who.int/medicines/services/expertcommittees/pharmprep/43rdpharmprep/en/index.html, and also with a direct link: http://www.who.int/medicines/

services/expertcommittees/pharmprep/170909Clean_GDP-counterfeits-QAS08252Rev1.pdf

The planned IMPACT meetings (subject to resources) were as follows:

— regional meeting in South Africa (9–10 November 2009);
— annual meeting of IMPACT Planning Group including all IMPACT Chairs and Co-Chairs (January 2010);
— Open Forum for WHO Member States and interested parties, involving IMPACT partners (January 2010);
— Working Group meetings (January 2010); and
— annual IMPACT meeting (after the World Health Assembly in May 2010).

The Committee was pleased to note the continued cooperation with other WHO departments and programmes.

3. Quality control — specifications and tests

3.1 The International Pharmacopoeia

Following the publication of the First Supplement to the Fourth Edition, the Expert Committee was informed that the final texts for the monographs adopted at the forty-second and forty-third meetings in October 2007 and 2008 had been made available to users of the WHO Medicines web site and that they were ready to be included in the forthcoming issue of *The International Pharmacopoeia* (Ph.Int.). While the format of this future publication was still to be defined (electronic, CD-ROM or book), a tentative table of contents of about 45 texts for inclusion in this publication was discussed and adopted.

Provisional list of contents for the forthcoming publication of *The International Pharmacopoeia*
Monographs adopted at the forty-second meeting of the Expert Committee in October 2007

Pharmaceutical substances

- Lumefantrine
- Zinc sulfate

Dosage forms

- Artemether and lumefantrine tablets
- Magnesium sulfate injection
- Rifampicin and isoniazid dispersible tablets
- Rifampicin, isoniazid and ethambutol tablets

- Rifampicin, isoniazid and pyrazinamide dispersible tablets
- Zinc sulfate oral solution (paediatric)
- Zinc sulfate tablets (paediatric)

Monographs adopted at the forty-third meeting of the Expert Committee in October 2008

Pharmaceutical substances

- Emtricitabine
- Mebendazole (revision of published monograph)
- Nevirapine (revision of published monograph)
- Oseltamivir phosphate

Dosage forms

- Artemether and lumefantrine oral suspension
- Mebendazole chewable tablets (revision of published monograph for mebendazole tablets)
- Chloroquine sulfate oral solution
- Cycloserine capsules
- Efavirenz capsules
- Efavirenz oral solution
- Ethambutol hydrochloride tablets (revision of published monograph)
- Nevirapine oral suspension
- Nevirapine tablets
- Quinine sulfate tablets
- Zidovudine, lamivudine and nevirapine tablets

Radiopharmaceuticals

General monograph and related texts

- General monograph
- Methods of analysis
- Supplementary information
- Individual monographs
- Fludeoxyglucose (^{18}F) injection
- Gallium citrate (^{67}Ga) injection
- Iobenguane (^{123}I) injection
- Iobenguane (^{131}I) injection
- Samarium ethylene diamine tetramethylene phosphonate complex (^{153}Sm) injection
- Sodium iodide (^{131}I) capsules
- Sodium iodide (^{131}I) injection
- Sodium iodide (^{131}I) solution
- Sodium iothalamate (^{125}I) injection

- Sodium pertechnetate (^{99m}Tc) injection (fission)
- Sodium pertechnetate (^{99m}Tc) injection (non-fission)
- Sodium phosphate (^{32}P) injection
- Strontium chloride (^{89}Sr) injection
- Technetium (^{99m}Tc) bicisate complex injection
- Technetium (^{99m}Tc) exametazime complex injection.
- Technetium (^{99m}Tc) mebrofenin complex injection
- Technetium (^{99m}Tc) mertiatide injection
- Technetium (^{99m}Tc) pentetate complex injection
- Technetium (^{99m}Tc) succimer complex injection
- Technetium (^{99m}Tc) sulfur colloid injection
- Technetium (^{99m}Tc) tetrofosmin complex injection
- Technetium (^{99m}Tc) tin colloidal injection
- Technetium(^{99m}Tc) pyrophoshate tin complex injection
- Technetium(^{99m}Tc) methylene diphosphonate (MDP) complex injection
- Technetium(^{99m}Tc) sestamibi complex injection
- Thallous chloride (^{201}Tl) injection
- Yttrium silicate (^{90}Y) colloid injection

The Expert Committee recommended that the texts adopted at the forty-fourth meeting also be considered for inclusion.

WHO Medicines web site — *International Pharmacopoeia* pages

The Expert Committee was pleased to note that regular updates had been made in 2009 of the web pages devoted to the Ph.Int. on the WHO Medicines web site to inform users in a timely manner about recently adopted texts and, when relevant, about specific aspects of the work carried out to develop or revise monographs (e.g. the rapid revision posted for heparins or the note on artemisinin derivatives revision).

In view of the particularity of some of the substances for which monographs had been recently adopted and the large number of new substances included in the 2009 work plan belonging to the same category of medicines, the number of web pages had been increased to include:

— radiopharmaceuticals; and
— anti-infectives (including antibacterial, antiprotozoal, antifungal, antiviral and antimycobacterial agents — for diseases other than HIV/AIDS, tuberculosis and malaria — and anthelmintics).

The Expert Committee noted with appreciation that there had been a positive response to these updates and that requests had been received regarding subscription to a mailing list for receiving alerts on the latest Ph.Int. activities. Recognizing that this mailing system would help users keep track of the latest changes and that this would also improve the dissemination

of information, the Expert Committee recommended the setting up of an automatic notification system of updates or news on the Ph.Int.

One-day briefing on *The International Pharmacopoeia*

The Secretariat informed the Expert Committee that a one-day overview of the Ph.Int. was given in April 2009 to industrial stakeholders. This included describing the process for developing monographs, together with explanations of the pharmacopoeial approach and policy on a variety of issues and of the role of the pharmacopoeia within WHO quality assurance activities. The meeting was interactive and informal to allow manufacturers (mostly those already collaborating with QSM) to raise issues and to have open discussions on the Ph.Int.

It was attended by representatives from generic and research-based pharmaceutical companies as well as pharmaceutical industry associations. The positive feedback received showed that the information provided was helpful and that the briefing session would assist in future collaborations in the development of monographs for the Ph.Int.

In response to requests from the participants to consider a future briefing with a larger audience, the Expert Committee recommended that the WHO Secretariat continue with organizing such information sessions.

3.2 Current work plan and future work programme

In order to respond to the needs of WHO programmes and partner organizations, the Expert Committee agreed in 2008 to only consider for inclusion in the work programme those substances that had been assigned a high priority. A work plan, including a first group of six active pharmaceutical ingredients (APIs) and 36 dosage forms for monograph initiation, was thus adopted.

Since good progress had been made in developing specifications from the 2009 work plan, a new work programme, including a second group for monograph initiation, was proposed to the Expert Committee, taking into account:

— substances remaining from the 2009 work plan;
— substances initially listed in the adopted work programme in 2008 that had now been prioritized, focusing on medicines for children, medicines important for the treatment of HIV/AIDS, tuberculosis and malaria and treatment of diseases with a high prevalence in developing countries);
— additions from the sixteenth Model list of essential medicines and the second List of essential medicines for children;
— additions from the expressions of interests (EOIs) within the WHO Prequalification Programme (PQP); and

— requests for priority medicines recommended in WHO specific disease programmes.

After discussion, the Expert Committee adopted the following new work programme.

Additions to the 2009 work plan are indicated below in bold.

Updated new work programme
Medicines used in the treatment of HIV/AIDS and related conditions

API

- **Atazanavir**

Dosage forms

- **Atazanavir capsules**
- Didanosine capsules
- Efavirenz tablets
- **Emtricitabine capsules**
- **Emtricitabine oral solution**
- Ritonavir capsules
- Ritonavir oral solution
- Stavudine powder for oral solution
- Zidovudine tablets

Fixed-dose combinations

- Lopinavir and ritonavir caspules
- Lopinavir and ritonavir oral solution

Dosage forms, including those for paediatric use, as available for:

- **Efavirenz + emtricitabine + tenofovir**
- Lamivudine + stavudine
- Lamivudine + stavudine + efavirenz
- Lamivudine + stavudine + nevirapine
- Lamivudine + zidovudine + efavirenz
- Tenofovir + emtricitabine

Medicines used in malaria treatment

API

- **Piperaquine phosphate**

Dosage forms

- Mefloquine tablets (*used in co-blisters*)

Fixed-dose combinations

- Artemether and lumefantrine capsules
- Artemether and lumefantrine dispersible tablets
- Artesunate and amodiaquine tablets
- Artesunate, sulfadoxine and pyrimethamine tablets
- Sulfadoxine and pyrimethamine tablets (*used in co-blisters*)

Dosage form, including that for paediatric use, as available for:

- Dihydroartemisinin + piperaquine phosphate

Revision

- Artemisinin derivatives (APIs and dosage forms) (see http://www.who.int/medicines/publications/pharmacopoeia/mon_mal/en/index.html)

Medicines used in tuberculosis treatment

APIs

- *p*-Aminosalicylic acid
- Capreomycin
- Levofloxacin
- Ofloxacin
- Terizidone

Dosage forms

- *p*-Aminosalicylic acid granules
- Capreomycin powder for injection
- Ethionamide tablets
- Levofloxacin tablets
- Ofloxacin tablets
- Protionamide tablets
- **Terizidone tablets**

Anti-infectives (antibacterials, antiprotozoal, antifungal, antiviral and antimycobacterial agents, anthelmintics)

APIs

- Ceftriaxone sodium
- Fluconazole
- Ivermectin

Dosage forms

- Albendazole chewable tablets
- Amoxicillin oral suspension
- Ceftriaxone injection
- Doxycycline dispersible tablets

- Fluconazole capsules
- Fluconazole injection
- Fluconazole oral solution/suspension
- Ivermectin tablets
- Levamisole tablets
- Metronidazole oral suspension
- Pyrantel chewable tablets
- Pyrantel oral solution/suspension
- Pyrimethamine tablets

Fixed-dose combinations

- Sulfamethoxazole and trimethoprim injection
- Sulfamethoxazole and trimethoprim oral solution/suspension
- Sulfamethoxazole and trimethoprim tablets

Oral rehydration therapy

APIs

- Zinc acetate
- Zinc gluconate

Dosage forms

- Paediatric zinc acetate oral solution
- Paediatric zinc acetate tablets
- Paediatric zinc gluconate oral solution
- Paediatric zinc gluconate tablets

Various other medicines (analgesics, antipyretics, palliative care, anti-epileptics, large volume parenterals, reproductive health)

Dosage forms

- Carbamazepine oral liquid
- Chewable carbamazepine tablets
- Chewable phenytoin tablets
- Crushable valproic acid tablets
- **Ethinylestradiol + levonorgestrel tablets**
- Glucose intravenous infusion
- **Levonorgestrel tablets**
- **Medroxyprogesterone acetate (DMPA), depot injection**
- Morphine oral solution
- Oseltamivir capsules
- Paediatric retinol capsules
- Paediatric retinol oral solution
- Paracetamol oral solution

- Paracetamol oral suspension
- Phenobarbital oral liquid
- Phenytoin oral liquid
- Sodium chloride and glucose intravenous infusion
- Sodium chloride intravenous infusion
- Valproic acid oral liquid

This updated new work programme would be made available on the WHO Medicines web site.

3.3 Specifications for medicines, including children's medicines

3.3.1 *Medicines for HIV and related conditions*

New monographs for the following antiretroviral active substances and dosage forms were presented to the Expert Committee for discussion. The monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the consultative process and those made during discussion.

APIs

- Lopinavir
- Tenofovir disoproxil fumarate

Dosage forms

- Indinavir capsules
- Saquinavir tablets
- Tenofovir tablets
- Lopinavir and ritonavir tablets

A revision of the published text of the following antiretroviral active substance was presented to the Expert Committee for discussion. The revised monograph was adopted, subject to confirmation of the proposed values for the specific absorbance by the collaborating laboratory:

- Efavirenz

3.3.2 *Antimalarial medicines*

New monographs for the following antimalarial dosage forms were presented to the Expert Committee for discussion. The monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the public inquiry and those made during the discussion:

- Amodiaquine tablets
- Quinine bisulfate tablets

Consequent to the development of a new monograph for Quinine bisulfate tablets, a revision of the published text for the quinine sulfate dosage form adopted in October 2008 was required to add an additional identity test allowing the differentiation between the two sulfate forms of quinine possibly used in tablet formulations.

A revision of the published text of the following antimalarial dosage form was thus presented to the Expert Committee for discussion. The revised monograph was adopted, subject to inclusion of the comments received during the public inquiry and those made during the discussion:

- Quinine sulfate tablets

3.3.3 *Antituberculosis medicines*

Revisions of the published texts of the following antibiotics' active substances, for which an International Chemical Reference Substance (ICRS) was no longer available and thus a new method for assay was needed, were presented for discussion (see paragraph 3.4.2 for antibiotics), together with a new monograph for the corresponding dosage form. The monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the public inquiry and those made during discussion:

APIs

- Amikacin
- Amikacin sulfate

Dosage form

- Amikacin injection

New monographs for the following antibiotics active substances and dosage form for which an ICRS was still available, and thus included an assay by a microbiological method, were also presented for discussion. The monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the public inquiry and those made during discussion:

APIs

- Kanamycin monosulfate
- Kanamycin acid sulfate

Dosage form

- Kanamycin injection

For the Kanamycin injection monograph, the issue of the determination of the conversion factor from international units (IU) to micrograms was raised. The Expert Committee recommended that this monograph be circulated again for comment on this specific aspect.

3.3.4 *Other medicines*

Oxytocin

A draft proposal for oxytocin was initially sent out for comment in 2007 and presented for discussion at the forty-second meeting of the Expert Committee in October 2008. A revised draft monograph, reflecting the comments received and the Expert Committee's recommendations, was recirculated for comment in January 2009. The new comments received were discussed during the consultation on specifications for medicines and quality control laboratory issues in June 2009, paying special attention to the following aspect of the monograph:

- limits for assay

A revised text was 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.

Oxytocin injection

A draft proposal for Oxytocin injection was initially sent out for comment in 2007 and presented for discussion at the forty-second meeting of the Expert Committee in 2008. A revised draft monograph, reflecting the comments received and the Expert Committee's recommendations, was recirculated for comment in January 2009. The new comments received were discussed during the consultation on specifications for medicines and quality control laboratory issues in June 2009, paying special attention to the aspects of the monograph presented below.

Storage/stability/pH

The storage of Oxytocin injection was a matter of concern since this injection was widely used in developing countries with hot climates and where refrigeration was not available. It was used by a range of health professionals and health providers (e.g. midwives) as well as in emergency situations. WHO was actively promoting its use by "skilled attendants" for the prevention and treatment of postpartum haemorrhage as part of "Making Pregnancy Safer" (http://www.who.int/making_pregnancy_safer/en/) (Millennium Development Goals for maternal and child health).

The draft monograph circulated in 2007 recommended a storage temperature of between 2°C and 8°C (i.e. in a refrigerator) in line with the recommendations of the major manufacturers. This aspect of the monograph was reviewed by the Secretariat in light of current debate on stability of Oxytocin formulations.

Bearing in mind the application of the Ph.Int., the revised draft circulated for comment in January 2009 retained 2–8°C as the default temperature recommended under Storage, but qualified it by including "unless otherwise indicated on the label". This recommendation was supplemented by Additional information concerning short-term storage at higher temperatures in line with statements in summary of product information/ patient information leaflets (SPCs/PILs) provided by major manufacturers. A Note from the Secretariat invited comment on this aspect of the revised draft together with any supporting data. Based on the above and the comments received, the storage temperature of 2–8°C for the injection was confirmed.

pH value

The lower limit in the revised draft was changed taking account of the limits currently given in other pharmacopoeias.

Related substances

Further to discussion in June 2009, a recently published article demonstrated that the high-performance liquid chromatography (HPLC) method used for the Related substances test currently described in the Ph.Int. monograph for Oxytocin was also suitable to detect the related substances for the injection. The Expert Committee thus recommended using this test in the Oxytocin injection monograph. The details of this method would be added to the revised draft.

The text was 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 discussion.

3.4 Revision of texts of *The International Pharmacopoeia*

3.4.1 *Antimalarials: artemisinin derivatives*

The revision of some aspects of the monographs for artemisinin derivatives (Artemether, Artemisinin, Artemotil, Artenimol and Artesunate and their associated dosage forms) was discussed by the Expert Committee in October 2008.

In view of the importance of this category of antimalarial medicines and the time that this extensive revision work would require, an explanatory note including preliminary variations to be carried out to improve the HPLC assay methods (sample preparation) had been posted on the WHO Medicines web site.

Following presentation of a detailed update the Committee was pleased to note that considerable progress had been made; specific revision proposals for two monographs had now been circulated for comment and laboratory work was in progress for other monographs.

The following revised antimalarial dosage forms monographs were presented to the Expert Committee for discussion with the comments received to date. The monographs were adopted, subject to inclusion of the agreed changes, based on the comments made during the discussion and provided no major comments were received during the public inquiry:

- Artesunate
- Artesunate tablets

3.4.2 *Antibiotics*

A number of revision issues related to antibiotics assay were identified and discussed by the Expert Committee at its meetings in October 2006 and 2008.

The Committee was pleased to note that a review had started of those monographs for antibiotics which specified a microbiological assay, with the aim of replacing this method by a chromatographic method where possible. Priority for revision had been awarded to those monographs in Volume 1 of the Fourth Edition of the Ph.Int. that still specified a microbiological assay while the relevant biological reference material (International Standards for Antibiotics (ISA9)) had been disestablished.

The following revision status for these texts (APIs and dosage forms) was presented:

- Amikacin and Amikacin sulfate monographs: the microbiological assay was replaced by an HPLC method using ultraviolet (UV) detection and an alternative method by non-aqueous titration had been added whenever possible. These texts were adopted by the Expert Committee (see paragraph 3.3.3 for antituberculosis drugs);
- Chlortetracycline hydrochloride, Oxytetracycline dehydrate, Oxytetracycline hydrochloride, Tetracycline, Tetracycline hydrochloride and Paromomycin monographs: the Committee agreed to revise these texts taking account of established pharmacopoeial HPLC methods which were also under active revision in other pharmacopoeias. It was, therefore, recommended to await the outcome of these efforts for further discussions of these monographs within the context of the Ph.Int.

As all these revisions were ongoing, the Expert Committee recommended that an information note on the revision status of these monographs be posted on the WHO Medicines web site.

3.4.3 *Other medicines*

Mebendazole

The Expert Committee adopted a modification to the text for mebendazole to improve the interpretation of the revised monograph adopted in October 2008.

Following adoption of the revised monographs for Mebendazole and Mebendazole chewable tablets by the Expert Committee in October 2008, the Secretariat had written to other pharmacopoeial authorities regarding the revision that had been carried out to explicitly restrict the substance to polymorph C in the Ph.Int. In view of the use of mebendazole in intestinal worm eradication programmes worldwide, harmonization of pharmacopoeial monographs had been suggested with respect to the control of polymorphism. The Committee appreciated the helpful replies received from several pharmacopoeias and noted that both the Chinese and European Pharmacopoeias also restricted mebendazole to polymorph C. The possibility of including an explicit statement to this effect within the European Pharmacopoeia (Ph. Eur) monograph was welcomed. It was noted that correspondence from the United States Pharmacopeia (USP) had indicated an interest in harmonizing the USP monograph (which currently did not control the polymorphic form). Members noted, however, that this would not currently be possible since the product currently licensed in the USA contained polymorph B.

The Secretariat undertook to provide feedback to the relevant pharmacopoeial authorities.

Oseltamivir phosphate

The monograph for Oseltamivir phosphate was adopted by the Expert Committee in October 2008 for addition to the Fourth Edition of *The International Pharmacopoeia*.

A further revision for this text was proposed following receipt of comments from manufacturers on the tests for Sulfated ash and related substances. The changes proposed would harmonize the Ph.Int. text with the specifications for oseltamivir phosphate that were now available in other pharmacopoeias (Ph.Eur and USP).

A revised text that included these proposed changes was presented to the Expert Committee for discussion. The monograph was adopted, subject to inclusion of the agreed changes, based on the comments received and those made during the discussion.

3.4.4 *Heparin*

Rapid revisions of the monographs in *The International Pharmacopoeia* for Heparin calcium and Heparin sodium were adopted by the Expert

Committee in October 2008 and had been published on the WHO Medicines web site, to bring them into line with the action of other pharmacopoeias concerning Heparin monographs. The statement on the web site indicated that the WHO Expert Committee on Specifications for Pharmaceutical Preparations, together with the WHO Expert Committee on Biological Standardization, would jointly review the scientific work being carried out by interested parties. The need for further revision of the monographs would be examined, and it was noted that discussion on heparin would be held during the next session of the Expert Committee on Biological Standardization.

Revision of the Heparin monographs was also discussed during the informal consultation in June 2009, when it was recommended to investigate the possible inclusion of a cellulose acetate plate electrophoresis method for the analysis of heparin and its potential glycosaminoglycan impurities, e.g. dermatan sulfate, chondroitin sulfate and oversulfated chondroitin sulfate.

This method, routinely used in industry, had been shown to have a high selectivity for heparinoid impurities and could be performed with low-cost instrumentation. Therefore, this method could be beneficial for small quality control laboratories not equipped for the compendial HPLC methods.

The Expert Committee endorsed the recommendation that the Secretariat, in collaboration with a WHO collaborating laboratory, review the suitability of this proposed method for inclusion in the Ph.Int. and circulate revised draft proposals of the Heparin monographs for comment.

3.5 Review of published general monographs for dosage forms

At its meeting in 2007, the Expert Committee agreed that the general monographs published in Volume 2 of *The International Pharmacopoeia* should be reviewed and revised as necessary, to follow a general monograph "template" that had been prepared, based on the texts adopted for inclusion in the first supplement.

Following the defined template, a draft revision of the general monograph for Tablets was discussed at the informal consultation in June 2009. It was then recommended that, based on the revision of the general monograph for Tablets, a similar revision should be done of the monograph for Capsules. Revised texts for the following monographs were presented to the Expert Committee for discussion. The revised monographs were adopted, subject to inclusion of the agreed changes, based on the comments received during the public inquiry and those made during the discussion:

— Tablets
— Capsules

3.6 General policy topics and general revision issues

Several documents including guidance and explanation of the current pharmacopoeial approach as well as a review of application to published monographs for the following general revision issues were presented to the Expert Committee for consideration:

— monographs title and strengths
— strengths available statement
— identity tests
— polymorphism

The Committee discussed the background documents, endorsed the explanatory texts as summarized below and adopted the proposed revisions of the relevant monographs. It further agreed that, as a basis for a future policy, these guidance documents and explanatory texts would be helpful to assist those involved in the development of new and revised monographs. In this respect, the guidance documents might also be made available more widely to provide explanatory information to users of the Ph.Int. by inclusion in the Supplementary information section of the Pharmacopoeia and on the WHO Medicines web site.

Monographs title and strengths

Titles

It was noted that for older monographs the full name of the API was normally included for the dosage form (e.g. Atropine sulfate tablets). In more recent monographs (new texts or revisions) the name of the salt was, whenever possible, usually omitted. There were, however, inconsistencies, e.g. Nelfinavir mesilate tablets.

Following the recommendation of the informal consultation in June 2009, the Expert Committee agreed that a standardized approach should be followed within *The International Pharmacopoeia*, which was to use the shortest title consistent with providing unambiguous information on the nature of the API. Such an approach was designed to facilitate the use of the monograph title for nonproprietary labelling and generic prescribing.

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

— Indinavir capsules (API — indinavir sulfate)
— Saquinavir tablets (API — saquinavir mesilate)
— Tenofovir tablets (API — tenofovir disoproxil fumarate)
— Amikacin injection (API — amikacin sulfate)

The Expert Committee endorsed the proposal that any change to the title agreed for published monographs could be made either when a monograph

was revised for technical reasons or on publication of a new edition. At such a time, where necessary, the heading Definition would be added together with a statement clarifying the nature of the API used in preparing the dosage form and the Labelling statement would be checked for consistency.

Strengths

How the strength was stated in monographs, and hence the terms in which the content was calculated, was dictated by how products available on the market were labelled. The Committee agreed that having established how the content was declared on the label by the manufacturer and having included in monographs an appropriate labelling statement, where necessary, the content statement under Definition, the calculation under Assay and the amounts of the preparation taken for testing should all be expressed in the same way.

It was noted, however, that problems could arise when product labelling was not clear or where there were inconsistencies between products available on the market. Although it was recognized that neither pharmacopoeial authorities nor WHO had control over product labelling and that this would fall within the responsibility of MRAs, the Committee was informed that a document gathering proposals concerning dosage form terminology and expression of medicine strength was presented by QSM to the Expert Committee for the Selection and Use of Essential Medicines for discussion at its meeting in March 2009.

The Expert Committee welcomed this initiative and was pleased to note that the Expert Committee for the Selection and Use of Essential Medicines broadly endorsed the QSM proposals. As a consequence, the expanded explanatory notes included in the sixteenth WHO Model List of Essential Medicines and in the second WHO Model List of Essential Medicines for Children now included:

- a link to the Quality assurance area of the WHO Medicines web site and to the online text of the current edition of the Ph.Int.; and
- an annex on dosage form terminology.

The Expert Committee for the Selection and Use of Essential Medicines agreed the principles that would be applied to the expression of medicines strengths in future lists and had requested its Secretariat to review current entries and revise them accordingly. These principles were set out in the corresponding Report of the Expert Committee for the Selection and Use of Essential Medicines. WHO Technical Report Series, No. 958, 2010 (in print) as follows.

When revised in accordance with these principles, entries where the active pharmaceutical substance is not the active moiety will more clearly distinguish between:

- those for which the strength is expressed in terms of active moiety (the salt will be indicated in parentheses, e.g. "50 mg (as sodium salt)"); and
- those for which the strength is expressed in terms of API (the salt will be given in full, e.g. "50 mg codeine phosphate").

Where necessary, in instances of potential confusion (e.g. amodiaquine, quinine salts) a warning note will be included.

Strengths available statement

Monographs in the Ph.Int. for individual dosage forms have included information concerning the strengths of preparations available, referring to "the current WHO Model List of Essential Medicines". For example, the monograph for Lamivudine tablets published in the first supplement stated:

> **Additional information**. Strengths in the current WHO Model List of Essential Medicines: 150 mg, 300 mg. Strength in the current WHO Model list of essential medicines for children: 150 mg.

This statement was based on information from the fifteenth Model List of Essential Medicines published in 2007. It was, however, noted in 2009 that for lamivudine the then current Model List included only the 150 mg tablets. This example, therefore, illustrated the problem of keeping the strengths available as indicated in Ph.Int. monographs in step with the current Model List of Essential Medicines.

To keep track of changes affecting Ph.Int. monographs each time a new Model List was published would require the user to check for changes frequently, and the Secretariat to continuously revise monographs to correct this non-mandatory information.

The Expert Committee, therefore, endorsed the recommendation that, for the next edition of *The International Pharmacopoeia*, individual monographs would simply include the strengths without the words "in the current WHO Model List of Essential Medicines". It was agreed instead that the General notices would state that, in general, the strengths indicated under Additional information in individual monographs for dosage forms were those given in the Model Lists. In addition a recommendation could be included to consult the current edition of the Model List and provide a reference to the appropriate page of the WHO Medicines web site (as a link in the electronic version). This would also strengthen the links between the Ph.Int. and the WHO Model List of Essential Medicines (http://www.who.int/medicines/publications/essentialmedicines/en/index.html).

Using terms such as "in general" or "wherever appropriate" in the General notices would accommodate the small number of exceptions where a

preparation that was the subject of a monograph was not included in the current Model Lists. Such exceptions included:

- certain preparations recommended by WHO treatment programmes and/or included in WHO treatment guidelines that were not in the Model Lists (e.g. paediatric didanosine oral liquid);
- strengths additional to those in the Model List that had been indicated for similar reasons (e.g. 20 mg Zn strength for zinc sulfate tablets); and
- monographs for products which had been or which might be removed from the Model Lists (e.g. stavudine capsules).

It was also emphasized that, unless restricted by the Definition to a particular strength, a monograph was intended to cover any strength. In this context it was noted that in certain tests (for example, dissolution) explicit reference to particular strengths might sometimes be necessary.

Identity test

Editorial guidance on selection, order and possibility for subsidiary choice of identity tests was discussed.

The current approach, which is to use a combination of different methods within the monograph rather than placing reliance on a single method, was reemphasized. This was particularly important since the Ph.Int. monographs might be applied to material from different manufacturers and by quality control laboratories equipped with different instruments.

Polymorphism

For an API known to exist in more than one morphic form, the way to frame the monograph would depend on whether or not it was restricted to a particular polymorph.

In most cases it was intended that the monograph place no restriction on morphic form. A statement had been included under Additional information to the effect that the substance "may exhibit polymorphism". In such cases, where an infrared identity test had been included, appropriate instructions were given on how to proceed (see, e.g. the monograph for Efavirenz). Without such instructions the monograph was, in effect, restricting the substance to the morphic form of the ICRS.

3.7 Radiopharmaceuticals

Work on the elaboration of specifications for radiopharmaceuticals was initiated in 2001, with the collaboration of WHO and the International Atomic Energy Agency (IAEA). Following consultations and discussion involving experts from both organizations, agreement was reached that this work would include inter alia the revision of the general monograph in *The International Pharmacopoeia*

and the elaboration of 30 monographs for individual radiopharmaceuticals preparations, to which IAEA had awarded priority in 2005.

Background information on the development of these monographs was presented to the Expert Committee in October 2008 and was described in the forty-third report.

As a result of this joint work, the final versions of the following texts adopted in October 2008 were made available on *The International Pharmacopoeia–Radiopharmaceuticals page* of the WHO Medicines web site.

General monograph and related texts

— General monograph
— Methods of analysis
— Supplementary information

Individual monographs

— Fludeoxyglucose (^{18}F) injection
— Gallium citrate (^{67}Ga) injection
— Iobenguane (^{123}I) injection
— Sodium iodide (^{131}I) injection
— Sodium iodide (^{131}I) solution
— Sodium Pertechnetate (^{99m}Tc) injection (fission)
— Sodium pertechnetate (^{99m}Tc) injection (non-fission)
— Technetium (^{99m}Tc) pentetate complex injection
— Thallous chloride (^{201}Tl) injection

Considering the extensive work already carried out and the need for specifications in *The International Pharmacopoeia* for these pharmaceutical preparations, the 20 remaining monographs (see the list below) were also adopted subject to final scrutiny of the reformatted texts by a small working group composed of experts from both the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and IAEA.

To undertake the editorial work needed to bring the remaining texts in line with those already published on the web site, the Secretariat had agreed with IAEA that the scrutiny would be carried out by the working group by correspondence, following a defined procedure.

Draft monographs for the following substances were sent to the working group in two series of about 10 texts for review:

— Iobenguane (^{131}I) injection
— Samarium ethylene diamine tetramethylene phosphonate complex (^{153}Sm) injection
— Sodium iodide (^{131}I) capsules
— Sodium iothalamate (^{125}I) injection

— Sodium phosphate (^{32}P) injection
— Strontium chloride (^{89}Sr) injection
— Technetium (^{99m}Tc) bicisate complex injection
— Technetium (^{99m}Tc) exametazime complex injection
— *Technetium (99mTc) mebrofenin complex injection*
— Technetium (^{99m}Tc) mertiatide injection
— Technetium (^{99m}Tc) succimer complex injection
— Technetium (^{99m}Tc) sulfur colloid injection
— Technetium (^{99m}Tc) tetrofosmin complex injection
— Technetium (^{99m}Tc) tin colloidal injection
— Technetium(^{99m}Tc) pyrophoshate tin complex injection
— Technetium(^{99m}Tc) methylene diphosphonate (MDP) complex injection
— Technetium(^{99m}Tc) sestamibi complex injection
— Yttrium silicate (^{90}Y) colloid injection
— Technetium (^{99m}Tc) labelled Macrosalb (^{99m}Tc MAA) injection*
— Technetium (^{99m}Tc) nanocolloid injection*

* Regarding the monographs for technetium (^{99m}Tc) nanocolloid injection and technetium (^{99m}Tc) labelled macrosalb (^{99m}Tc MAA) injection, the Committee referred to its decision taken in October 2008 for technetium (^{99m}Tc) labelled red blood cells injection, when it had been decided that the quality specifications for this type of blood product or derivative, not covered by the Ph.Int., would normally be the responsibility of the WHO Expert Committee on Biological Standardization or would be dealt with through the Blood Regulators Network for which WHO provided the Secretariat. Therefore, it was recommended that the quality specifications for these three biological products derived from albumin be dealt with by the above-mentioned committees.

The comments received thereon were discussed at the informal consultation on specifications for medicines and quality control laboratory issues in June 2009. Revised texts, reflecting the comments confirmed by IAEA, were presented to the Expert Committee for information.

While formatting and reviewing these remaining texts, it was decided that, for the purposes of consistency, some changes needed to be made to all the individual monographs, including to the texts already published on the web site. Revised drafts for those texts were also presented to the Expert Committee for information.

The Expert Committee noted with appreciation the completion of this work and endorsed the reformatted monographs prepared following the recommendations made in 2008. It further agreed that those final texts be placed on *The International Pharmacopoeia–Radiopharmaceuticals page* of the WHO Medicines web site, bringing the number of new individual monographs for radiopharmaceutical preparations for inclusion in the Fourth Edition of *The International Pharmacopoeia* to 27.

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

4.1 Annual report of the WHO Collaborating Centre

The Expert Committee noted with appreciation the work carried out by the WHO Collaborating Centre for Chemical Reference Substances as presented in its report for 2008. It was noted that the total number of International Chemical Reference Substances (ICRS) distributed from the Centre in 2008 was 2153 compared to the 2332 reported in 2007. The most frequently requested substances included artesunate, artemether, prednisolone, artemisinin and zidovudine impurity B.

The Expert Committee adopted the report for 2008.

4.2 Adoption of new International Chemical Reference Substances

Nine ICRS were established in 2008, including the following seven new substances:

- carbidopa
- colchicine
- lumefantrine
- DL-methionine
- naloxone hydrochloride
- oseltamivir for system suitability
- oseltamivir phosphate

and the following replacements:

- artemisinin
- prednisone

The Expert Committee adopted the above-listed ICRS.

4.3 New institution for the establishment of international reference materials

While adopting its activities report for 2008, the Expert Committee was also informed that, since May 2009, Apoteket AB in Sweden had ceased its activities as host of the WHO Collaborating Centre for Chemical Reference Substances and that these activities were in the process of being transferred to a new institution.

It was emphasized with appreciation that Apoteket AB had started its collaboration with WHO and specifically *The International Pharmacopoeia* in 1956. In recognition of Apoteket AB's longstanding services to WHO, the Expert Committee expressed its gratitude to the WHO Collaborating Centre on Chemical Reference Substances and to the Government of Sweden which had supported these activities over the past 53 years.

Recognizing the inconvenience caused by this transition from the former Collaborating Centre to the new institution, notably for the distribution of ICRS, the Expert Committee welcomed the announcements posted on the WHO Medicines web site to inform users during this transitional period. As this process was nearing finalization, another announcement indicating the new contact details for ordering ICRS was soon expected to be published.

As regards the new institution, the Committee made some proposals on the content of the future activity report and encouraged the possibility of reflecting in more detail certain activities such as the stability monitoring of ICRS. The Expert Committee also welcomed the future efforts of the Secretariat in assisting the new institution with regard to collaborative trials to identify any additional laboratories for the establishment of new ICRS. Pricing for the distribution of ICRS was also discussed and the Expert Committee was informed that owing to the change of currency with which the new institution would operate, the price of the ICRS would need to be adjusted. It, therefore, agreed that the price, which had not been changed over the past decade, be increased.

The Committee stated that it would look forward to receiving annual reports on work carried out on ICRS from the new institution.

5. Quality control — national laboratories

5.1 External Quality Assurance Assessment Scheme

The External Quality Assurance Assessment Scheme (EQAAS) aimed to give each 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 was aimed at reinforcing mutual confidence within this network.

With a view to continuing the promotion of quality assurance in drug quality control laboratories in WHO Member States, five test series of Phase 4 of a proficiency testing scheme had taken place. Some 50 laboratories had participated in this phase of the Scheme, which was now finalized.

The Committee noted the final reports on the five tests and the preliminary summary report for Phase 4 of this Scheme. The results reported were:

— final report procedure 1: determination of water by the Karl Fischer method
— final report procedure 2: dissolution testing
— final report procedure 3: assay of tablets by HPLC
— final report procedure 4: assay by titration
— final report procedure 5: optical rotation by polarimetry
— summary report, Phase 4

During the informal consultation held in June 2009, the experts considered the Scheme to be most efficient, both for the participating laboratories and for the feedback on the methods from the Ph.Int. used in the Scheme. They strongly recommended continuation of the Scheme starting with a new phase. In addition they advised on how to revise the Ph.Int. methods used, e.g. in procedure 4.

Regarding the samples, the experts from the consultation advised the retention of extra samples from each procedure for those laboratories which gave doubtful or unsatisfactory results and which would need to redo testing. Moreover, WHO should strongly encourage the participating laboratories to report back to WHO on the outcome of such investigations and follow-up actions, as necessary.

The Expert Committee acknowledged with thanks receipt of the samples from UNICEF and from the manufacturers involved.

Further to the previous agreements between WHO and EDQM (dated 21 March 2000, 26 January 2001, 8 July 2004 and 15 March 2007), it was decided to continue collaboration during the period 1 January 2010–31 December 2012 with a view to evaluating the technical performance of 60 drug quality control laboratories designated by WHO for participation in the EQAAS, in accordance with the programme of proficiency testing schemes developed by EDQM, in the following analytical procedures:

— assay by titration (sample: metronidazole)
— water content by Karl Fischer (sample: amodiaquine dihydrochloride dihydrate)
— dissolution test (sample: artemether and lumefantrine tablets)
— related substances by HPLC (sample: abacavir oral solution)
— assay by HPLC (sample: amodiaquine tablets)
— dissolution test (sample: rifampicin capsules)
— related substances by thin-layer chromatography (TLC) (sample: artemether and lumefantrine oral suspension)

The proposed programme could be modified depending on the availability/expiry dates of the substances (testing samples and reference materials) and/or the availability of the methods.

The Expert Committee endorsed the recommendation of the informal consultation and welcomed the new phase currently in preparation with EDQM.

5.2 WHO good practices for quality control laboratories

Revision of WHO good practices for pharmaceutical quality control laboratories (GPCL)

At its forty-third meeting the Expert Committee recommended that the WHO Secretariat initiate the process of revision of the *WHO good practices for national pharmaceutical control laboratories* (*Good practices for national pharmaceutical control laboratories,* Annex 3, WHO Technical Report Series, No. 902, 2002 (http://whqlibdoc.who.int/trs/WHO_TRS_902.pdf#page=37)).

The following requirements were set for the revision, based on the recommendations of the Expert Committee at its forty-third meeting:

— include the most important parts of the WHO GMP guide, which were relevant to quality control laboratories, directly in the GPCL guideline and add references to other relevant parts of the WHO GMP guide;
— provide detailed guidance for the areas identified as being often deficient during inspections performed by the PQP;
— align the guidance with the requirements of ISO/IEC 17025:2005;
— apply to any pharmaceutical quality control laboratory, be it national, commercial or another nongovernmental laboratory; and
— harmonization of terms used in other WHO documents.

The first draft revision was prepared in March 2009 and was widely commented on. The comments received were discussed with laboratory experts at the informal consultation on specifications for medicines and quality control laboratory issues in June 2009 following which a second draft revision was prepared. The second draft revision was further discussed with inspectors in the informal consultation on WHO guidelines for medicines quality assurance, quality control laboratories and transfer of technology in July 2009, resulting in a third draft revision which was distributed for comments in September 2009.

This third draft revision was presented for discussion to the forty-fourth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

The following changes were made to the original guidelines published in 2002:

— ***Explanatory notes***

In order to differentiate between requirements and advice, explanatory notes were introduced in the text.

— ***Glossary***

Definitions were revised to bring them into line with current WHO documents and 15 definitions were added as a reflection of the extended text. Definitions from WHO guidelines were used where available, or else definitions were adopted from widely accepted documents such as *International Vocabulary of Metrology* published by the Joint Committee for Guides in Metrology.

— ***Part one — Management and infrastructure***

The *Organization and management* and *Quality system* sections were amended and structured in such a way as to provide clearer guidance. Explicit requirements on internal audits, management review of quality issues, corrective and preventive measures were included. The *Control of documentation* section was substantially extended and the *Record* section was amended to provide electronic records. The section on *Personnel* was simplified to provide a laboratory with more flexibility in organization while assuring the essential functions. Requirements on *Premises* were focused more on chemical testing and for the requirements for microbiological testing and testing on animals, readers were referred to other guidelines. The section on *Contracts* was added, differentiating between contracts to purchase services and supplies and subcontracting tests.

— ***Part two — Materials, equipment, instruments and other devices***

Requirements on labelling of reagents, reagent solutions and volumetric solutions were specified in detail. Reference substances and reference materials were differentiated and clarification was provided on retesting of various types of reference substances. Requirements relating to the qualification of laboratory equipment were added, referring to the WHO guidelines. The section on *Traceability* was simplified.

— ***Part three — Working procedures***

The requirement for review of a test request by the laboratory was included. In the case of a pharmaceutical manufacturer's laboratory, the test request form could be replaced by a master production instruction. A section was added dealing with validation of analytical procedures and system suitability test, including the requirement to demonstrate that a pharmacopoeial method or externally validated analytical method was suitable for the substance or product to be tested. Detailed guidance on

the procedure for out-of-specification results, including references to the US Food and Drug Administration (FDA) and the European Official Medicines Control Laboratories (OMCL) network under the *Note* was provided. A brief explanation of uncertainty of measurement with further references was included. The contents of the analytical test report, which was used in investigative testing, and of the certificate of analysis were specified.

— ***Part four — Safety***

No major changes were made to part four.

— ***References***

References to WHO documents were updated and a number of references to documents of other organizations, such as the International Organization for Standardization, Joint Committee for Guides in Metrology, US FDA, International Society for Pharmaceutical Engineering, European Union guidelines, the OMCL Network of the Council of Europe, US Pharmacopeia, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and Eurachem/Cooperation on International Traceability in Analytical Chemistry (CITAC), were included under *Notes*.

— ***Appendices***

Appendix 1: *Model analytical test report for active pharmaceutical ingredients, excipients and pharmaceutical products* was deleted and was replaced by a reference to existing WHO guidelines.

Appendix 2 (now Appendix 1): *Equipment for a first-stage and medium-size pharmaceutical quality control laboratory* did not represent any requirement; it would be helpful in establishing a new laboratory in a developing country. The list, which covered chemical and microbiological units, was updated according to currently used analytical methods and equipment and specific requirements for a pharmacognosy/phytochemistry unit were added.

— ***Applicability to any pharmaceutical quality control laboratory, be it national, commercial or another nongovernmental laboratory***

Due attention was paid to the applicability of the guidelines. The inappropriateness of some requirements in the first draft, specifically to laboratories belonging to a pharmaceutical manufacturer, was commented upon by several organizations. The text was subsequently thoroughly discussed with GMP inspectors during the aforementioned informal consultation and modified accordingly. Recommendations specific to national pharmaceutical quality control laboratories were stressed and some flexibility was introduced.

The revised guidance text was presented to the Expert Committee for discussion of comments and this was adopted (Annex 1).

5.3 WHO good practices for pharmaceutical microbiology laboratories

Introduction

In addition to the above-discussed update 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 by a specific text for pharmaceutical microbiology laboratories.

In light of the above, the Expert Committee recommended that the WHO Secretariat initiate the process of revision of these good practices and in addition prepare a new text on good practices for pharmaceutical microbiology laboratories. The Committee took note that these guidelines were in production and would be sent out for comments.

6. Quality assurance — good manufacturing practices

6.1 WHO good manufacturing practices: main principles for pharmaceutical products

An informal consultation on WHO guidelines for medicines quality assurance, quality control laboratories and technology transfer was held in Geneva from 27 to 31 July 2009. *WHO GMP: main principles for pharmaceutical products* was discussed with the following outcomes:

The main changes recommended during that meeting and subject to presentation to the Expert Committee for review and possible approval were as follows:

— quality unit concept to be included in the main principles;
— inclusion of the quality risk management;
— addition of a reference and link to the product quality review; and
— more detailed review of the responsibilities of key personnel.

The main changes recommended were:

— Quality unit concept
— Quality risk management
— Product quality review
— Responsibilities of key personnel.

The Expert Committee endorsed the suggested recommendations and recommended that the Secretariat distribute the revised text for comment.

6.2 WHO good manufacturing practices for active pharmaceutical ingredients

During several previous meetings of the Expert Committee, the revision of WHO GMP for active pharmaceutical ingredients (APIs) had been discussed. The Committee also closely followed development of the ICH GMP guidelines for APIs, including their initial preparation by the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

In the past the Committee had recognized the difficulty that countries would have in implementing the ICH GMP guide in a short period of time. It, therefore, agreed that WHO should revise the current WHO GMP for APIs to reflect current GMP requirements and to take into account other published guidelines, including the ICH guide. The Committee endorsed the step-wise approach to the implementation of GMP for APIs.

In the meantime, the principles described in the ICH GMP for APIs had been recognized and implemented by numerous national inspectorates. In addition, they had been field-tested when inspecting in the context of the WHO PQP (for medicines).

The Secretariat had, therefore, prepared a WHO-style, edited version of this guide, fully in line with the internationally used text developed following the ICH process.

This draft working document was reviewed and discussed with inspectors, experts and interested parties during the informal consultation in July 2009. During this meeting it was recommended that the text be fully retained in line with the ICH principles in order to avoid any challenges regarding the further global implementation of this standard internationally.

In order to further assist with its implementation, the experts decided to add clarifying notes and explanations for some of the parts that had been questioned during inspections, i.e.

- definition of API starting material;
- (para. 2.1.1) role of senior management regarding the implementation of an effective quality management system;
- (para. 2.3) delegation of the responsibility for production activities;
- need for manufacturers of intermediates and/or APIs to have a system for evaluating the suppliers of critical materials in place;
- examination of each container or grouping of containers of materials upon receipt and before acceptance;
- identification of batch material;
- reserve samples; and
- inclusion of cross-references to *Good trade and distribution practices* (GTDP) and GMP for excipients in the section entitled: Agents, brokers, traders, distributors, repackers and relabellers.

The Expert Committee endorsed the above recommendations and considered the establishment of a small working group to finalize the wording of the explanatory notes. It agreed to the publication of the supplementary GMP text for APIs together with the explanatory notes to replace the GMP for APIs published in 1992 (Annex 2).

6.3 WHO good manufacturing practices for pharmaceutical products containing hazardous substances

A working document ("WHO guidance to the inspection of hormone product manufacturing facilities") had been prepared previously and tabled at the Expert Committee meeting held in October 2008. These particular guidelines were intended to provide GMP principles for the production and control of products containing certain hormones or other hazardous substances.

There was international concern about the low quality of reproductive health products and the lack of compliance with GMP principles in manufacturing facilities. The PQP included reproductive health products, and to further facilitate improved quality of manufacture of these products, the Expert Committee acknowledged its previous recommendation to provide guidance in this area.

A discussion with experts and interested parties took place during the consultation held from 27 to 31 July 2009. Considering all recommendations for amendment, the group recommended that the title of the document be changed to address not only products containing certain hormones, but also to ensure that the document and the title reflected the wider group of products containing hazardous substances. A revised version of the working document was, therefore, prepared for circulation and was mailed out for comments.

The new working document QAS/08.256/Rev.1 was submitted to the Expert Committee.

The text was presented to the Expert Committee for discussion of comments and the guidelines were adopted (Annex 3) after a review of all outstanding questions.

6.4 WHO good manufacturing practices for sterile pharmaceutical products

The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted in its thirty-sixth report in 1999, WHO good manufacturing practices for sterile pharmaceutical products (WHO Technical Report Series, No. 902, 2002, Annex 6) (http://whqlibdoc.

who.int/trs/WHO_TRS_902.pdf). This guidance was also published in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2. Second updated edition. Good manufacturing practices and inspection* (2007).

Following implementation of these WHO GMP within the context of the PQP, a proposal for revision was being submitted to take into consideration new developments and to bring it into line with International Standardization Organization standard ISO 14644-1 and recent EU, Japanese, PIC/S and US practices.

The following major changes had been made to the text published in 1999:

- New chapters on "Isolator technology" and "Blow/fill/seal technology" had been added.
- The chapter on "Finishing of sterile products" had been amended and provisions had been given for capping of vials.
- The chapter entitled "Manufacture of sterile preparations" had been amended and provisions given for clean-room and clean-air-device monitoring.

Implementation of certain parts of these new practices might need to be undertaken for using a step-wise approach, especially the part relating to the provision for capping in a clean or sterile environment, as this was currently not implemented in most industries.

The text was presented to the Expert Committee for discussion of comments and the guidelines were adopted (Annex 4), after review of the additional comments received by the deadline set for comments to be discussed at the meeting.

6.5 Updates of other WHO good manufacturing practices texts

It was reported that during inspections when implementing the GMP for heating, ventilation and air-conditioning (HVAC) a need for slight revisions to certain chapters was noted. It was, therefore, suggested that these chapters be sent out for comments.

The Expert Committee endorsed this suggestion and recommended that the Secretariat distribute the revised text for comment.

6.6 Good manufacturing practices for blood establishments

An update on the developments of the WHO GMP for blood establishments was presented to the Committee. There was an agreed need for quality and safety requirements, specifications and standards for blood and plasma collection, preparation, testing and distribution activities, the

implementation of internationally agreed quality and safety standards in the blood establishments, a harmonized and systematic approach to ensure compliance at all steps involved (from donor acceptance to release of products), and enforcement by competent MRAs.

ICDRA had recommended the following at its 13th meeting held in Berne in 2008:

> "Recognizing the worldwide need for blood products regulation to ensure availability of safe blood and blood products in the face of known and emerging threats, including emerging infectious diseases, WHO should:
>
> - Take steps to further develop and strengthen national/regional blood regulatory authorities and to promote cooperation
> - Provide harmonized 'assessment criteria for blood regulatory systems' (BRN): convene a consultation of NMRAs to review Draft assessment tool
> - Prioritize development of WHO Guidelines on GMP for Blood Establishments
> - Promote introduction of WHO recommended plasma standards by NMRAs."

WHO had issued requirements for the collection, processing and quality control of blood components and plasma derivatives (WHO Technical Report Series, No. 840, 1994, Annex 2) and recommendations for the production, control and regulation of plasma for fractionation (WHO Technical Report Series, No. 941, Annex 4). In addition, the GMP guide for blood establishments had been published by bodies such as the PIC/S.

Based on the above, the project for WHO guidelines on GMP for blood establishments was intended to respond to the ICDRA recommendation, without inventing a new GMP standard, but taking into account the specifics of blood products, blood establishments and all existing complementary GMP standards.

The aim of the new document was to establish a wide international consensus on quality standards among blood establishments and among inspectors to ensure high-quality products and safety of recipients. It would then become a guidance document for blood establishments, for NMRAs to refer, implement and enforce GMP in blood establishments and to become widely applicable, independent of the activities of a single blood establishment.

The document addressed the general GMP topics, e.g. quality management, as well as the topics specific to manufacturing of blood products, from donor selection through distribution of final products and the newer GMP concepts, e.g. risk management and product quality review.

The detailed structure of the current working document was presented. This included the following chapters: Introduction, Glossary, Quality management, Manufacturing, Contract manufacturing, Analysis and services and a section on Authors, References and History.

The chapter on manufacturing included detailed process-specific guidance, covering donor registration, donor selection, collection, component preparation, laboratory testing, quality control, labelling, release, dispatch, shipping and returns. The product characteristics comprised whole blood, red cells, platelets, plasma for transfusion/fractionation and cryoprecipitate/CPP. The points to consider for validation of preparation steps would focus on centrifugation, separation, freezing, leukocyte reduction and irradiation.

The drafting process had started in January 2008. The text was reviewed during a WHO training workshop (in Teheran) in November 2008 and again in its revised format by a consultation of experts from July to September 2009. The text would also be presented for discussion to the ECBS in October 2009 and released for open consultation. It was expected that subsequent to the global consultation, review of comments and further revision of the document, it would be presented to the ECBS in 2010 with a view to adoption.

The comprehensive consultation process involved WHO Member States through WHO channels (e.g. ministries of health), WHO Regional Advisers, targeted regulatory authorities, blood transfusion services and professional institutions and associations and other interested parties through its publication on the WHO web site.

The Expert Committee took note of the progress made and recommended that this text be mailed out for comment to the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and again be presented at the next meeting of the Committee with a view to its adoption within the full set of GMP texts.

7. Quality assurance — new approaches

7.1 Risk analysis

Introduction

During the meeting of the Expert Committee in October 2007, an update on the new ICH Q10 was given to the Committee by the Secretariat. The Committee concluded that the ICH Q8, Q9 and Q10 documents were useful tools.

On the topic of risk analysis, the Committee made recommendations for WHO to:

- review and update the WHO guidelines on hazard analysis and critical control points (HACCP);
- revise the main text of the WHO GMP to include the principles of application of risk management.

Considering the changes in the approach to quality risk management in the regulatory environment and the use of different tools to analyse risk, the Secretariat had started the process of reviewing the WHO guidelines on HACCP and expected to submit the proposed revised guidelines to the Expert Committee at its next meeting.

Recommendation

The Expert Committee:

- supported the Secretariat in continuing the preparation of the revised draft guideline on HACCP; and
- encouraged the Secretariat to include the principles of quality risk management and to provide examples of possible tools that may be used in quality risk management — not only focusing on HACCP.

7.2 WHO guidelines on technology transfer

The need for new WHO guidance on transfer of technology was discussed at the forty-second meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2007. Colleagues from the WHO PQP shared their experience of recently submitted dossiers by, and inspections carried out in, plants that had undergone technology transfer. Technology transfer was happening worldwide both within and between companies, and within the same country as well as between countries. The Expert Committee, therefore, recommended that WHO guidelines on transfer of technology be developed. A draft document was subsequently prepared and sent out for comment. It was then discussed during the consultation on WHO guidelines for medicines quality assurance, quality control laboratories and transfer of technology on 27–31 July 2009 and a revision was prepared.

The Expert Committee discussed and reviewed the major points that were raised during the commentary period, keeping the balance between GMP and business criteria. Inclusion of the concept of quality by design and the possibility of optional requirements depended on the type of transfer. The Committee took note that the Secretariat would organize a consultation and prepare a new working document for wide circulation following the usual consultation procedure.

8. Quality assurance — distribution and trade of pharmaceuticals

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

The WHO Certification Scheme for finished pharmaceutical products was an international voluntary agreement intended to provide assurance to countries participating in the Scheme, about the quality of pharmaceutical products moving in international commerce (World Health Assembly resolution WHA22.50 (1969), World Health Assembly resolution WHA28.65 (1975), World Health Assembly resolution WHA41.18 (1988), World Health Assembly resolution WHA45.29 (1992), World Health Assembly resolution WHA50.3 (1997)). The primary document of the Scheme was the Certificate of Pharmaceutical Product (CPP).

The Expert Committee had recommended during discussion in 2008 that the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce should be reviewed in light of the changing environment, including the rapid globalization of the pharmaceutical manufacturing sector coupled with changes in the make-up of both the regulators and the groups involved in procurement. In addition, it acknowledged that legislation had been put in place in various countries and regions to assess products manufactured in them and produced for "export only", for which there was currently no adequate provision in the Scheme.

An oral presentation was given by the Secretariat of the work it had done following the recommendations made at the previous meeting of the Expert Committee.

Questions and answers

Based on the Committee's recommendations a question and answer paper was prepared in the interim on the function of the Scheme.

The first working document was based on the feedback, draft questions and answers received from the International Federation of Pharmaceutical Manufacturers and Associations/European Federation of Pharmaceutical Industries and Associations (IFPMA/EFPIA). The working document was subsequently circulated for comments.

Reviewing all the comments received and the materials already available, a new set of questions and answers was prepared and made available.

An additional question and answer was provided for further discussion at the Expert Committee, raised by the specialist who had reviewed all

comments received and who had drafted a new set of questions and answers. This question referred to the possibility of a CPP to be used to provide evidence of an administrative review and approval (e.g. as certification of acceptability of a company name change).

The Expert Committee:

— noted the updated report from the Secretariat;
— reviewed the document and considered the additional question; and
— approved the questions and answers for posting on the WHO web site and publication in *WHO Drug Information*, with the possibility to receive comments and to review any question(s) and answers.

8.2 WHO good distribution practices for pharmaceutical products

Following the adoption of the WHO guidelines for good distribution practices (GDP) by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its fortieth meeting in October 2005 (http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=191) (WHO Technical Report Series, No. 937, Annex 5, 2006) these guidelines had been revised by the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) partnership to strengthen the potential for prevention of counterfeit and other illegal medicines entering the supply chain. The following text outlines the process followed.

At an IMPACT meeting held in Bonn, Germany, in November 2006, the existing GDP was reviewed and amendments proposed relating to the specific issue of improving the security of the distribution chain vis-à-vis counterfeits. This was based on the consideration that even in highly regulated countries counterfeit medicines reached patients through the regulated distribution chain.

A first draft was circulated in March 2007 to all the members of IMPACT's Regulatory Implementation Working Group (IRIWG). The IRIWG subsequently met in Washington, DC, USA from 23 to 25 April 2007 and discussed inter alia the draft and recommended amendments. A revised draft was circulated among the members of IRIWG and a final draft was then made available on the WHO web site for further comments. All IMPACT members (including the MRAs of 60 WHO Member States, plus other stakeholders) were actively encouraged to provide comments.

The draft was further revised and then finalized at the General Meeting of IMPACT held in Lisbon, Portugal, in December 2007. This text reflected the consensus reached at the Lisbon meeting and was submitted to the

WHO Expert Committee in 2008 as a recommendation from the IMPACT partners.

During its forty-third meeting the Committee recommended discussing the document further with IMPACT, the EU and with WHO in view of the comments received. A meeting was subsequently arranged in Geneva on 31 August–1 September 2009 with a view to preparing a new document containing all comments received from the various parties and members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations. The revised document resulting from this meeting was presented to the Expert Committee at its current meeting and the main comments received up until the date of the meeting were identified and discussed. A small subgroup was formed to review all comments received by the permissible deadline. The Committee adopted the text subject to input from this subgroup and provided no major additional comments were received. The Committee members would be duly informed of the outcome (Annex 5), in order to allow them to reconfirm their decision in light of the deliberations of this Expert Committee subgroup.

8.3 Regulatory oversight on pharmaceutical cold chain management

Following-up on the 2008 joint session of topics with common interest, the Secretary of the Expert Committee for Biological Standardization (ECBS) arranged for an update in relation to the draft *Regulatory oversight on pharmaceutical cold chain management. Harmonized guidance for the storage and transport of temperature–sensitive pharmaceutical products*. The table of contents of the current draft working document was presented to the Committee for information.

The document had been developed with a group of experts and took forward the agreement from the joint meeting between the two Committees in 2008, as one of the cross-cutting issues. The document was considered to be fairly mature and would be presented at the 2009 ECBS meeting to obtain feedback, with a view to possible adoption of the document in 2010.

An oral update by video was given by the technical officer responsible for this project.

The Expert Committee noted this update and suggested circulation of the document to the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and to the IMPACT IRIWG that developed the revision of the GDP.

9. Prequalification of priority essential medicines

9.1 Prequalification Programme managed by WHO

The WHO Prequalification Programme (PQP) ensured that medicines procured with international funds were assessed and that the manufacturers of these medicines were inspected, in order to provide a high level of assurance of their quality, efficacy and safety. This was supported by building national regulatory capacity, providing technical assistance to selected manufacturers and postmarket monitoring through quality control (QC) testing by prequalified quality control laboratories. Ultimately the aim was to make low-cost quality priority medicines available for the benefit of those in need.

PQP continued to expand in order to meet the needs of procurers and currently covered priority essential medicines in the following areas:

— HIV/AIDS
— tuberculosis
— malaria
— reproductive health
— selected individual products for other diseases such as oseltamivir and zinc sulfate.

Manufacturers were invited to apply for prequalification of medicines included in invitations for Expressions of Interest (EOI) published on the PQP web site.

The Programme was reliant upon and appreciated the assistance and support of many partners, including national medicines regulatory authorities (NMRAs), QC laboratories, WHO disease departments and programmes, regional and country offices, United Nations and other drug procurement agencies (including UNICEF, the Global Fund and Médecins Sans Frontières) and donors such as the Bill and Melinda Gates Foundation and UNITAID, as well as the colleagues of the Medicines Quality Assurance and Regulatory Support Programmes of WHO. The Programme relied heavily on the standards and guidelines adopted by this Expert Committee.

Assessment of product dossiers (see Table 1)

Assessment of product dossiers was conducted both in-house and by external international experts. WHO standards as defined in WHO guidelines and *The International Pharmacopoeia* were applied. If these did not exist, ICH guidelines were used and, in case of need, guidelines of stringent

regulatory authorities were applied. Much of the assessment work was done in Copenhagen during bimonthly meetings of 15–20 assessors. Variations to prequalified products were processed in-house and during the meetings in Copenhagen.

Table 1
Assessment of product dossiers: statistics

	2007	2008	2009 (As at 16/09/2009)
Products prequalified	21	40	24
Dossiers submitted	90	92	55

Medicines assessed and prequalified by WHO were included in a List of WHO Prequalified Medicinal Products on the PQP web site. Also listed were medicines assessed by SRAs, following an abbreviated procedure.

Currently prequalified products (16 September 2009):

— 247 for treatment of HIV/AIDS and related diseases
— one for treatment of influenza (prequalified in 2009)
— 23 for treatment of tuberculosis
— 16 for treatment of malaria
— 2 for reproductive health (prequalified in 2009)
— Total: 289

Inspections of manufacturers (see Table 2)

Manufacturers of finished products, selected APIs and also selected contract research organizations (CROs) (which carried out clinical/bioequivalence studies) were inspected as part of the prequalification process.

Inspections were conducted by a team of inspectors consisting of:
— a WHO lead GMP inspector
— an inspector from a well-established inspectorate
— national inspectors from the country of the manufacturer, who were invited to be part of the team as observers but had no decision-making power (because of different GMP standards and potential conflict of interest)
— inspectors from developing target countries who might also be invited as observers, for capacity-building purposes.

Table 2
Inspections carried out since 2005

Manufacturer:	2005	2006	2007	2008	2009 (to September)
Finished product	20	17	26	27	22
Active pharmaceutical ingredient	10	10	6	11	5
Contract research organization	14	15	13	14	6
Quality control laboratory	3	1	1	6	3

Prequalification of medicines — transparency

The World Health Assembly through Resolution WHA57.14 of 22 May 2004, requested WHO:

"3. (4) to ensure that the prequalification review process and the results of inspection and assessment reports of the listed products, aside from proprietary and confidential information, are made publicly available."

A WHO Public Assessment Report (WHOPAR) provided a summary of the dossier assessment (where found to be compliant).

A WHO Public Inspection Report (WHOPIR) provided a summary of the inspection (where found to be GMP-complaint).

A Notice of Concern (NOC) was a letter reflecting areas of concern where the non-compliances required urgent attention and corrective action by the manufacturer or research organization.

A Notice of Suspension was a letter reflecting areas of concern when deficiencies identified during an inspection indicate significant non-compliance with GMP, good clinical practices (GCP) or good laboratory practices (GLP), as relevant, resulting in inadequate assurance of product quality.

Prequalification of QC laboratories

The PQP was established in 2004 for QC laboratories in Africa only; however, the programme had since broadened its scope for participation and was now voluntary and without regional limitation. Any laboratory (private or governmental) could participate and the programme was free of charge. The third invitation for EOI was published in September 2007 at the following address: http://www.who.int/prequal/info_applicants/eoi/EOI-QCLabsV3.pdf.

Priority regarding assessment was given to national QC laboratories, laboratories providing testing services to the government, and QC laboratories in areas where United Nations agencies had identified the need for quality testing.

Monitoring after prequalification involved:

- re-inspections at regular intervals
  - — normally three years
  - — two re-inspections performed;
- a brief report to be submitted annually
  - — summary of services provided to United Nations agencies, number of samples analysed, methods used, complaints received
  - — brief details of proficiency testing
  - — changes to key personnel, facility, equipment or other change with significant impact on the laboratory
  - — update of the laboratory information file (LIF), in case of changes with significant impact on LIF content;
- evaluation of results from participation in proficiency testing
  - — WHO EQAAS, Agence française de sécurité sanitaire des produits de santé (AFSSAPS) network of francophone African countries;
- WHO might suspend or withdraw a laboratory from the list when there was evidence of noncompliance.

At present the PQP had surpassed expectations and a significant number of laboratories around the world were applying for prequalification.

The object was to increase access to QC laboratories that met recommended standards and that were committed to providing a service to United Nations agencies for testing of medicines, including but not limited to HIV/AIDS, tuberculosis and malaria products.

As of September 2009, there were 11 prequalified laboratories in: Algeria; France; India; Kenya (2); Morocco; Singapore (2); South Africa (2); and Viet Nam.

The PQP was also involved in capacity building: technical assistance provided to eight national medicines QC laboratories; training in quality assurance, quality control and Ph.Int. (2007); a seminar on rational sampling and testing in quality control of medicines (2009); and participation in EDQM in quality assurance training for official medicines control laboratories (2007). The Programme also monitored the quality of medicines through its policy, sampling and testing projects and prequalified laboratories or laboratories for which the evidence of reliability was available. The major quality monitoring projects were the following:

Quality monitoring of medicines funded by UNITAID (2008/9)

The pilot phase focused on paediatric and second-line antiretrovirals and co-trimoxazole-containing medicines. In cooperation with NMRAs in Kenya, Uganda, the United Republic of Tanzania and Zambia, 378 samples produced by 24 manufacturers were collected, mostly from treatment centres and tested in the laboratory. Only three samples did not

comply with specifications and none of the failures were life-threatening for patients. The majority of the products collected were prequalified by WHO. The project served to strengthen quality control of medicines funded by UNITAID and to capacity building of NMRAs involved.

Quality survey of antimalarial medicines in Africa (2008-2009)

A quality survey of antimalarial medicines focused on artemisinin-based combination therapies (ACTs) and sulfadoxine-pyrimethamine oral dosage forms was performed in six African countries; 936 medicine samples were collected at all levels of the distribution chain and the informal market and were screened by Minilab in cooperation with NMRAs. Three hundred and six samples were then tested fully in the laboratory, of which 74 were found to be non-compliant with a range of quality problems, from very minor non-compliance to absence of the API in two samples.

Quality survey of antituberculosis medicines in Eastern Europe (2009)

A quality survey of antituberculosis medicines focused on products containing rifampicin, isoniazid, kanamycin and ofloxacin was initiated in Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine and Uzbekistan; 291 samples were collected and testing is ongoing.

Several other quality monitoring projects had been conducted since 2005.

Training and capacity building

Training and capacity building were important components of the PQP with the aim of increasing the regulatory capacity of NMRAs in developing countries and to assist manufacturers, CROs and QC laboratories in these countries to improve standards and meet prequalification requirements.

Training was generally provided through seminars and workshops, and might include visits to manufacturers. It was based on prequalification and WHO requirements, but might also be problem-oriented, e.g. relating to a specific product type. NMRA staff and manufacturers frequently participated together in the same training programme and, where possible, the focus was on "train the trainer" for maximum effect.

Thirteen training sessions were organized or supported by WHO in 2007, 15 in 2008 and seven up to September 2009.

In addition to training activities, capacity building of regulatory authorities was supported by the programme hosting rotational posts for assessors in Geneva. These were available for periods of three months during which the participant worked alongside WHO experts and also attended the sessions in Copenhagen to learn from external international experts.

Technical assistance

Technical assistance might be provided to a specific manufacturer, which was committed to participation in the PQP, found to be capable and willing to improve, and was located in a developing country. The products manufactured were to be included in an EOI list, must be of high value for public health purposes and must be poorly represented on the list of prequalified medicines.

Expert consultants were provided by WHO to assist a manufacturer with compliance with GMP, GCP or GLP, as well as with data development and compilation of dossiers or regulatory guidance.

To avoid conflict of interest, technical assistance was independent from dossier assessments and inspections.

During 2008 technical assistance was provided to eight manufacturers.

Future challenges

Some of the key challenges facing the PQP were:

- motivating manufacturers to apply for prequalification and maintain prequalification, to ensure the continued supply of essential priority medicines;
- submission of incomplete or poor quality dossiers;
- non-compliance with GMP by all types of manufacturers;
- difficulty in filling technical positions within PQP;
- lack of availability of national experts (assessors and inspectors);
- reducing the total time taken to prequalify;
- an increasing demand for capacity building (shift from general to more specific technical training); and
- trust-building and information exchange to avoid duplication of effort.

The Committee was provided with an update on the PQP activities in 2009 and took note of the progress made.

9.2 Guidelines on requalification of prequalified dossiers

Section 12 (Maintenance of prequalification status) of WHO's *Procedure for prequalification of pharmaceutical products* (WHO Technical Report Series, No. 953, Annex 3, 2009) stated under "Maintenance of prequalification status" that:

> "WHO will furthermore arrange for the products and manufacturing sites included in the list to be re-evaluated at regular intervals. If, as a result of this re-evaluation, it is found that a product and/or specified manufacturing site no longer complies with the WHO-recommended standards, such products and manufacturing sites will be removed from

the list. Failure of a manufacturer or applicant to participate in the re-evaluation procedure will also lead to removal from the list.

Re-evaluation, including re-inspections of manufacturing sites and CROs, would be done at regular intervals, based on risk assessment, but at least once every five years.

Re-evaluation, including re-inspections, should 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, became evident; and
- if WHO or any United Nations agency considered that a batch or batches of supplied prequalified pharmaceutical products were not in compliance with the specifications which were found to be applicable upon prequalification."

In order to define the documentation and information required from the applicants or manufacturers whereby the quality part of the prequalified product could be re-evaluated by WHO, a draft of the *Guidelines on the requalification of prequalified dossiers* had been developed by the quality assessors of the PQP.

These draft guidelines were circulated for comment and discussed at a meeting of the PQP assessment and inspector teams. The resulting revised draft was tabled and discussed at the consultation on WHO guidelines for medicines quality assurance, quality control laboratories and technology transfer in July 2009. At this meeting it was recommended that the document be tabled at the Expert Committee meeting for possible adoption. Following review during the consultation, the revised guidelines were once again circulated for comments.

The comments received were provided to the Committee in the form of a table.

Following discussion, the Expert Committee adopted these new guidelines (Annex 6).

9.3 Guidelines for the preparation of a contract research organization master file

WHO, PIC/S and several NMRAs recommended that manufacturers submit a site master file (SMF) for review when applying for registration of a medicine. An SMF is a document prepared by the manufacturer containing specific and factual GMP information about the production and/or control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations carried out in adjacent and nearby buildings. If only part of a pharmaceutical operation was carried out on

the site, the SMF needed to describe only those operations, e.g. analysis or packaging.

Some NMRAs were also inspecting clinical trials. Clinical trials were often conducted at CROs. During inspections at CROs by WHO prequalification inspectors it was observed that not all information regarding such CROs was available to inspectors when preparing for their inspections. In addition, in several cases, significant changes had been implemented by the CROs from the time of the conduct of a trial or bioequivalence study opposed to what was reflected in the study report. These included changes in key personnel, activities, and even location of the site. This often made inspections problematic as some of the core information regarding the site could no longer be verified.

After consultation with inspectors from NMRAs, sponsors and CROs, it was suggested that a document similar to the SMF would provide useful information in the preparation for an inspection, and for those responsible to review or perform a risk analysis when planning GCP or GLP inspections. The proposal of the establishment of a contract research organization master file (CROMF) was welcomed by all parties contacted. It could be seen as an extension of the existing recommendation for the SMF of a manufacturing facility.

An initial draft CROMF was prepared and circulated to specialists for initial comments. The comments were reviewed by the Secretariat and incorporated where appropriate. The draft was then widely circulated for comments, which were discussed and incorporated, after which the document was again widely circulated in line with the usual procedure.

The comments received were provided to the Expert Committee.

The Expert Committee took note of the update, reviewed the major comments received, and agreed and adopted the general principles. It furthermore agreed to the formation of a subgroup of specialists to review all comments in more detail and to prepare a new version of this working document for circulation to the Expert Committee members for ratification. This document was, therefore, adopted provided no major comments were received (Annex 7).

10. Nomenclature, terminology and databases

10.1 Quality assurance terminology

The update of the database, available on the WHO quality assurance web site (http://www.who.int/medicines/areas/quality_safety/quality_assurance/en/) was presented to the Committee, as well as a document

containing quality assurance terminology. The Expert Committee thanked the Secretariat for its work on the database and suggested making this information widely available.

In connection with the discussions during the WHO Governing Bodies' meetings, the issue of terminology for "counterfeit" and "substandard" medicines was raised.

Counterfeit medicines

Within the context of the work of the Expert Committee, definitions for "counterfeit medicines" were included in the glossaries of the following WHO guidelines (WHO Database on Quality Assurance: for updates see documents included in the meeting file and also on the Medicines web site: http://www.who.int/medicines/services/expertcommittees/pharmprep/TermListcategory.pdf).

In: WHO good distribution practices for pharmaceutical products *(fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations,* WHO Technical Report Series, No. 937, *2006)*.

In: WHO Guidelines for inspection of drug distribution channels *(thirty-fifth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations,* WHO Technical Report Series, No. 885, *1999)*.

In: WHO Guidelines on import procedures for pharmaceutical products *(thirty-fourth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations,* WHO Technical Report Series, No. 863, *1996)*.

Within the context of the work of the IMPACT Annual Meeting held in December 2008 in Hammamet, Tunisia) and based on the work done by the IMPACT Working group on Legislative and Regulatory Infrastructure, a new definition had been developed and was available at: http://www.who.int/impact/resources/IMPACTthirdgeneralmeeting_%20report.pdf.

These definitions are included in the *Draft principles and elements for national legislation against counterfeit medical products* which has been circulated for comments.

The Expert Committee:

— took note of the above and suggested closely following the feedback received regarding the suggested IMPACT definition with a view to further discussion of the outcome during the next meeting of the Expert Committee; and
— recommended the preparation of an overview on the definitions used in the various international, regional and national contexts.

The importance of including NMRAs in this discussion was stressed as their expertise was needed to differentiate between the different issues. It was proposed that this discussion take place during the upcoming ICDRA in 2010.

"Substandard medicines"

Within the context of the work of this Expert Committee, no officially adopted definition currently existed for "substandard medicines". As this question was raised frequently a "question and answer" had been introduced on the WHO web site as follows:

"What are substandard medicines?

Substandard medicines (also called out-of-specification (OOS) products) are genuine medicines produced by manufacturers authorized by the NMRA which do not meet quality specifications set for them by national standards.

Normally, each medicine that a manufacturer produces has to comply with quality standards and specifications. These standards and specifications are reviewed and assessed by the NMRA before the product is authorized for marketing."

The Expert Committee discussed the issue and agreed that there was a need for a definition. It suggested circulation of the proposal as amended during the meeting for comments within the usual consultative procedure.

10.2 International Nonproprietary Names

The Expert Committee was briefed on the activities of the International Nonproprietary Names (INN) Programme. In the past 11 years 1445 INN had been named. The Programme had developed an integrated data management system which would permit access from the Internet, allow worldwide multiusers, multiplatform application, with all the user tasks "integrated" within the process, standard and open-source technologies, secure and protected environment: confidentiality of data and process steps, electronic documentation at each step and track of each process step. The future steps for INN included the online INN Application, Report and Statistic Generator, offline use and integration with other databases.

10.3 Pharmacopoeial references

An update was given to the Expert Committee on the ongoing revision of the pharmacopoeial references and pharmacopoeia commission secretariats would be contacted. The updated references would be posted on the Medicines web site. The Committee welcomed this information being made available in its updated form.

11. Miscellaneous

11.1 WHO Model List of Essential Medicines

A paper presented by QSM (working document QAS/09.293/Rev.1) was discussed by the Expert Committee for the Selection and Use of Essential Medicines at its meeting in March 2009. The Expert Committee broadly endorsed the QSM proposals concerning:

- dosage form terminology; and
- expression of medicine strength.

The expanded Explanatory notes in the sixteenth edition of the WHO Model List of Essential Medicines (and in the second edition of the WHO Model List of Essential Medicines for Children) included a link to the Quality assurance area of the WHO Medicines web site and to the online text of the current edition of *The International Pharmacopoeia*. In addition, an Annex on dosage form terminology had been included. The Explanatory notes and Annex 1 (as published on the Medicines web site: http://www.who.int/selection_medicines/committees/expert/17/en/index.html) were presented to the Expert Committee on Specifications for Pharmaceutical Preparations for information.

With respect to the expression of medicines strengths, the Expert Committee for the Selection and Use of Essential Medicines agreed the principles that would be applied in future lists and requested its Secretariat to review the current entries and revise them accordingly. The principles were set out in the report of the Expert Committee; an extract from the unedited report, as made available on the WHO Medicines web site, was presented for information.

When revised in accordance with these principles, entries in cases where the API was not the active moiety would more clearly distinguish between:

- those for which the strength was expressed in terms of active moiety (the salt would be indicated in parentheses, e.g. “50 mg (as sodium salt)”)
- those for which the strength was expressed in terms of API (the salt would be given in full, e.g. “50 mg codeine phosphate”).

Where necessary, in instances of potential confusion (e.g. amodiaquine, quinine salts) a warning note would be included.

The Committee congratulated the Secretariat on its efforts to provide more clarity with regard to strengths and dosage form references within the Model List.

11.2 Update on stability

The revised working document on *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* was adopted by the Expert

Committee at its forty-third meeting after a long and intensive consultation process (see *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products,* Annex 2, WHO Technical Report Series, No. 953, 2009).

Appendix 1 included a *List of WHO Member States' required long-term stability conditions* as per information received from countries. Preference was given — based on the comments received from NMRAs — to providing "real" conditions required by national authorities. Completing the table for all WHO Member States proved to be a major challenge. However, thanks to IFPMA and special efforts made during and subsequent to the ICDRA meeting, the list could be completed. As a consequence the list comprised three different types of entries as follows.

Entries in bold type:
Information obtained through respective regional harmonization groups (e.g. Association of Southeast Asian Nations (ASEAN, ICH) and Gulf Cooperation Council (GCC)) and from official communications from NMRAs to WHO.

Entries in normal type:
Information collated during the 13th ICDRA in September 2008, from representatives of NMRAs.

Entries in italic type:
Information provided by IFPMA based on the references given in the guidelines.

Moreover, during and following the preparation of the Expert Committee report, the Secretariat actively contacted again, with the help of colleagues from the Medicines Regulatory Support Programme, those national authorities for which the entries were "informal" and/or in accordance with published studies.

The aim was to update the list on the Medicines web site upon receipt of confirmed new information from NMRAs. Any changes would be based on information received through official correspondence with accompanying reference to national guidance.

Detailed feedback was received from IFPMA regarding possible updates of the stability testing conditions for Afghanistan, Canada, Chile, India and Israel, as well as the labelling statements listed in Appendix 3 of the guidelines.

In accordance with the process described and suggested above for the update of the table in Appendix 1 of the stability guidelines, the Secretariat would, with the agreement of the Expert Committee:

— update the entry for Canada, as the official information had been received; and
— continue to contact the NMRAs of the other countries listed above with respect to the correctness of their entries.

As regards the proposal for the labelling information, intensive discussions were held on this topic during the consultation process. The final decision was to add the labelling statements in an Appendix as a recommendation. IFPMA might submit a concrete proposal which could be circulated for comments and discussed at the next Expert Committee meeting.

Implementation

Following the intense cooperation with the Quality Expert Working Groups within the ICH, the ICH web site included a new reference to the WHO stability guidelines as follows:

"Q1F: Stability Data Package for Registration Applications in Climatic Zones III and IV

➔ The ICH Steering Committee endorsed the withdrawal of the Q1F guideline at its meeting in Yokohama, June 2006 and decided to leave definition of storage conditions in Climatic Zones III and IV to the respective regions and WHO. Click here to open the Explanatory Note and have access to the WHO Stability Guideline in the electronic version of this report."

The Expert Committee endorsed:

— that updates of long-term conditions required for marketing authorization in WHO Member States would be made as received from authorities; and
— the suggestion to include the details of this major harmonization effort and resolution of any possible further concerns during the ICDRA meeting to be held in Singapore in 2010.

11.3 Diethylene glycol

Over the years accidental or deliberate counterfeiting of medicines with diethylene glycol (DEG) had occurred many times and in many countries. The first recorded incident occurred in the USA in 1937. The episode killed a large number of Americans, mostly children. The latest incident happened in Nigeria where an equally large number of people were reported to have died. Beyond Nigeria the toxic chemical had caused mass poisoning in Argentina, Bangladesh, China, Haïti, India, Nigeria, Panama and South Africa. Numerous articles and references have referred to detected cases

of deaths due to DEG poisoning during the past decades. However, it was not known how many unreported deaths had actually occurred since some victims might have perished without visiting a health-care facility or seeing medical doctors.

Investigation of some of the above-mentioned incidents had revealed the main contributing factors for the incidents to be:

- absence of control by NMRAs of the manufacture, export and import of glycerol and propylene glycol;
- purchase of glycerol and propylene glycol by pharmaceutical manufacturers from unreliable sources or through brokers and traders; and
- lack of testing of the quality of glycerol and propylene glycol prior to using them in the manufacture of pharmaceutical products.

The above situation clearly showed that unless strict controls and safeguard measures were put in place by NMRAs, more people would fall victim to DEG poisoning.

Following up on the recurring incidents of DEG poisoning the Expert Committee discussed a proposal to send out a general alert to the NMRAs which should include recommendations to prevent such events in the future. Extensive discussion took place and the proposed text was amended to include further details. It was decided to form a small group to work out the final text. The Committee endorsed the proposal in general and agreed that the working group should submit the final text to the Committee members for final adoption.

12. 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 in the area of quality assurance of medicines.

This Expert Committee 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 Committee 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 Programme on Prequalification of Medicines 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 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:

— WHO good practices for pharmaceutical quality control laboratories (Annex 1)
— WHO good manufacturing practices for active pharmaceutical ingredients (Annex 2)
— WHO good manufacturing practices for pharmaceutical products containing hazardous substances (Annex 3)

— WHO good manufacturing practices for sterile pharmaceutical products (Annex 4)
— WHO good distribution practices for pharmaceutical products (Annex 5)
— Guidelines on the requalification of prequalified dossiers (Annex 6)
— Guidelines for the preparation of a contract research organization master file (Annex 7)

For inclusion in *The International Pharmacopoeia*

The following monographs were adopted:

- *For antiretroviral medicines*
  - Lopinavir
  - Tenofovir disoproxil fumarate
  - Indinavir capsules
  - Saquinavir tablets
  - Tenofovir tablets
  - Lopinavir and ritonavir tablets
  - Efavirenz

- *For antimalarial medicines*
  - Amodiaquine tablets
  - Artesunate
  - Artesunate tablets
  - Quinine bisulfate tablets
  - Quinine sulfate tablets

- *For antituberculosis medicines*
  - Amikacin
  - Amikacin sulfate
  - Amikacin injection
  - Kanamycin monosulfate
  - Kanamycin acid sulfate
  - Kanamycin injection

- *For radiopharmaceuticals*
  - Iobenguane (^{131}I) injection
  - Samarium ethylene diamine tetramethylene phosphonate complex (^{153}Sm) injection
  - Sodium iodide (^{131}I) capsules
  - Sodium iothalamate (^{125}I) injection
  - Sodium phosphate (^{32}P) injection
  - Strontium chloride (^{89}Sr) injection
  - Technetium (^{99m}Tc) bicisate complex injection
  - Technetium (^{99m}Tc) exametazime complex injection
  - Technetium (^{99m}Tc) mebrofenin complex injection

- Technetium (^{99m}Tc) mertiatide injection
- Technetium (^{99m}Tc) succimer complex injection
- Technetium (^{99m}Tc) sulfur colloid injection
- Technetium (^{99m}Tc) tetrofosmin complex injection
- Technetium (^{99m}Tc) tin colloidal injection
- Technetium (^{99m}Tc) pyrophoshate tin complex injection
- Technetium (^{99m}Tc) methylene diphosphonate (MDP) complex injection
- Technetium (^{99m}Tc) sestamibi complex injection
- Yttrium silicate (^{90}Y) colloid injection

- *Other medicines*
  - Mebendazole
  - Oseltamivir phosphate
  - Oxytocin
  - Oxytocin injection

- *General monographs for*
  - Tablets
  - Capsules

- *General policy topics and general revision issues for*
  - Monographs title and strengths
  - Strengths available statement
  - Identity tests
  - Polymorphism

Adoption of new International Chemical Reference Substances

- Carbidopa
- Colchicine
- Lumefantrine
- DL-Methionine
- Naloxone hydrochloride
- Oseltamivir phosphate for system suitability
- Oseltamivir phosphate

And the following replacements

- Artemisinin
- Prednisone

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.

The International Pharmacopoeia

- Continue development of specifications for medicines in accordance with the work plan revised and adopted at this meeting.
- Continue the efforts of international collaboration in relation to the revision and inclusion of general methods and new monographs for excipients.
- Continue the preparatory work on the supplements to *The International Pharmacopoeia*, 4th edition and towards the 5th 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 of the ICRS web site.

External Quality Assurance Assessment Scheme

- Continue the External Quality Assurance Assessment Scheme (EQAAS) for pharmaceutical quality control laboratories with a new phase 5.

Good practices for pharmaceutical microbiology laboratories

- Continue the consultation process through preparation of a new text on good practices for pharmaceutical microbiology laboratories.

Good manufacturing practices (GMP) and manufacture

- Follow up on the revision process for GMP for biologicals currently being undertaken under the aegis of the Expert Committee on Biological Standardization.
- Follow up on development of the WHO guidelines on GMP for blood establishments currently being undertaken under the aegis of the Expert Committee on Biological Standardization and ensure that these new guidelines also be sent for comment to the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.
- Initiate the consultation process for a revision of the main principles of GMP, considering inclusion of the quality unit concept, quality risk management and product quality review.
- Initiate a revision process as identified for some paragraphs of the GMP for heating, ventilation and air-conditioning (HVAC).
- Review and initiate an update of the WHO guidelines on Hazard Analysis and Critical Control Points (HACCP) to cover new trends in quality risk management.

Transfer of technology

- Continue the development of the *WHO guidelines on transfer of technology*, giving special consideration to keeping the balance between GMP and business criteria, including the concept of quality by design and the possibility of optional requirements depending on the type of transfer.

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.
- Post the revised "Questions and Answers" on the functioning of the Scheme on the revised document on the WHO web site and include it in *WHO Drug Information*, with the possibility of receiving comments and reviewing any question(s) that might raise major concerns.

Good distribution practices (GDP) for pharmaceutical products

Follow up on development of the WHO guidelines on regulatory oversight on pharmaceutical cold chain management. Harmonized guidance for the storage and transport of temperature-sensitive pharmaceutical products is currently being developed under the aegis of the Expert Committee on Biological Standardization. Ensure that these new guidelines are also sent for comment to the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and to the IMPACT working group that developed the revision of the GDP.

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 updating the long-term stability testing requirements for marketing authorization in WHO Member States as received from authorities.
- Follow up on the recurring incidents of DEG poisoning, prepare a proposal for a general alert to the NMRAs, including recommendations to prevent such events in the future.

Quality assurance terminology

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

- Provide feedback from the Circular Letter mailed to all Member States regarding the terminology used within the national legislation for "counterfeit medicines" or equivalent terms used, with a view to further discussion of the outcome during the next meeting of the Expert Committee and possibly during the ICDRA.
- Circulate a proposal for a new definition for "substandard medicines" as discussed during the meeting.

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 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/FIP Training Workshop on Pharmaceutical Development with Focus on Paediatric Formulations, Mumbai, India; 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

WHO good practices for pharmaceutical quality control laboratories

General considerations

Glossary

Part one. Management and infrastructure

1. Organization and management
2. Quality management system
3. Control of documentation
4. Records
5. Data-processing equipment
6. Personnel
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8. Equipment, instruments and other devices
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Part two. Materials, equipment, instruments and other devices

10. Reagents
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Part three. Working procedures

14. Incoming samples
15. Analytical worksheet
16. Validation of analytical procedures
17. Testing
18. Evaluation of test results
19. Certificate of analysis
20. Retained samples

Part four. Safety

21. General rules

References

Appendix

Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

General considerations

The WHO Expert Committee on Specifications for Pharmaceutical Products adopted in 1999 the guidelines entitled *WHO Good practices for national pharmaceutical control laboratories*, which were published as Annex 3 of the WHO Technical Report Series, No. 902, 2002. As the other guidelines related to laboratory quality assurance have been updated and subsequent inspections for the compliance with the guidelines on good practices for national pharmaceutical control laboratories indicated that some sections were in need of improvement and clarification, it was considered necessary to prepare a revised text.

These guidelines provide advice on the quality management system within which the analysis of active pharmaceutical ingredients (APIs), excipients and pharmaceutical products should be performed to demonstrate that reliable results are obtained.

Compliance with the recommendations provided in these guidelines will help promote international harmonization of laboratory practices and will facilitate cooperation among laboratories and mutual recognition of results.

Special attention should be given to ensure the correct and efficient functioning of the laboratory. Planning and future budgets should ensure that the necessary resources are available inter alia for the maintenance of the laboratory, as well as for an appropriate infrastructure and energy supply. Means and procedures should be in place (in case of possible supply problems) to ensure that the laboratory can continue its activities.

These guidelines are applicable to any pharmaceutical quality control laboratory, be it national, commercial or nongovernmental. However, they do not include guidance for those laboratories involved in the testing of biological products, e.g. vaccines and blood products. Separate guidance for such laboratories is available.

These guidelines are consistent with the requirements of the *WHO guidelines for good manufacturing practices* (*1*) and with the requirements of the International Standard ISO/IEC 17025:2005 (*2*), and provide detailed guidance for laboratories performing quality control of medicines. The guidance specific to microbiology laboratories can be found in the draft working document *WHO guideline on good practices for pharmaceutical microbiology laboratories* (reference QAS/09.297).

The good practice outlined below is to be considered as a general guide and it may be adapted to meet individual needs provided that an equivalent level of quality assurance is achieved. The notes given provide clarification of the text or examples; they do not contain requirements which should be fulfilled to comply with these guidelines.

Pharmaceutical quality control testing is usually a matter of repetitive testing of samples of APIs or of a limited number of pharmaceutical products, whereas national quality control laboratories have to be able to deal with a much wider range of pharmaceutical substances and products and, therefore, have to apply a wider variety of test methods. Specific recommendations for national pharmaceutical quality control laboratories are addressed in the following text. Particular consideration is given to countries with limited resources wishing to establish a governmental pharmaceutical quality control laboratory, having recently done so, or which are planning to modernize an existing laboratory.

Quality control laboratories may perform some or all quality control activities, e.g. sampling, testing of APIs, excipients, packaging materials and/or pharmaceutical products, stability testing, testing against specifications and investigative testing.

For the quality of a medicine sample to be correctly assessed:

- The submission of a sample of an API, excipient or pharmaceutical product or a suspected counterfeit material to the laboratory, selected in accordance with national requirements, should be accompanied by a statement of the reason why the analysis has been requested.
- The analysis should be correctly planned and meticulously executed.
- The results should be competently evaluated to determine whether the sample complies with the specifications or other relevant criteria.

National pharmaceutical quality control laboratories

The government, normally through the national medicines regulatory authority (NMRA), may establish and maintain a pharmaceutical quality control laboratory to carry out the required tests and assays to verify that APIs, excipients and pharmaceutical products meet the prescribed specifications. Large countries may require several pharmaceutical quality control laboratories which conform to national legislation, and appropriate arrangements should, therefore, be in place to monitor their compliance with a quality management system. Throughout the process of marketing authorization and postmarketing surveillance, the laboratory or laboratories work closely with the NMRA.

A national pharmaceutical quality control laboratory provides effective support for an NMRA acting together with its inspection services. The analytical results obtained should accurately describe the properties of the samples assessed, permitting correct conclusions to be drawn about the quality of the samples of medicines analysed, and also serving as an adequate basis for any subsequent administrative regulations and legal action.

National pharmaceutical quality control laboratories usually encompass essentially two types of activity:

— compliance testing of APIs, pharmaceutical excipients and pharmaceutical products employing "official" methods including pharmacopoeial methods, validated analytical procedures provided by the manufacturer and approved by the relevant government authority for marketing authorization or validated analytical procedures developed by the laboratory; and
— investigative testing of suspicious, illegal, counterfeit substances or products, submitted for examination by medicine inspectors, customs or police.

To ensure patient safety, the role of the national pharmaceutical quality control laboratory should be defined in the general pharmaceutical legislation of the country in such a way that the results provided by it can, if necessary, lead to enforcement of the law and legal action.

Glossary

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

acceptance criterion for an analytical result

Predefined and documented indicators by which a result is considered to be within the limit(s) or to exceed the limit(s) indicated in the specification.

accuracy

The degree of agreement of test results with the true value or the closeness of the results obtained by the procedure to the true value (*1*).

Note: It is normally established on samples of the material to be examined that have been prepared to quantitative accuracy. Accuracy should be established across the specified range of the analytical procedure. It is generally acceptable to use a "spiked" placebo which contains a known quantity or concentration of a reference substance.

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 (*1*).

analytical test report

An analytical test report usually includes a description of the test procedure(s) employed, results of the analysis, discussion and conclusions and/or recommendations for one or more samples submitted for testing (see Part three, sections 18.7–18.11).

analytical worksheet

A printed form, an analytical workbook or electronic means (e-records) for recording information about the sample, as well as reagents and solvents used, test procedure applied, calculations made, results and any other relevant information or comments (see Part three, section 15).

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 should 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 (*1*).

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 (*1*).

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 (*1*).

certificate of analysis

The list of test procedures applied to a particular sample with the results obtained and the acceptance criteria applied. It indicates whether or not the sample complies with the specification (*3*).

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 (*4*).

compliance testing

Analysis of active pharmaceutical ingredients (APIs), pharmaceutical excipients, packaging material or pharmaceutical products according to the requirements of a pharmacopoeial monograph or a specification in an approved marketing authorization.

control sample

A sample used for testing the continued accuracy and precision of the procedure. It should have a matrix similar to that of the samples to be analysed. It has an assigned value with its associated uncertainty.

design qualification (DQ)

Documented collection of activities that define the functional and operational specifications of the instrument and criteria for selection of the vendor, based on the intended purpose of the instrument.

Note: Selection and purchase of a new instrument should follow a conscious decision process, based on the needs of the technical management. When designing a new laboratory facility, the design specification and the requirements for services should be agreed between the management team and the agreed suppliers and documented.

good manufacturing practice(s) (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 (*1*).

installation qualification (IQ)

The performance of tests to ensure that the analytical equipment used in a laboratory is correctly installed and operates in accordance with established specifications.

management review

A formal, documented review of the key performance indicators of a quality management system performed by top management.

manufacturer

A company that carries out operations such as production, packaging, testing, repackaging, labelling and/or relabelling of pharmaceuticals (*1*).

marketing authorization (product licence, registration certificate)

A legal document issued by the competent medicines regulatory authority that authorizes the marketing or free distribution of a pharmaceutical product in the respective country after evaluation for safety, efficacy and quality. In terms of quality it establishes inter alia the detailed composition and formulation of the pharmaceutical product and the quality requirements for the product and its ingredients. It also includes details of packaging, labelling, storage conditions, shelf-life and approved conditions of use.

measurement uncertainty

Non-negative parameter characterizing the dispersion of quantity values being attributed to a measurand (analyte), based on the information used (*4*).

metrological traceability

Property of a measurement result whereby the result can be related to a reference through a documented, unbroken chain of calibrations, each contributing to the measurement uncertainty (*4*).

operational qualification (OQ)

Documented verification that the analytical equipment performs as intended over all anticipated operating ranges.

out-of-specification (OOS) result

All test results that fall outside the specifications or acceptance criteria established in product dossiers, drug master files, pharmacopoeias or by the manufacturer (*5*).

performance qualification (PQ)

Documented verification that the analytical equipment operates consistently and gives reproducibility within the defined specifications and parameters for prolonged periods.

pharmaceutical excipient

A substance, other than the active pharmaceutical ingredient (API), which has been appropriately evaluated for safety and is included in a medicines delivery system to:

— aid in the processing of the medicines delivery system during its manufacture;
— protect, support or enhance stability, bioavailability or patient acceptability;
— assist in pharmaceutical product identification; or
— enhance any other attribute of the overall safety and effectiveness of the medicine during its storage or use (*6*, *7*).

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, which is subject to control by pharmaceutical legislation in the exporting state and/or the importing state (*1*).

precision

The degree of agreement among individual results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample. Precision, usually expressed as relative standard deviation, may be considered at three levels: repeatability (precision under the same operating conditions over a short period of time), intermediate precision (within laboratory variations — different days, different analysts or different equipment) and reproducibility (precision between laboratories).

primary reference substance (or standard)

A substance that is widely acknowledged to possess the appropriate qualities within a specified context, and whose assigned content is accepted without requiring comparison with another chemical substance (*8*).

Note: Pharmacopoeial chemical reference substances are considered to be primary reference substances. In the absence of a pharmacopoeial reference substance, a manufacturer should establish a primary reference substance.

qualification of equipment

Action of proving and documenting that any analytical equipment complies with the required specifications and performs suitably for its intended purpose (see Part two, section 12).

quality control

All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

quality management system

An appropriate infrastructure, 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 (see Part one, section 2).

quality manager

A member of staff who has a defined responsibility and authority for ensuring that the management system related to quality is implemented and followed at all times (see Part one, section 1.3(j)).

quality manual

A handbook that describes the various elements of the quality management system for assuring the quality of the test results generated by a laboratory (see Part one, sections 2.1–2.2).

quality unit(s)

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

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 (*4*).

reference substance (or standard)

An authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use (*8*).

secondary reference substance (or standard)

A substance whose characteristics are assigned and/or calibrated by comparison with a primary reference substance. The extent of characterization and testing of a secondary reference substance may be less than for a primary reference substance (*8*).

Note: Often referred to as an "in-house" working standard.

signature (signed)

Record of the individual who performed a particular action or review. The record can be initials, full handwritten signature, personal seal or authenticated and secure electronic signature.

specification

A list of detailed requirements (acceptance criteria for the prescribed test procedures) with which the substance or pharmaceutical product has to conform to ensure suitable quality.

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations both general and specific.

standard uncertainty

Uncertainty of the result of a measurement expressed as a standard deviation (*4*, *9*, *10*).

system suitability test

A test which is performed to ensure that the analytical procedure fulfils the acceptance criteria which had been established during the validation of the procedure. This test is performed before starting the analytical procedure and is to be repeated regularly, as appropriate, throughout the analytical run to ensure that the system's performance is acceptable at the time of the test.

validation of an analytical procedure

The documented process by which an analytical procedure (or method) is demonstrated to be suitable for its intended use.

verification of an analytical procedure

Process by which a pharmacopoeial method or validated analytical procedure is demonstrated to be suitable for the analysis to be performed.

verification of performance

Test procedure regularly applied to a system (e.g. liquid chromatographic system) to demonstrate consistency of response.

Part One. Management and infrastructure

1. Organization and management

1.1 The laboratory, or the organization of which it is part, should be an entity that is legally authorized to function and can be held legally responsible.

1.2 The laboratory should be organized and operate so as to meet the requirements laid down in these guidelines.

1.3 The laboratory should:

(a) have managerial and technical personnel with the authority and resources needed to carry out their duties and to identify the occurrence of departures from the quality management system or the procedures for performing tests and/or calibrations, validation and verification, and to initiate actions to prevent or minimize such departures;

(b) have arrangements to ensure that its management and personnel are not subject to commercial, political, financial and other

pressures or conflicts of interest that may adversely affect the quality of their work;

(c) have a policy and procedure in place to ensure confidentiality of
— information contained in marketing authorizations,
— transfer of results or reports,
— and to protect data in archives (paper and electronic);

(d) define, with the aid of organizational charts, the organization and management structure of the laboratory, its place in any parent organization (such as the ministry or the NMRA in the case of a national pharmaceutical quality control laboratory), and the relationships between management, technical operations, support services and the quality management system;

(e) specify the responsibility, authority and interrelationships of all personnel who manage, perform or verify work which affects the quality of the tests and/or calibrations, validations and verifications;

(f) ensure the precise allocation of responsibilities, particularly in the designation of specific units for particular types of medicines;

(g) nominate trained substitutes/deputies for key management and specialized scientific personnel;

(h) provide adequate supervision of staff, including trainees, by persons familiar with the test and/or calibration, validation and verification methods and procedures, as well as their purpose and the assessment of the results;

(i) have management which has overall responsibility for the technical operations and the provision of resources needed to ensure the required quality of laboratory operations;

(j) designate a member of staff as quality manager who, irrespective of other duties he/she may have, will ensure compliance with the quality management system. The nominated quality manager should have direct access to the highest level of management at which decisions are taken on laboratory policies or resources;

(k) ensure adequate information flow between staff at all levels. Staff are to be made aware of the relevance and importance of their activities;

(l) ensure the traceability of the sample from receipt, throughout the stages of testing, to the completion of the analytical test report;

(m) maintain an up-to-date collection of all specifications and related documents (paper or electronic) used in the laboratory; and

(n) have appropriate safety procedures (see Part four).

1.4 The laboratory should maintain a registry with the following functions:

(a) receiving, distributing and supervising the consignment of the samples to the specific units; and
(b) keeping records on all incoming samples and accompanying documents.

1.5 In a large laboratory, it is necessary to guarantee communication and coordination between the staff involved in the testing of the same sample in different units.

2. Quality management system

2.1 The laboratory or organization management should establish, implement and maintain a quality management system appropriate to the scope of its activities, including the type, range and volume of testing and/or calibration, validation and verification activities it undertakes. The laboratory management should ensure that its policies, systems, programmes, procedures and instructions are described to the extent necessary to enable the laboratory to assure the quality of the test results that it generates. The documentation used in this quality management system should be communicated, available to, and understood and implemented by, the appropriate personnel. The elements of this system should be documented, e.g. in a quality manual, for the organization as a whole and/or for a laboratory within the organization.

Note: Quality control laboratories of a manufacturer may have this information in other documents than a quality manual.

2.2 The quality manual should contain as a minimum:

(a) a quality policy statement, including at least the following:
  (i) a statement of the laboratory management's intentions with respect to the standard of service it will provide,
  (ii) a commitment to establishing, implementing and maintaining an effective quality management system,
  (iii) the laboratory management's commitment to good professional practice and quality of testing, calibration, validation and verification,
  (iv) the laboratory management's commitment to compliance with the content of these guidelines,
  (v) a requirement that all personnel concerned with testing and calibration activities within the laboratory familiarize themselves with the documentation concerning quality and

the implementation of the policies and procedures in their work;

(b) the structure of the laboratory (organizational chart);
(c) the operational and functional activities pertaining to quality, so that the extent and the limits of the responsibilities are clearly defined;
(d) outline of the structure of documentation used in the laboratory quality management system;
(e) the general internal quality management procedures;
(f) references to specific procedures for each test;
(g) information on the appropriate qualifications, experience and competencies that personnel are required to possess;
(h) information on initial and in-service training of staff;
(i) a policy for internal and external audit;
(j) a policy for implementing and verifying corrective and preventive actions;
(k) a policy for dealing with complaints;
(l) a policy for performing management reviews of the quality management system;
(m) a policy for selecting, establishing and approving analytical procedures;
(n) a policy for handling of OOS results;
(o) a policy for the employment of appropriate reference substances and reference materials;
(p) a policy for participation in appropriate proficiency testing schemes and collaborative trials and the evaluation of the performance (applicable to national pharmaceutical quality control laboratories, but may be applied by other laboratories); and
(q) a policy to select service providers and suppliers.

2.3 The laboratory should establish, implement and maintain authorized written SOPs including, but not limited to, administrative and technical operations, such as:

(a) personnel matters, including qualifications, training, clothing and hygiene;
(b) the change control;
(c) internal audit;
(d) dealing with complaints;
(e) implementation and verification of corrective and preventive actions;
(f) the purchase and receipt of consignments of materials (e.g. samples, reagents);

(g) the procurement, preparation and control of reference substances and reference materials (*8*);
(h) the internal labelling, quarantine and storage of materials;
(i) the qualification of equipment (*11*);
(j) the calibration of equipment;
(k) preventive maintenance and verification of instruments and equipment;
(l) sampling, if performed by the laboratory, and visual inspection;
(m) the testing of samples with descriptions of the methods and equipment used;
(n) atypical and OOS results;
(o) validation of analytical procedures;
(p) cleaning of laboratory facilities, including bench tops, equipment, work stations, clean rooms (aseptic suites) and glassware;
(q) monitoring of environmental conditions, e.g. temperature and humidity;
(r) monitoring storage conditions;
(s) disposal of reagents and solvent samples; and
(t) safety measures.

2.4 The activities of the laboratory should be systematically and periodically audited (internally and, where appropriate, by external audits or inspections) to verify compliance with the requirements of the quality management system and to apply corrective and preventive actions, if necessary. The audits should be carried out by trained and qualified personnel, who are independent of the activity to be audited. The quality manager is responsible for planning and organizing internal audits addressing all elements of the quality management system. Such audits should be recorded, together with details of any corrective and preventive action taken.

2.5 Management review of quality issues should be regularly undertaken (at least annually), including:

(a) reports on internal and external audits or inspections and any follow-up required to correct any deficiencies;
(b) the outcome of investigations carried out as a result of complaints received, doubtful (atypical) or aberrant results reported in collaborative trials and/or proficiency tests; and
(c) corrective actions applied and preventive actions introduced as a result of these investigations.

3. Control of documentation

3.1 Documentation is an essential part of the quality management system. The laboratory should establish and maintain procedures

to control and review all documents (both internally generated and from external sources) that form part of the quality documentation. A master list identifying the current version status and distribution of documents should be established and readily available.

3.2 The procedures should ensure that:

(a) each document, whether a technical or a quality document, has a unique identifier, version number and date of implementation;
(b) appropriate, authorized SOPs are available at the relevant locations, e.g. near instruments;
(c) documents are kept up to date and reviewed as required;
(d) any invalid document is removed and replaced with the authorized, revised document with immediate effect;
(e) a revised document includes references to the previous document;
(f) old, invalid documents are retained in the archives to ensure traceability of the evolution of the procedures; any copies are destroyed;
(g) all relevant staff are trained for the new and revised SOPs; and
(h) quality documentation, including records, is retained for a minimum of five years.

3.3 A system of change control should be in place to inform staff of new and revised procedures. The system should ensure that:

(a) revised documents are prepared by the initiator, or a person who performs the same function, reviewed and approved at the same level as the original document and subsequently released by the quality manager (quality unit); and
(b) staff acknowledge by a signature that they are aware of applicable changes and their date of implementation.

4. Records

4.1 The laboratory should establish and maintain procedures for the identification, collection, indexing, retrieval, storage, maintenance and disposal of and access to all quality and technical/scientific records.

4.2 All original observations, including calculations and derived data, calibration, validation and verification records and final results, should be retained on record for an appropriate period of time in accordance with national regulations and, if applicable, contractual arrangements, whichever is longer. The records should include the data recorded in the analytical worksheet by the technician or analyst

on consecutively numbered pages with references to the appendices containing the relevant recordings, e.g. chromatograms and spectra. The records for each test should contain sufficient information to permit the tests to be repeated and/or the results to be recalculated, if necessary. The records should include the identity of the personnel involved in the sampling, preparation and testing of the samples. The records of samples to be used in legal proceedings should be kept according to the legal requirements applicable to them.

Note: The generally accepted retention period of shelf-life plus one year for a pharmaceutical product on the market and 15 years for an investigational product is recommended, unless national regulations are more stringent or contractual arrangements do not require otherwise.

4.3 All quality and technical/scientific records (including analytical test reports, certificates of analysis and analytical worksheets) should be legible, readily retrievable, stored and retained within facilities that provide a suitable environment that will prevent modification, damage or deterioration and/or loss. The conditions under which all original records are stored should be such as to ensure their security and confidentiality and access to them should be restricted to authorized personnel. Electronic storage and signatures may also be employed but with restricted access and in conformance with requirements for electronic records (*12–16*).

4.4 Quality management records should include reports from internal (and external if performed) audits and management reviews, as well as records of all complaints and their investigations, including records of possible corrective and preventive actions.

5. Data-processing equipment

5.1 Detailed recommendations are provided in Appendix 5 to Annex 4 of the *Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*: Supplementary guidelines in good manufacturing practice: validation. Validation of computerized systems (*12*).

5.2 For computers, automated tests or calibration equipment, and the collection, processing, recording, reporting, storage or retrieval of test and/or calibration data, the laboratory should ensure that:

(a) computer software developed by the user is documented in sufficient detail and appropriately validated or verified as being suitable for use;

(b) procedures are established and implemented for protecting the integrity of data. Such procedures should include, but are not limited to, measures to ensure the integrity and confidentiality of data entry or collection and the storage, transmission and processing of data. In particular, electronic data should be protected from unauthorized access and an audit trail of any amendments should be maintained;
(c) computers and automated equipment are maintained so as to function properly and are provided with the environmental and operating conditions necessary to ensure the integrity of test and calibration data;
(d) procedures are established and implemented for making, documenting and controlling changes to information stored in computerized systems; and
(e) electronic data should be backed up at appropriate regular intervals according to a documented procedure. Backed-up data should be retrievable and stored in such a manner as to prevent data loss.

Note: For further guidance on validation of data-processing equipment, refer to documents published by the International Society for Pharmaceutical Engineering (*13, 14*), US Food and Drug Administration (*15*), European Commission (*16*) and the Official Medicines Control Laboratories Network of the Council of Europe (*17*).

6. Personnel

6.1 The laboratory should have sufficient personnel with the necessary education, training, technical knowledge and experience for their assigned functions.

6.2 The technical management should ensure the competence of all personnel operating specific equipment, instruments or other devices, who are performing tests and/or calibrations, validations or verifications. Their duties also involve the evaluation of results as well as signing analytical test reports and certificates of analysis (see Part three, sections 18.7–18.11 and 19).

6.3 Staff undergoing training should be appropriately supervised and should be assessed on completion of the training. Personnel performing specific tasks should be appropriately qualified in terms of their education, training and experience, as required.

6.4 The laboratory personnel should be permanently employed or under contract. The laboratory should ensure that additional technical and key support personnel who are under contract are supervised and

sufficiently competent and that their work is in accordance with the quality management system.

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

6.6 The laboratory should have the following managerial and technical personnel:

(a) a head of laboratory (supervisor), who should have qualifications appropriate to the position, with extensive experience in medicines analysis and laboratory management in a pharmaceutical quality control laboratory in the regulatory sector or in industry. The head of laboratory is responsible for the content of certificates of analysis and analytical testing reports. This person is also responsible for ensuring that:
  (i) all key members of the laboratory staff have the requisite competence for the required functions and their grades reflect their responsibilities,
  (ii) the adequacy of existing staffing, management and training procedures is reviewed periodically,
  (iii) the technical management is adequately supervised;

(b) the technical management who ensure that:
  (i) procedures for performing calibration, verification and (re-) qualification of instruments, monitoring of environmental and storage conditions are in place and are conducted as required,
  (ii) regular in-service training programmes to update and extend the skills of both professionals and technicians are arranged,
  (iii) the safekeeping of any materials subject to poison regulation or to the controls applied to narcotic and psychotropic substances (see Part one, section 7.12) kept in the workplace is under the supervision of an authorized person,
  (iv) national pharmaceutical quality control laboratories regularly participate in suitable proficiency testing schemes and collaborative trials to assess analytical procedures or reference substances;

(c) analysts, who should normally be graduates in pharmacy, analytical chemistry, microbiology or other relevant subjects,

with the requisite knowledge, skills and ability to adequately perform the tasks assigned to them by management and to supervise technical staff;

(d) technical staff, who should hold diplomas in their subjects awarded by technical or vocational schools; and

(e) a quality manager (see Part one, section 1.3(j)).

7. Premises

7.1 The laboratory facilities are to be of a suitable size, construction and location. These facilities are to be designed to suit the functions and operations to be conducted in them. Rest and refreshment rooms should be separate from laboratory areas. Changing areas and toilets should be easily accessible and appropriate for the number of users.

7.2 The laboratory facilities should have adequate safety equipment located appropriately and measures should be in place to ensure good housekeeping. Each laboratory should be equipped with adequate instruments and equipment, including work benches, work stations and fume hoods.

7.3 The environmental conditions, including lighting, energy sources, temperature, humidity and air pressure, are to be appropriate to the functions and operations to be performed. The laboratory should ensure that the environmental conditions are monitored, controlled and documented and do not invalidate the results or adversely affect the quality of the measurements.

7.4 Special precautions should be taken and, if necessary, there should be a separate and dedicated unit or equipment (e.g. isolator, laminar flow work bench) to handle, weigh and manipulate highly toxic substances, including genotoxic substances. Procedures should be in place to avoid exposure and contamination.

7.5 Archive facilities should be provided to ensure the secure storage and retrieval of all documents. The design and condition of the archives should be such as to protect the contents from deterioration. Access to the archives should be restricted to designated personnel.

7.6 Procedures should be in place for the safe removal of types of waste including toxic waste (chemical and biological), reagents, samples, solvents and air filters.

7.7 Microbiological testing, if performed, should be contained in an appropriately designed and constructed laboratory unit. For further guidance see the draft working document *WHO guideline on good*

practices for pharmaceutical microbiology laboratories (reference QAS/09.297).

7.8 If in vivo biological testing (e.g. rabbit pyrogen test) is included in the scope of the laboratory activities then the animal houses should be isolated from the other laboratory areas with a separate entrance and air-conditioning system. The relevant guidance and regulations are to be applied (*18*).

Laboratory storage facilities

7.9 The storage facilities should be well organized for the correct storage of samples, reagents and equipment.

7.10 Separate storage facilities should be maintained for the secure storage of samples, retained samples (see Part three, section 20), reagents and laboratory accessories (see Part two, sections 10.13–10.14), reference substances and reference materials (see Part two, section 11). Storage facilities should be equipped to store material, if necessary, under refrigeration (2–8°C) and frozen (-20°C) and securely locked. All specified storage conditions should be controlled, monitored and records maintained. Access should be restricted to designated personnel.

7.11 Appropriate safety procedures should be drawn up and rigorously implemented wherever toxic or flammable reagents are stored or used. The laboratory should provide separate rooms or areas for storing flammable substances, fuming and concentrated acids and bases, volatile amines and other reagents, such as hydrochloric acid, nitric acid, ammonia and bromine. Self-igniting materials, such as metallic sodium and potassium, should also be stored separately. Small stocks of acids, bases and solvents may be kept in the laboratory store but the main stocks of these items should preferably be retained in a store separate from the laboratory building.

7.12 Reagents subject to poison regulations or to the controls applied to narcotic and psychotropic substances should be clearly marked as required by national legislation. They should be kept separately from other reagents in locked cabinets. A designated responsible member of staff should maintain a register of these substances. The head of each unit should accept personal responsibility for the safekeeping of any of these reagents kept in the workplace.

7.13 Gases also should be stored in a dedicated store, if possible isolated from the main building. Wherever possible gas bottles in the laboratory are to be avoided and distribution from an external gas

store is preferred. If gas bottles are present in the laboratory they should be safely secured.

Note: Consideration should be given to the installation of gas generators.

8. Equipment, instruments and other devices

8.1 Equipment, instruments and other devices should be designed, constructed, adapted, located, calibrated, qualified, verified and maintained as required by the operations to be carried out in the local environment. The user should purchase the equipment from an agent capable of providing full technical support and maintenance when necessary.

8.2 The laboratory should have the required test equipment, instruments and other devices for the correct performance of the tests and/or calibrations, validations and verifications (including the preparation of samples and the processing and analysis of test and/or calibration data).

8.3 Equipment, instruments and other devices, including those used for sampling, should meet the laboratory's requirements and comply with the relevant standard specifications, as well as being verified, qualified and/or calibrated regularly (see Part two, section 12).

9. Contracts

Purchasing services and supplies

9.1 The laboratory should have a procedure for the selection and purchasing of services and supplies it uses that affect the quality of testing.

9.2 The laboratory should evaluate suppliers of critical consumables, supplies and services which affect quality of testing, maintain records of these evaluations and list approved suppliers, which have been demonstrated to be of a suitable quality with respect to the requirements of the laboratory.

Subcontracting of testing

9.3 When a laboratory subcontracts work, which may include specific testing, it is to be done with organizations approved for the type of activity required. The laboratory is responsible for periodically assessing the competence of a contracted organization.

9.4 When a laboratory performs testing for a customer and subcontracts part of the testing, it should advise the customer of the arrangement in writing and, if appropriate, gain his or her approval.

9.5 There should be a written contract which clearly establishes the duties and responsibilities of each party, defines the contracted work and any technical arrangements made in connection with it. The contract should permit the laboratory to audit the facilities and competencies of the contracted organization and ensure the access of the laboratory to records and retained samples.

9.6 The contracted organization should not pass to a third party any work entrusted to it under contract without the laboratory's prior evaluation and approval of the arrangements.

9.7 The laboratory should maintain a register of all subcontractors that it uses and a record of the assessment of the competence of subcontractors.

9.8 The laboratory takes the responsibility for all results reported, including those furnished by the subcontracting organization.

Part two. Materials, equipment, instruments and other devices

10. Reagents

10.1 All reagents and chemicals, including solvents and materials used in tests and assays, should be of appropriate quality.

10.2 Reagents should be purchased from reputable, approved suppliers and should be accompanied by the certificate of analysis, and the material safety data sheet, if required.

10.3 In the preparation of reagent solutions in the laboratory:

(a) responsibility for this task should be clearly specified in the job description of the person assigned to carry it out; and
(b) prescribed procedures should be used which are in accordance with published pharmacopoeial or other standards where available. Records should be kept of the preparation and standardization of volumetric solutions.

10.4 The labels of all reagents should clearly specify:

(a) content;
(b) manufacturer;
(c) date received and date of opening of the container;
(d) concentration, if applicable;
(e) storage conditions; and
(f) expiry date or retest date, as justified.

10.5 The labels of reagent solutions prepared in the laboratory should clearly specify:

(a) name;
(b) date of preparation and initials of technician or analyst;
(c) expiry date or retest date, as justified; and
(d) concentration, if applicable.

10.6 The labels for volumetric solutions prepared in the laboratory should clearly specify:

(a) name;
(b) molarity (or concentration);
(c) date of preparation and initials of technician/analyst;
(d) date of standardization and initials of technician/analyst; and
(e) standardization factor.

Note: The laboratory should ensure that the volumetric solution is suitable for use at the time of use.

10.7 In the transportation and subdivision of reagents:

(a) whenever possible they should be transported in the original containers; and
(b) when subdivision is necessary, clean containers should be used and appropriately labelled.

Visual inspection

10.8 All reagent containers should be visually inspected to ensure that the seals are intact, both when they are delivered to the store and when they are distributed to the units.

10.9 Reagents that appear to have been tampered with should be rejected; however, this requirement may exceptionally be waived if the identity and purity of the reagent concerned can be confirmed by testing.

Water

10.10 Water should be considered as a reagent. The appropriate grade for a specific test should be used as described in the pharmacopoeias or in an approved test when available.

10.11 Precautions should be taken to avoid contamination during its supply, storage and distribution.

10.12 The quality of the water should be verified regularly to ensure that the various grades of water meet the appropriate specifications.

Storage

10.13 Stocks of reagents should be maintained in a store under the appropriate storage conditions (ambient temperature, under refrigeration or frozen). The store should contain a supply of clean bottles, vials, spoons, funnels and labels, as required, for dispensing reagents from larger to smaller containers. Special equipment may be needed for the transfer of larger volumes of corrosive liquids.

10.14 The person in charge of the store is responsible for looking after the storage facilities and their inventory and for noting the expiry date of chemicals and reagents. Training may be needed in handling chemicals safely and with the necessary care.

11. Reference substances and reference materials

11.1 Reference substances (primary reference substances or secondary reference substances (*8*)) are used for the testing of a sample.

Note: Pharmacopoeial reference substances should be employed when available and appropriate for the analysis. When a pharmacopoeia reference substance has not been established then the manufacturer should use its own reference substance.

11.2 Reference materials may be necessary for the calibration and/or qualification of equipment, instruments or other devices.

Registration and labelling

11.3 An identification number should be assigned to all reference substances, except for pharmacopoeial reference substances.

11.4 A new identification number should be assigned to each new batch.

11.5 This number should be marked on each vial of the reference substance.

11.6 The identification number should be quoted on the analytical worksheet every time the reference substance is used (see Part three, section 15.5). In the case of pharmacopoeial reference substances the batch number and/or the batch validity statement should be attached to the worksheet.

11.7 The register for all reference substances and reference materials should be maintained and contain the following information:

(a) the identification number of the substance or material;
(b) a precise description of the substance or material;
(c) the source;

(d) the date of receipt;
(e) the batch designation or other identification code;
(f) the intended use of the substance or material (e.g. as an infrared reference substance or as an impurity reference substance for thin-layer chromatography);
(g) the location of storage in the laboratory, and any special storage conditions;
(h) any further necessary information (e.g. the results of visual inspections);
(i) expiry date or retest date;
(j) certificate (batch validity statement) of a pharmacopoeial reference substance and a certified reference material which indicates its use, the assigned content, if applicable, and its status (validity); and
(k) in the case of secondary reference substances prepared and supplied by the manufacturer, the certificate of analysis.

11.8 A person should be nominated to be responsible for reference substances and reference materials.

11.9 If a national pharmaceutical quality control laboratory is required to establish reference substances for use by other institutions, a separate reference substances unit should be established.

11.10 In addition a file should be kept in which all information on the properties of each reference substance is entered including the safety data sheets.

11.11 For reference substances prepared in the laboratory, the file should include the results of all tests and verifications used to establish the reference substances and expiry date or retest date; these should be signed by the responsible analyst.

Retesting (monitoring)

11.12 All reference substances prepared in the laboratory or supplied externally should be retested at regular intervals to ensure that deterioration has not occurred. The interval for retesting depends on a number of factors, including stability of the substance, storage conditions employed, type of container and extent of use (how often the container is opened and closed). More detailed information on the handling, storage and retesting of reference substances is given in the *WHO General guidelines for the establishment, maintenance and distribution of chemical reference substances* (*8*).

11.13 The results of these tests should be recorded and signed by the responsible analyst.

11.14 In the case that the result of retesting of a reference substance is non-compliant, a retrospective check of tests performed using this reference substance since its previous examination should be carried out. For evaluation of outcomes of retrospective checks and consideration of possible corrective actions, risk analysis should be applied.

11.15 Pharmacopoeial reference substances are regularly retested and the validity (current status) of these reference substances is available from the issuing pharmacopoeia by various means, e.g. web sites or catalogues. Retesting by the laboratory is not necessary, provided the reference substances are stored in accordance with the storage conditions indicated.

12. Calibration, verification of performance and qualification of equipment, instruments and other devices

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

12.2 All equipment, instruments and other devices (e.g. volumetric glassware and automatic dispensers) requiring calibration should be labelled, coded or otherwise identified to indicate the status of calibration and the date when recalibration is due.

12.3 Laboratory equipment should undergo design qualification, installation qualification, operation qualification and performance qualification (for definitions of these terms see the Glossary) (*11*). Depending on the function and operation of the instrument, the design qualification of a commercially available standard instrument may be omitted as the installation qualification, operational qualification and performance qualification may be considered to be a sufficient indicator of its suitable design.

12.4 As applicable, the performance of equipment should be verified at appropriate intervals according to a plan established by the laboratory.

12.5 Measuring equipment should be regularly calibrated according to a plan established by the laboratory (*11*).

12.6 Specific procedures should be established for each type of measuring equipment, taking into account the type of equipment, the extent of use and supplier's recommendations. For example:

— pH meters are verified with standard certified buffer solutions before use;

— balances are to be checked daily using internal calibration and regularly using suitable test weights, and requalification should be performed annually using certified reference weights.

12.7 Only authorized personnel should operate equipment, instruments and devices. Up-to-date SOPs on the use, maintenance, verification, qualification and calibration of equipment, instruments and devices (including any relevant manuals provided by the manufacturer) should be readily available for use by the appropriate laboratory personnel together with a schedule of the dates on which verification and/or calibration is due.

12.8 Records should be kept of each item of equipment, instrument or other device used to perform testing, verification and/or calibration. The records should include at least the following:

(a) the identity of the equipment, instrument or other device;
(b) the manufacturer's name and the equipment model, serial number or other unique identification;
(c) the qualification, verification and/or calibration required;
(d) the current location, where appropriate;
(e) the equipment manufacturer's instructions, if available, or an indication of their location;
(f) the dates, results and copies of reports, verifications and certificates of all calibrations, adjustments, acceptance criteria and the due date of the next qualification, verification and/or calibration;
(g) the maintenance carried out to date and the maintenance plan; and
(h) a history of any damage, malfunction, modification or repair.

It is also recommended that records should be kept and additional observations made of the time for which the equipment, instruments or devices were used.

12.9 Procedures should include instructions for the safe handling, transport and storage of measuring equipment. On reinstallation, requalification of the equipment is required to ensure that it functions properly.

12.10 Maintenance procedures should be established, e.g. regular servicing should be performed by a team of maintenance specialists, whether internal or external, followed by verification of performance.

12.11 Equipment, instruments and other devices, either subjected to overloading or mishandling, giving suspect results, shown to be defective or outside specified limits, should be taken out of service and clearly labelled or marked. Wherever possible they should not be used until they have been repaired and requalified.

12.12 When the equipment, instruments and other devices are outside the direct control of the laboratory for a certain period or have undergone major repair, the laboratory should requalify the equipment to ensure its suitability for use.

Note: For further guidance on calibration, verification of performance and qualification of equipment refer to:

- *Procedures for verifying and calibrating refractometers, thermometers used in determinations of melting temperatures and potentiometers for pH determinations and methods for verifying the reliability of scales for ultraviolet and infrared spectrophotometers and spectrofluorometers in* The International Pharmacopoeia (*19*);
- *Specific guidelines for qualification of equipment elaborated by the European Network of Official Medicines Control Laboratories* (*OMCL*) (*20*); and
- *General chapter of the* US Pharmacopeia *on Analytical instrument qualification* (*21*).

13. Traceability

13.1 The result of an analysis should be traceable, when appropriate, ultimately to a primary reference substance.

13.2 All calibrations or qualification of instruments should be traceable to certified reference materials and to SI units (metrological traceability).

Part Three. Working procedures

14. Incoming samples

Sections 14.1–14.3 are applicable to national pharmaceutical quality control laboratories.

14.1 Samples received by a laboratory may be for compliance testing or for investigative testing. Samples for compliance testing include routine samples for control, samples suspected of not complying with the specifications or samples submitted in connection with a marketing authorization process. Close collaboration with the providers of the samples is important. In particular it is important that the sample is large enough to enable, if required, a number of replicate tests to be carried out (see Part three, section 14.3) and for part of the sample to be retained (see Part three, section 20).

14.2 Samples for investigative testing may be submitted by various sources including customs, police and medicines inspectors. These samples comprise suspicious, illegal or counterfeit substances or products. Usually, the primary objective of investigative testing is to identify the substance or the ingredient in the product and, if sufficient substance or product is available, to estimate the purity or content. Well-documented screening procedures should be in place as well as confirmatory analytical procedures to positively identify the substance or the ingredient(s). If an estimation of the content of an identified ingredient is required then an appropriate quantitative analytical procedure should be applied. The value obtained should be reported with an indication of the uncertainty of measurement if required (see Part three, section 18.10).

14.3 It is common for a sample to be taken and divided into three approximately equal portions for submission to the laboratory:

— one for immediate testing;
— the second for confirmation of testing if required; and
— the third for retention in case of dispute.

14.4 If the laboratory is responsible for sampling of substances, materials or products for subsequent testing then it should have a sampling plan and an internal procedure for sampling available to all analysts and technicians working in the laboratory. Samples should be representative of the batches of material from which they are taken and sampling should be carried out so as to avoid contamination and other adverse effects on quality, or mix-up of or by the material being sampled. All the relevant data related to sampling should be recorded.

Note: Guidelines for sampling of pharmaceutical products and related materials were adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-ninth meeting (*22*).

Test request

14.5 A standard test request form should be filled out and should accompany each sample submitted to the laboratory. In the case of a pharmaceutical manufacturer's laboratory the requirements may be given in the master production instructions.

14.6 The test request form should provide or leave space for the following information:

(a) the name of the institution or inspector that supplied the sample;
(b) the source of the material;

(c) a full description of the medicine, including its composition, international nonproprietary name (INN) (if available) and brand name(s);
(d) dosage form and concentration or strength, the manufacturer, the batch number (if available) and the marketing authorization number;
(e) the size of the sample;
(f) the reason for requesting the analysis;
(g) the date on which the sample was collected;
(h) the size of the consignment from which it was taken, when appropriate;
(i) the expiry date (for pharmaceutical products) or retest date (for APIs and pharmaceutical excipients);
(j) the specification to be used for testing;
(k) a record of any further comments (e.g. discrepancies found or associated hazard); and
(l) the required storage conditions.

14.7 The laboratory should review the test request to ensure that:

(a) the requirements are adequately defined and the laboratory has the capability and resources to meet them; and
(b) the appropriate tests and/or methods are selected and are capable of meeting customers' requirements.

Any issue should be resolved with the originator of the request for analysis before testing starts and a record of the review should be kept.

Registration and labelling

14.8 All newly delivered samples and accompanying documents (e.g. the test request) should be assigned a registration number. Separate registration numbers should be assigned to requests referring to two or more medicines, different dosage forms, or different batches of the same medicine or different sources of the same batch. If applicable, a unique registration number should also be assigned to any incoming retained sample (see Part three, section 20).

14.9 A label bearing the registration number should be affixed to each container of the sample. Care should be taken to avoid obscuring any other markings or inscriptions.

14.10 A register should be kept, which may be a record book, a card file or data-processing equipment, in which the following information is recorded:

(a) the registration number of the sample;
(b) the date of receipt; and
(c) the specific unit to which the sample was forwarded.

Visual inspection of the submitted sample

14.11 The sample received should be visually inspected by laboratory staff to ensure that the labelling conforms with the information contained in the test request. The findings should be recorded, dated and signed. If discrepancies are found, or if the sample is obviously damaged, this fact should be recorded without delay on the test request form. Any queries should be immediately referred back to the provider of the sample.

Storage

14.12 The sample prior to testing, the retained sample (see Part three, section 20) and any portions of the sample remaining after performance of all the required tests should be stored safely, taking into account the storage conditions (*22*, *23*) specified for the sample.

Forwarding to testing

14.13 The specific unit to which the sample is sent for testing is determined by the person responsible.

14.14 The examination of a sample should not be started before the relevant test request has been received.

14.15 The sample should be properly stored until all relevant documentation has been received.

14.16 A request for analysis may be accepted verbally only in emergencies. All details should immediately be placed on record pending the receipt of written confirmation.

14.17 Unless a computerized system is used, copies or duplicates of all documentation should accompany each numbered sample when sent to the specific unit.

14.18 Testing should be performed as described under Part three, section 17.

15. Analytical worksheet

15.1 The analytical worksheet is an internal document to be used by the analyst for recording information about the sample, the test procedure, calculations and the results of testing. It is to be complemented by the raw data obtained in the analysis.

Purpose

15.2 The analytical worksheet contains documentary evidence either:

— to confirm that the sample being examined is in accordance with the requirements; or
— to support an OOS result (see Part three, sections 18.1–18.3).

Use

15.3 A separate analytical worksheet should usually be used for each numbered sample or group of samples.

15.4 Analytical worksheets from different units relating to the same sample should be assembled together.

Content

15.5 The analytical worksheet should provide the following information:

(a) the registration number of the sample (see Part three, section 14.9);
(b) page numbering, including the total number of pages (and including annexes);
(c) the date of the test request;
(d) the date on which the analysis was started and completed;
(e) the name and signature of the analyst;
(f) a description of the sample received;
(g) references to the specifications and a full description of test methods by which the sample was tested, including the limits;
(h) the identification of the test equipment used (see Part two, section 12.1);
(i) the identification number of any reference substance used (see Part two, section 11.5);
(j) if applicable, the results of the system suitability test;
(k) the identification of reagents and solvents employed;
(l) the results obtained;
(m) the interpretation of the results and the final conclusions (whether or not the sample was found to comply with the specifications), approved and signed by the supervisor; and
(n) any further comments, for example, for internal information (see Part three, section 17.1), or detailed notes on the specifications selected and the methods of assessment used (see Part three, section 15.9), or any deviation from the prescribed procedure, which should be approved and reported, or whether and when portions of the sample were forwarded to other units for special tests and the date on which the results were received.

15.6 All values obtained from each test, including blank results, should immediately be entered on the analytical worksheet and all graphical data, whether obtained from recording instruments or plotted by hand, should be attached or be traceable to an electronic record file or document where the data are available.

15.7 The completed analytical worksheet should be signed by the responsible analyst(s), verified and approved and signed by the supervisor.

15.8 When a mistake is made in an analytical worksheet or when data or text need to be amended, the old information should be deleted by putting a single line through it (it should not be erased or made illegible) and the new information added alongside. All such alterations should be signed by the person making the correction and the date of the change inserted. The reason for the change should also be given on the worksheet (suitable procedures should be in place for amending electronic worksheets).

Selection of the specifications to be used

15.9 The specification necessary to assess the sample may be that given in the test request or master production instructions. If no precise instruction is given, the specification in the officially recognized national pharmacopoeia may be used or, failing this, the manufacturer's officially approved or other nationally recognized specification. If no suitable method is available:

(a) the specification contained in the marketing authorization or product licence may be requested from the marketing authorization holder or manufacturer and verified by the laboratory; or
(b) the requirements may be set by the laboratory itself on the basis of published information and any procedure employed is to be validated by the testing laboratory (see Part three, section 16).

15.10 For official specifications the current version of the relevant pharmacopoeia should be available.

Filing

15.11 The analytical worksheet should be kept safely together with any attachments, including calculations and recordings of instrumental analyses.

16. Validation of analytical procedures

16.1 All analytical procedures employed for testing should be suitable for the intended use. This is demonstrated by validation (*24*). Validation

also serves to establish acceptance criteria for system suitability tests which are subsequently employed for the verification of the analytical procedure before analysis.

16.2 Validation should be performed according to a validation protocol, which includes analytical performance characteristics to be verified for various types of analytical procedures. Typical characteristics which should be considered are listed in Table 1 (in the development phase of an analytical procedure, robustness, i.e. the ability of the procedure to provide results of acceptable accuracy and precision under a variety of conditions should also be considered). The results are to be documented in the validation report.

Table 1

Characteristics to consider during validation of analytical procedures

Type of analytical Procedure	Identification	Testing for impurities		Assay
		Quantitative tests	Limit tests	• dissolution (measurement only) • content/potency
Characteristics				
Accuracy	–	+	–	+
Precision				
Repeatability	–	+	–	+
Intermediate precision[a]	–	+	–	+
Specificity	+	+	+	+
Detection limit	–	–[b]	+	–
Quantitation limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

– Characteristic is normally not evaluated; + characteristic should normally be evaluated.

[a] In cases where a reproducibility study has been performed, intermediate precision is not needed.

[b] May be needed in some cases.

16.3 Pharmacopoeial methods are considered to be validated for the intended use as prescribed in the monograph(s). However, the laboratory should also confirm that, for example, for a particular finished pharmaceutical product (FPP) examined for the first time, no interference arises from the excipients present, or that for an API, impurities coming from a new route of synthesis are adequately differentiated. If the pharmacopoeial method is adapted for another use then it should be validated for such a use to demonstrate that it is fit-for-purpose.

16.4 System suitability testing is an integral part of many analytical procedures. The tests are based on the fact that the equipment, electronics, analytical operations and samples to be analysed contribute to the system. Which system suitability tests are to be applied depends on the type of procedure to be used. System suitability tests are employed for the verification of pharmacopoeial methods or validated analytical procedures and should be performed prior to the analysis. Provided the system suitability criteria are fulfilled the method or procedure is considered to be suitable for the intended purpose.

Note: If a large number of samples is being analysed in sequence, then appropriate system suitability tests are to be performed throughout the sequence to demonstrate that the performance of the procedure is satisfactory.

Verification is not required for basic pharmacopoeial methods such as (but not limited to) pH, loss on drying and wet chemical methods.

16.5 A major change to the analytical procedure, or in the composition of the product tested, or in the synthesis of the API, will require revalidation of the analytical procedure.

Note: Further guidance on validation of analytical procedures is available in the following:

- *Guideline elaborated by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)* (*25*);
- *Guideline elaborated by the European Network of Official Medicines Control Laboratories (OMCL)* (*26*);
- *General chapters of the* US Pharmacopeia *on Validation of compendial procedures and on Verification of compendial procedures* (*27*).

17. Testing

17.1 The sample should be tested in accordance with the work plan of the laboratory after completion of the preliminary procedures. If this is not feasible the reasons should be noted, e.g. in the analytical worksheet (see Part three, section 15), and the sample should be stored in a special place which is kept locked (see Part three, section 14.12).

17.2 Specific tests required may need to be carried out by another unit or by a specialized external laboratory (see Part one, section 9). The responsible person should prepare the request and arrange for the

transfer of the required number of units (bottles, vials or tablets) from the sample. Each of these units should bear the correct registration number. When the analytical test report contains results of tests performed by subcontractors, these results should be identified as such.

17.3 Detailed guidance on official pharmacopoeial requirements is usually given in the general notices and specific monographs of the pharmacopoeia concerned. Test procedures should be described in detail and should provide sufficient information to allow properly trained analysts to perform the analysis in a reliable manner. Where system suitability criteria are defined in the method they should be fulfilled. Any deviation from the test procedure should be approved and documented.

18. Evaluation of test results

18.1 Test results should be reviewed and, where appropriate, evaluated statistically after completion of all the tests to determine whether they are mutually consistent and if they meet the specifications used. The evaluation should take into consideration the results of all the tests (all test data). Whenever doubtful (atypical) results are obtained they should be investigated. The complete testing procedure needs to be checked according to the internal quality management system (see also Part one, section 2).

18.2 When a doubtful result (suspected OOS result) has been identified, a review of the different procedures applied during the testing process is to be undertaken by the supervisor with the analyst or technician before retesting is permitted. The following steps should be followed:

(a) confirm with the analyst or technician that the appropriate procedure(s) was (were) applied and followed correctly;
(b) examine the raw data to identify possible discrepancies;
(c) check all calculations;
(d) check that the equipment used was qualified and calibrated, and that system suitability tests were performed and were acceptable;
(e) ensure that the appropriate reagents, solvents and reference substances were used;
(f) confirm that the correct glassware was used; and
(g) ensure that original sample preparations are not discarded until the investigation is complete.

18.3 The identification of an error which caused an aberrant result will invalidate the result and a retest of the sample will be necessary.

Doubtful results can be rejected only if they are clearly due to an identified error. Sometimes the outcome of the investigation is inconclusive — no obvious cause can be identified — in which case a confirmatory determination is to be performed by another analyst who should be at least as experienced and competent in the analytical procedure as the original analyst. A similar value would indicate an OOS result. However, further confirmation using another validated method, if available, may be advised.

18.4 An SOP should be in place for the conduct of an investigation of an OOS test result. The SOP should give clear guidance on the number of retests allowed (based on sound statistical principles). All investigations and their conclusions should be recorded. In the event of an error, any corrective action taken and any preventive measure introduced should be recorded and implemented.

18.5 All individual results (all test data) with acceptance criteria should be reported.

18.6 All conclusions should be entered on the analytical worksheet (see Part three, section 15) by the analyst and signed by the supervisor.

Note: Further guidance on evaluation and reporting of test results is available in the following:

- *Guideline elaborated by the US Food and Drug Administration* (*5*);
- *Guideline elaborated by the European Network of Official Medicines Control Laboratories (OMCL)* (*28*).

Analytical test report

18.7 The analytical test report is a compilation of the results and states the conclusions of the examination of a sample. It should be:

(a) issued by the laboratory; and
(b) based on the analytical worksheet (see Part three, section 15).

18.8 Any amendments to the original analytical test report will require the issue of a new corrected document.

18.9 Pharmacopoeial content limits are set taking into account the uncertainty of measurement, and the production capability and acceptance criteria for an analytical result should be predefined. Under presently applicable rules neither the pharmacopoeias nor the NMRAs require the value found to be expressed with its associated expanded uncertainty for compliance testing. However, when reporting the results of investigative testing, although the primary objective is to identify a substance in the sample, a determination of

its concentration may be also requested, in which case the estimated uncertainty should also be given.

18.10 Measurement uncertainty can be estimated in a number of ways, e.g.:

(a) by preparing an uncertainty budget for each uncertainty component identified in an analytical procedure (bottom-up approach);
(b) from validation data and control charts (*29*); and
(c) from the data obtained from proficiency tests or collaborative trials (top-down approach).

Note: Further guidance can be found in various guidelines (*9*, *10*, *30*, *31, 32*).

Content of the analytical test report

18.11 The analytical test report should provide the following information:

(a) the laboratory registration number of the sample;
(b) the laboratory test report number;
(c) the name and address of the laboratory testing the sample;
(d) the name and address of the originator of the request for analysis;
(e) the name, description and batch number of the sample, where appropriate;
(f) an introduction giving the background to and the purpose of the investigation;
(g) a reference to the specifications used for testing the sample or a detailed description of the procedures employed (sample for investigative testing), including the limits;
(h) the results of all the tests performed or the numerical results with the standard deviation of all the tests performed (if applicable);
(i) a discussion of the results obtained;
(j) a conclusion as to whether or not the sample(s) was (were) found to be within the limits of the specifications used, or for a sample for investigative testing, the substance(s) or ingredient(s) identified;
(k) the date on which the test(s) was (were) completed;
(l) the signature of the head of the laboratory or authorized person;
(m) the name and address of the original manufacturer and, if applicable, those of the repacker and/or trader;
(n) whether or not the sample(s) complies (comply) with the requirements;
(o) the date on which the sample was received;
(p) the expiry date or retest date, if applicable; and

(q) a statement indicating that the analytical test report, or any portion thereof, cannot be reproduced without the authorization of the laboratory.

19. Certificate of analysis

19.1 A certificate of analysis is prepared for each batch of a substance or product and usually contains the following information:

(a) the registration number of the sample;
(b) date of receipt;
(c) the name and address of the laboratory testing the sample;
(d) the name and address of the originator of the request for analysis;
(e) the name, description and batch number of the sample where appropriate;
(f) the name and address of the original manufacturer and, if applicable, those of the repacker and/or trader;
(g) the reference to the specification used for testing the sample;
(h) the results of all tests performed (mean and standard deviation, if applicable) with the prescribed limits;
(i) a conclusion as to whether or not the sample was found to be within the limits of the specification;
(j) expiry date or retest date if applicable;
(k) date on which the test(s) was (were) completed; and
(l) the signature of the head of laboratory or other authorized person.

Note: The *Guideline on model certificate of analysis* was adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-sixth meeting (*3*).

20. Retained samples

20.1 Samples should be retained as required by the legislation or by the originator of the request for analysis. There should be a sufficient amount of retained sample to allow at least two re-analyses. The retained sample should be kept in its final pack.

Part four. Safety

21. General rules

21.1 General and specific safety instructions reflecting identified risk, should be made available to each staff member and supplemented regularly as appropriate (e.g. with written material, poster displays, audiovisual material and occasional seminars).

21.2 General rules for safe working in accordance with national regulations and SOPs normally include the following requirements:

(a) safety data sheets should be available to staff before testing is carried out;
(b) smoking, eating and drinking in the laboratory should be prohibited;
(c) staff should be familiar with the use of fire-fighting equipment, including fire extinguishers, fire blankets and gas masks;
(d) staff should wear laboratory coats or other protective clothing, including eye protection;
(e) special care should be taken, as appropriate, in handling, for example, highly potent, infectious or volatile substances;
(f) highly toxic and/or genotoxic samples should be handled in a specially designed facility to avoid the risk of contamination;
(g) all containers of chemicals should be fully labelled and include prominent warnings (e.g. "poison", "flammable", "radioactive") whenever appropriate;
(h) adequate insulation and spark-proofing should be provided for electrical wiring and equipment, including refrigerators;
(i) rules on safe handling of cylinders of compressed gases should be observed and staff should be familiar with the relevant colour identification codes;
(j) staff should be aware of the need to avoid working alone in the laboratory; and
(k) first-aid materials should be provided and staff instructed in first-aid techniques, emergency care and the use of antidotes.

21.3 Protective clothing should be available, including eye protection, masks and gloves. Safety showers should be installed. Rubber suction bulbs should be used on manual pipettes and siphons. Staff should be instructed in the safe handling of glassware, corrosive reagents and solvents and particularly in the use of safety containers or baskets to avoid spillage from containers. Warnings, precautions and instructions should be given for work with violent, uncontrollable or dangerous reactions when handling specific reagents (e.g. mixing water and acids, or acetone–chloroform and ammonia), flammable products, oxidizing or radioactive agents and especially biologicals such as infectious agents. Peroxide-free solvents should be used. Staff should be aware of methods for the safe disposal of unwanted corrosive or dangerous products by neutralization or deactivation and of the need for safe and complete disposal of mercury and its salts.

21.4 Poisonous or hazardous products should be singled out and labelled appropriately, but it should not be taken for granted that all other

chemicals and biologicals are safe. Unnecessary contact with reagents, especially solvents and their vapours, should be avoided. The use of known carcinogens and mutagens as reagents should be limited or totally excluded if required by national regulations. Replacement of toxic solvents and reagents by less toxic materials or reduction of their use should always be the aim, particularly when new techniques are developed.

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Appendix

Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

A list of equipment considered by the Committee to be adequate either for a first-stage or medium-sized pharmaceutical quality control laboratory is given in the table. In the case of a medium-sized laboratory, specific sections are devoted to a microbiology unit and pharmacognosy/phytochemistry unit. For a first-stage laboratory testing herbal medicines, the additional equipment recommended is specified in the table.

This list does not represent any requirements which should be fulfilled to comply with these guidelines. NMRAs or laboratories wishing to perform pharmaceutical analyses may consider the following list in the establishment or upgrading of their testing facilities. For budgetary reasons it is necessary, besides the cost of equipment, to take into consideration the cost of reference materials, reagents, solvents, glassware, other laboratory commodities and personnel. Experience has shown that for sustainability, a laboratory should allow a margin of 10–15% per year of the purchasing expenditure on equipment to cover the cost of maintenance.

Table

Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

First-stage laboratory	
Equipment and major instruments	***Quantity***
Top-loading balance	1
Analytical balance (5 digits)	1 or 2
Melting-point apparatus	1
pH meter (with assorted electrodes)	1
Microscope	1
Polarimeter	1
High-performance liquid chromatograph with ultraviolet detector	2
Ultraviolet/visible spectrophotometer	1
Infrared spectrophotometer with pellet press	1
Karl Fischer titrator (semi-micro determination of water)	1
Agate mortar with pestle	1
Equipment for thin-layer chromatography	1
Thin-layer chromatography spotter	1
Developing chambers	6 + 1[a]
Atomizers	6

First-stage laboratory (cont.)	
Ultraviolet viewing lamp	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution apparatus	1
Soxhlet extraction apparatus (60 ml)	3 + 1[a]
Micrometer callipers	1
Pycnometers	2
Burettes/pipettes (10 ml and 25 ml/1, 2, 5, 10, 20, 25, 50 ml)	3 of each
Desiccator	1 + 1[a]
Centrifuge (table-top model, 4-place swing rotor)	1
Water-bath (20 litres)	1
Hot plates with magnetic stirrers	3
Vacuum pump (rotary, oil)	1
Drying oven (60 litres)	1
Vacuum oven (17 litres)	1
Muffle furnace	1
Refrigerator (explosion-proof)	1
Water distilling apparatus (8 litres/hour)	1
Water deionizer (10 litres/hour)	1
Dehumidifier (where needed)	1
Fume hood	1
Optional items	
Analytical microbalance	1
Flame photometer (including air compressor)	1
Refractometer	1
Viscometer	1
Vortex mixer	1
Shaker (wrist-action)	1
Pipette rinser	1
Constant temperature water-bath	1
Ultrasonic cleaner (5 litres)	1
Medium-sized laboratory	
Equipment and major instruments	***Quantity***
Top-loading balance	1 or 2
Analytical balance (5 digits)	2
Analytical microbalance	1

Medium-sized laboratory (cont.)	
Microscope	1 or 2
Equipment for thin-layer chromatography	1
Thin-layer chromatography multispotter	1
Developing chambers	6
Atomizers	6
Ultraviolet viewing lamp	1
Potentiometric titrimeter	1
Micro-Kjeldahl equipment (including fume flasks)	1
Soxhlet extraction apparatus (60 ml)	3
Pycnometers	2
Burettes/pipettes (10 ml and 25 ml/1, 2, 5, 10, 20, 25, 50 ml)	6 of each
Micrometer callipers	1
Heating mantles for flasks (assorted sizes: 50, 200 and 2000 ml)	6
Sieves (assorted sizes)	1 set
Centrifuge (floor model)	1
Shaker (wrist-action)	1
Vortex mixers	2
Water-bath (electrical, 20 litres)	2 or 3
Hot plates with magnetic stirrers	3 or 4
Vacuum pump (rotary, oil)	2
Vacuum rotary evaporator	1
Drying oven (60 litres)	2 or 3
Muffle furnace (23 litres)	1
Vacuum oven (17 litres)	1
Desiccators	2
Refrigerator (explosion-proof)	2
Freezer	1
Ultrasonic cleaners (5 litres)	2
Laboratory glassware washing machine	1
Water distilling apparatus (8 litres/hour)	1
Water deionizing equipment (10 litres/hour)	1
Fume hoods	2
Melting-point apparatus	1
Polarimeter	1
pH meters (with assorted electrodes)	2
High-performance liquid chromatograph with variable wavelength Ultraviolet/visible detector	3 or 4

Medium-sized laboratory (cont.)	
Ultraviolet/visible spectrophotometer, double-beam	1
Infrared spectrophotometer with pellet press	1
Agate mortar with pestle	1
Gas chromatograph (flame ionization, direct and static head space injection)	1
Refractometer	1
Karl Fischer titrators (1 semi-micro and 1 coulometric for micro-determination of water)	2
Oxygen flask combustion apparatus	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution test equipment (for 6 tablets/capsules)	1
Optional items	
Atomic absorption spectrophotometer	1
Spectrofluorometer	1
High-performance liquid chromatograph detectors:	
— fluorescence	1
— diode-array	1
— refractive index	1
— evaporative light scattering (ELSD)	1
— charged aerosol (CAD)	1
— mass spectrometric (MS)	1
Gas chromatograph detectors:	
— conductivity	1
— nitrogen/phosphorous (NPD)	1
— mass spectrometric (MS)	1
Capillary electrophoresis equipment	1
Thin-layer chromatography scanner	1
Crushing strength tester	1
Friability tester	1
Viscometer	1
Ice machine	1
Solvent-recovery apparatus	1
Equipment for microbiology unit	
pH meter	1
Ultraviolet/visible spectrophotometer, single-beam	1
Microscopes (for bacteriology)	2

Medium-sized laboratory (cont.)	
Membrane filter assembly for sterility tests	1
Colony counter with magnifier	1
Laminar air flow unit	1
Hot-air sterilizer	1
Incubators, 60 litres	2 or 3
Anaerobic jar	1
Zone reader	1
Centrifuge	1
Water-bath (thermostatically controlled)	2
Autoclaves (100 litres, top-loading)	2
Refrigerators (340 litres)	2
Deep freeze	1
Laboratory glassware washing machine	1
Equipment for pharmacognosy/phytochemistry unit	
Grinder/mill (for preparation of sample of herbal materials)	1
Top loading balance	1
Sieves	1 set
Microscope[b]	1
Soxhlet extraction apparatus	2 or 3
Water-bath	1
Heating mantles for flasks	1 or 2
Hot plates with magnetic stirrers	2
Equipment for thin-layer chromatography	1 or 2
Developing chambers	3 or 4
Desiccators	2
Rotary vacuum apparatus	1
Distillation equipment	1
Conical percolators	2 or 3
Apparatus for determination of water content by azeotropic method[b]	1
Apparatus for determination of volatile oils[b]	1
Apparatus for determination of arsenic limit test[c]	1

[a] Needed in the case that herbal medicines are also tested.
[b] *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1998.
[c] *WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues*. Geneva, World Health Organization, 2006.

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Annex 2

WHO good manufacturing practices for active pharmaceutical ingredients

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References

Appendix 1
List of references for related WHO guidelines

Appendix 2
General notes: additional clarifications and explanations

This text is based on the International Conference on Harmonisation (ICH) Q7: *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*. November 2000.

1. Introduction

1.1 Objective

This document (guide) is intended to provide guidance regarding good manufacturing practices (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

In this guide "manufacturing" is defined to include all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and the related controls. In this guide the term "should" indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance. For the purposes of this guide, the terms "current good manufacturing practices" and "good manufacturing practices" are equivalent.

The guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This guide is not intended to define registration and filing requirements or modify pharmacopoeial requirements. This guide does not affect the ability of the responsible regulatory agency to establish specific registration or filing requirements regarding APIs within the context of marketing or manufacturing authorizations or pharmaceutical applications. All commitments in registration and filing documents must be met.

1.2 Regulatory applicability

Within the world community, materials may vary as to the legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a pharmaceutical product, it should be manufactured according to this guide.

1.3 Scope

This guide applies to the manufacture of APIs for use in finished pharmaceutical products (FPPs). It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but should be performed in accordance with GMP guidelines for FPPs as defined by local authorities.

This guide covers APIs that are manufactured by chemical synthesis, extraction, cell culture or fermentation, by recovery from natural sources, or by any combination of these processes.

Specific guidance for APIs manufactured by cell culture or fermentation is described in section 18.

This guide excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it does include APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this guide. In addition, the guide does not apply to medical gases, bulk-packaged FPPs, and manufacturing and control aspects specific to radiopharmaceuticals.

Section 19 contains guidance that only applies to the manufacture of APIs used in the production of FPPs specifically for clinical trials (investigational medicinal products).

An "API starting material" is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in house.

API starting materials normally have defined chemical properties and structure. The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which "API starting materials" are entered into the process. For other processes (e.g. fermentation, extraction or purification), this rationale should be established on a case-by-case basis.

Table 1 gives guidance on the point at which the API starting material is normally introduced into the process. From this point on, appropriate GMP as defined in this guide should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.

The guidance in this document would normally be applied to the steps shown in grey in Table 1. It does not imply that all steps shown should be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification and packaging. Physical processing of APIs, such as granulation, coating

or physical manipulation of particle size (e.g. milling and micronizing), should be conducted at least to the standards of this guide.

This GMP guide does not apply to steps prior to the introduction of the defined "API starting material".

Table 1[a]

Application of this guide to API manufacturing

Type of manufacturing	Application of this guide to steps (shown in grey) used in this type of manufacturing				
Chemical manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/ or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plants	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/ or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

[a] This table has been taken from the ICH Harmonised Tripartite Guideline: Active Pharmaceutical Ingredients Q7. Current *Step 4* version, dated 10 November 2000.

2. Quality management

2.1 Principles[1]

2.10 Quality should be the responsibility of all persons involved in manufacturing.

2.11 Each manufacturer should establish, document and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

2.12 The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality-related activities should be defined and documented.

2.13 There should be a quality unit(s) that is independent of production and that 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.

2.14 The persons authorized to release intermediates and APIs should be specified.

2.15 All quality-related activities should be recorded at the time they are performed.

2.16 Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

2.17 No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine as described in section 10.20 or the use of raw materials or intermediates pending completion of evaluation).

2.18 Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g. quality related complaints, recalls and regulatory actions).

2.2 Responsibilities of the quality unit(s)

2.20 The quality unit(s) should be involved in all quality-related matters.

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[1] This system of numbering sections is different to the usual WHO style. It is used here to harmonize with the guide used in inspection reports internationally.

2.21 The quality unit(s) should review and approve all appropriate quality-related documents.

2.22 The main responsibilities of the independent quality unit(s) should not be delegated.

These responsibilities should be described in writing and should include but not necessarily be limited to:

1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company.
2. Establishing a system to release or reject raw materials, intermediates, packaging and labelling materials.
3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution.
4. Making sure that critical deviations are investigated and resolved.
5. Approving all specifications and master production instructions.
6. Approving all procedures impacting the quality of intermediates or APIs.
7. Making sure that internal audits (self-inspections) are performed.
8. Approving intermediate and API contract manufacturers.
9. Approving changes that potentially impact quality of intermediates or APIs.
10. Reviewing and approving validation protocols and reports.
11. Making sure that quality-related complaints are investigated and resolved.
12. Making sure that effective systems are used for maintaining and calibrating critical equipment.
13. Making sure that materials are appropriately tested and the results are reported.
14. Making sure that there are stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate.
15. Performing product quality reviews (as defined in section 2.5).

2.3 Responsibility for production activities

The responsibility for production activities should be described in writing, and should include but not necessarily be limited to:

1. Preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures.
2. Producing APIs and, when appropriate, intermediates according to pre-approved instructions.
3. Reviewing all production batch records and ensuring that these are completed and signed.

4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded.
5. Making sure that production facilities are clean and when appropriate disinfected.
6. Making sure that the necessary calibrations are performed and records kept.
7. Making sure that the premises and equipment are maintained and records kept.
8. Making sure that validation protocols and reports are reviewed and approved.
9. Evaluating proposed changes in product, process or equipment.
10. Making sure that new and, when appropriate, modified facilities and equipment are qualified.

2.4 Internal audits (self-inspection)

2.40 In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.

2.41 Audit findings and corrective actions should be documented and brought to the attention of the responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

2.5 Product quality review

2.50 Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least a review of:

— critical in-process control and critical API test results;
— all batches that failed to meet established specification(s);
— all critical deviations or non-conformances and related investigations;
— any changes carried out to the processes or analytical methods;
— results of the stability monitoring programme;
— quality-related returns, complaints and recalls; and
— adequacy of corrective actions.

2.51 The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

3. Personnel

3.1 Personnel qualifications

3.10 There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.

3.11 The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.

3.12 Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs, and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

3.2 Personnel hygiene

3.20 Personnel should practice good sanitation and health habits.

3.21 Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand and arm coverings, should be worn when necessary, to protect intermediates and APIs from contamination.

3.22 Personnel should avoid direct contact with intermediates or APIs.

3.23 Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

3.24 Personnel with an infectious disease or who have open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where their health condition could adversely affect the quality of the APIs, until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

3.3 Consultants

3.30 Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

3.31 Records should be maintained stating the name, address, qualifications and type of service provided by these consultants.

4. Buildings and facilities

4.1 Design and construction

4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

4.12 Where the equipment itself (e.g. closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

4.13 The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

4.14 There should be defined areas or other control systems for the following activities:

— receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection;
— quarantine before release or rejection of intermediates and APIs;
— sampling of intermediates and APIs;
— holding rejected materials before further disposition (e.g. return, reprocessing or destruction);
— storage of released materials;
— production operations;
— packaging and labelling operations; and
— laboratory operations.

4.15 Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single-use towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

4.16 Laboratory areas and operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.

4.2 Utilities

4.20 All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

4.21 Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

4.22 If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.

4.23 Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.

4.24 Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

4.3 Water

4.30 Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.

4.31 Unless otherwise justified, process water should, at a minimum, meet WHO guidelines for drinking (potable) water quality.

4.32 If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical and chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.

4.33 Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

4.34 Where the manufacturer of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile FPP, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms and endotoxins.

4.4 Containment

4.40 Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.

4.41 Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g. certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

4.42 Appropriate measures should be established and implemented to prevent cross-contamination, e.g. from personnel or materials, moving from one dedicated area to another.

4.43 Any production activities (including weighing, milling or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.

4.5 Lighting

4.50 Adequate lighting should be provided in all areas to facilitate cleaning, maintenance and proper operations.

4.6 Sewage and refuse

4.60 Sewage, refuse and other waste (e.g. solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

4.7 Sanitation and maintenance

4.70 Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

4.71 Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment and materials to be used in cleaning buildings and facilities.

4.72 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging or labelling materials, intermediates and APIs.

5. Process equipment

5.1 Design and construction

5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate) and maintenance.

5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

5.12 Production equipment should only be used within its qualified operating range.

5.13 Major equipment (e.g. reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food-grade lubricants and oils should be used.

5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

5.16 A set of current drawings should be maintained for equipment and critical installations (e.g. instrumentation and utility systems).

5.2 Equipment maintenance and cleaning

5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventive maintenance of equipment.

5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

— assignment of responsibility for cleaning of equipment;
— cleaning schedules, including, where appropriate, sanitizing schedules;
— a complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;

— when appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;
— instructions for the removal or obliteration of previous batch identification;
— instructions for the protection of clean equipment from contamination prior to use;
— inspection of equipment for cleanliness immediately before use, if practical; and
— establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.

5.22 Equipment and utensils should be cleaned, stored and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, this equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of microorganisms).

5.24 Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

5.26 Equipment should be identified as to its contents and its cleanliness status by appropriate means.

5.3 Calibration

5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

5.31 Equipment calibrations should be performed using standards traceable to certified standards, if these exist.

5.32 Records of these calibrations should be maintained.

5.33 The current calibration status of critical equipment should be known and verifiable.

5.34 Instruments that do not meet calibration criteria should not be used.

5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an

impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

5.4 Computerized systems

5.40 GMP-related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.

5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.

5.42 Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at the time of installation, a retrospective validation could be conducted if appropriate documentation is available.

5.43 Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g the system being turned off and data not captured). There should be a record of any data change made, the previous entry, the person who made the change and when the change was made.

5.44 Written procedures should be available for the operation and maintenance of computerized systems.

5.45 Where critical data are being entered manually, there should be an additional check on the accuracy of the data entered. This can be done by a second operator or by the system itself.

5.46 Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

5.47 Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

5.48 If system breakdowns or failures will result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.

5.49 Data can be recorded by a second means in addition to the computer system.

6. Documentation and records

6.1 Documentation system and specifications

6.10 All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.

6.11 The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.

6.12 A procedure should be established for retaining all appropriate documents (e.g. development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records and distribution records). The retention periods for these documents should be specified.

6.13 All production, control and distribution records should be retained for at least one year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least three years after the batch is completely distributed.

6.14 Entries in records should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed ensuring that the original entry remains readable.

6.15 During the retention period, originals or copies of records should be readily available at the establishment where the activities described in these records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

6.16 Specifications, instructions, procedures and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

6.17 Specifications should be established and documented for raw materials, intermediates where necessary, APIs and labelling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.

6.18 If electronic signatures are used on documents they should be authenticated and secure.

6.2 Equipment cleaning and use record

6.20 Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time (if appropriate), product and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

6.21 If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance and use can be part of the batch record or maintained separately.

6.3 Records of raw materials, intermediates, API labelling and packaging materials

6.30 Records of raw materials, intermediates, API labelling and packaging materials should be maintained including:

— the name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for APIs; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt;
— the results of any test or examination performed and the conclusions derived from this;
— records tracing the use of materials;
— documentation of the examination and review of API labelling and packaging material for conformity with established specifications; and
— the final decision regarding rejected raw materials, intermediates or API labelling and packaging materials.

6.31 Master (approved) labels should be maintained for comparison to issued labels.

6.4 Master production instructions (master production and control records)

6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated and signed by one person and independently checked, dated and signed by a person in the quality unit(s).

6.41 Master production instructions should include:

- the name of the intermediate or API being manufactured and an identifying document reference code, if applicable;

- a complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;
- an accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified;
- the production location and major production equipment to be used;
- detailed production instructions, including the:
  — sequences to be followed,
  — ranges of process parameters to be used,
  — sampling instructions and in-process controls with their acceptance criteria, where appropriate,
  — time limits for completion of individual processing steps and/or the total process, where appropriate, and
  — expected yield ranges at appropriate phases of processing or time;
- where appropriate, special notations and precautions to be followed, or cross-references to these; and
- the instructions for storage of the intermediate or API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

6.5 Batch production records (batch production and control records)

6.50 Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and is a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

6.51 These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code, together with the date and time, can serve as the unique identifier until the final number is allocated.

6.52 Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

— dates and, when appropriate, times;
— identity of major equipment (e.g., reactors, driers and mills) used;

— specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing;
— actual results recorded for critical process parameters;
— any sampling performed;
— signatures of the persons performing and directly supervising or checking each critical step in the operation;
— in-process and laboratory test results;
— actual yield at appropriate phases or times;
— description of packaging and label for intermediate or API;
— representative label of API or intermediate if made commercially available;
— any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately; and
— results of release testing.

6.53 Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

6.6 Laboratory control records

6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

— a description of samples received for testing, including the name of the material or its source, batch number or other distinctive code, the date the sample was taken and, where appropriate, the quantity and date the sample was received for testing;
— a statement of or reference to each test method used;
— a statement of the weight or measure of sample used for each test as described by the method;
— data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions;
— a complete record of all raw data generated during each test, in addition to graphs, charts and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested;
— a record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors and equivalency factors;
— a statement of the test results and how they compare with established acceptance criteria;

— the signature of the person who performed each test and the date(s) the tests were performed; and
— the date and signature of a second person showing that the original records have been reviewed for accuracy, completeness and compliance with established standards.

6.61 Complete records should also be maintained for:

— any modifications to an established analytical method;
— periodic calibration of laboratory instruments, apparatus, gauges and recording devices;
— all stability testing performed on APIs; and
— out-of-specification (OOS) investigations.

6.7 Batch production record review

6.70 Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labelling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

6.71 Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).

6.72 All deviation, investigation and OOS reports should be reviewed as part of the batch record review before the batch is released.

6.73 The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

7. Materials management

7.1 General controls

7.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials.

7.11 Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.

7.12 Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).

7.13 If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known to the intermediate and/or API manufacturer.

7.14 Changing the source of supply of critical raw materials should be done according to section 13, Change control.

7.2 Receipt and quarantine

7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labelling (including correlation between the name used by the supplier and the in-house name, if these are different), damage to containers, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and then released for use.

7.21 Before incoming materials are mixed with existing stocks (e.g. solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.

7.22 If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:

— certificate of cleaning;
— testing for trace impurities;
— audit of the supplier.

7.23 Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.

7.24 Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

7.3 Sampling and testing of incoming production materials

7.30 At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below in section 7.32. A supplier's certificate of analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

7.31 Supplier approval should include an evaluation that provides adequate evidence (e.g. past quality history) that the manufacturer can consistently

provide material meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the certificates of analysis. Reliability of certificates of analysis should be checked at regular intervals.

7.32 Processing aids, hazardous or highly toxic raw materials, other special materials or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's certificate of analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

7.33 Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The decision on the number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, variability of the material, past quality history of the supplier and the quantity needed for analysis.

7.34 Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

7.35 Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

7.4 Storage

7.40 Materials should be handled and stored in such a manner as to prevent degradation, contamination and cross-contamination.

7.41 Materials stored in fibre drums, bags or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

7.42 Materials should be stored under conditions and for a period that will have no adverse affect on their quality and should normally be controlled so that the oldest stock is used first.

7.43 Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

7.44 Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.

7.5 Re-evaluation

7.50 Materials should be re-evaluated as appropriate to determine their suitability for use (e.g. after prolonged storage or exposure to heat or humidity).

8. Production and in-process controls

8.1 Production operations

8.10 Raw materials for manufacturing of intermediates and APIs should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

8.11 If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

— material name and/or item code;
— receiving or control number;
— weight or measure of material in the new container; and
— re-evaluation or retest date if appropriate.

8.12 Critical weighing, measuring or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

8.13 Other critical activities should be witnessed or subjected to an equivalent control.

8.14 Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

8.15 Any deviation should be documented and explained. Any critical deviation should be investigated.

8.16 The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems or alternative means.

8.17 Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

8.2 Time limits

8.20 If time limits are specified in the master production instruction (see section 6.41), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g. pH adjustment, hydrogenation or drying to a predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

8.21 Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

8.3 In-process sampling and controls

8.30 Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.

8.31 The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g. isolation and purification steps).

8.32 Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).

8.33 In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s)' approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.

8.34 Written procedures should describe the sampling methods for in-process materials, intermediates and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.

8.35 In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or

APIs. Procedures should be established to ensure the integrity of samples after collection.

8.36 OOS investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

8.4 Blending batches of intermediates or APIs

8.40 For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g. collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

8.41 OOS batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

8.42 Acceptable blending operations include but are not limited to:

— blending of small batches to increase batch size;
— blending of tailings (i.e. relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.

8.43 Blending processes should be adequately controlled and documented and the blended batch should be tested for conformance to established specifications where appropriate.

8.44 The batch record of the blending process should allow traceability back to the individual batches that make up the blend.

8.45 Where physical attributes of the API are critical (e.g. APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g. particle size distribution, bulk density and tap density) that may be affected by the blending process.

8.46 If the blending could adversely affect stability, stability testing of the final blended batches should be performed.

8.47 The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

8.5 Contamination control

8.50 Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carry-over should not result in the carry-over of degradants or microbial contamination that may adversely alter the established impurity profile of the API.

8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.

8.52 Precautions to avoid contamination should be taken when APIs are handled after purification.

9. Packaging and identification labelling of APIs and intermediates

9.1 General

9.10 There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release and handling of packaging and labelling materials.

9.11 Packaging and labelling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.

9.12 Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing and whether they are accepted or rejected.

9.2 Packaging materials

9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

9.21 Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive or absorptive to ensure that they do not alter the quality of the intermediate or API beyond the specified limits.

9.22 If containers are reused, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

9.3 Label issuance and control

9.30 Access to the label storage areas should be limited to authorized personnel.

9.31 Procedures should be used to reconcile the quantities of labels issued, used and returned and to evaluate discrepancies found between the number of containers labelled and the number of labels issued. Such discrepancies should be investigated and the investigation should be approved by the quality unit(s).

9.32 All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be retained and stored in a manner that prevents mix-ups and provides proper identification.

9.33 Obsolete and outdated labels should be destroyed.

9.34 Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

9.35 Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.

9.36 A printed label representative of those used should be included in the batch production record.

9.4 Packaging and labelling operations

9.40 There should be documented procedures designed to ensure that the correct packaging materials and labels are used.

9.41 Labelling operations should be designed to prevent mix-ups. They should be physically or spatially separated from operations involving other intermediates or APIs.

9.42 Labels used on containers of intermediates or APIs should indicate the name or identifying code, the batch number of the product and the storage conditions, when such information is critical to assure the quality of the intermediate or API.

9.43 If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents and special transport conditions and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, this date should be indicated on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis.

9.44 Packaging and labelling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log or other documentation system.

9.45 Packaged and labelled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.

9.46 Intermediate or API containers that are transported outside the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

10. Storage and distribution

10.1 Warehousing procedures

10.10 Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.

10.11 Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

10.2 Distribution procedures

10.20 APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.

10.21 APIs and intermediates should be transported in a manner that does not adversely affect their quality.

10.22 Special transport or storage conditions for an API or intermediate should be stated on the label.

10.23 The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

10.24 A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

11. Laboratory controls

11.1 General controls

11.10 The independent quality unit(s) should have at its disposal adequate laboratory facilities.

11.11 There should be documented procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data. Laboratory records should be maintained in accordance with section 6.6.

11.12 All specifications, sampling plans and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).

11.13 Appropriate specifications should be established for APIs in accordance with accepted standards and be consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.

11.14 Laboratory controls should be followed and documented at the time of performance. Any departures from the above-described procedures should be documented and explained.

11.15 Any OOS result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.

11.16 Reagents and standard solutions should be prepared and labelled following written procedures. “Use by” dates should be applied as appropriate for analytical reagents or standard solutions.

11.17 Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

11.18 Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

11.19 Secondary reference standards should be appropriately prepared, identified, tested, approved and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

11.2 Testing of intermediates and APIs

11.20 For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.

11.21 An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed and classification of each identified impurity (e.g. inorganic, organic or solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs of herbal or animal tissue origin. Biotechnology considerations are covered in ICH Guideline Q6B (*1*).

11.22 The impurity profile should be compared at appropriate intervals with the impurity profile in the regulatory submission or compared with historical data in order to detect changes to the API resulting from modifications to raw materials, equipment operating parameters or the production process.

11.23 Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

11.3 Validation of analytical procedures

See section 12.

11.4 Certificates of analysis

11.40 Authentic certificates of analysis should be issued for each batch of intermediate or API on request.

11.41 Information on the name of the intermediate or API, including where appropriate its grade, the batch number and the date of release, should be provided on the certificate of analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis.

11.42 The certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits and the numerical results obtained (if test results are numerical).

11.43 Certificates should be dated and signed by authorized personnel from the quality unit(s) and should show the name, address and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the certificate of analysis should show the name, address and telephone number of the repacker or reprocessor and a reference to the name of the original manufacturer.

11.44 If new certificates are issued by or on behalf of repackers or reprocessors, agents or brokers, these certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch certificate, a copy of which should be attached.

11.5 Stability monitoring of APIs

11.50 A documented, ongoing testing programme should be designed to monitor the stability characteristics of APIs and the results should be used to confirm appropriate storage conditions and retest or expiry dates.

11.51 The test procedures used in stability testing should be validated and be stability-indicating.

11.52 Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fibre drums, stability samples can be packaged in bags of the same material and in smaller drums of similar or identical material composition to the drums in which the API is marketed.

11.53 Normally the first three commercial production batches should be placed on the stability monitoring programme to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least two years, fewer than three batches can be used.

11.54 Thereafter at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring programme and tested at least annually to confirm the stability.

11.55 For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biological and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first three months, and at three-monthly intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g. nine-month testing) can be considered.

11.56 Where appropriate, the stability storage conditions should be consistent with the WHO guidelines on stability.

11.6 Expiry and retest dating

11.60 When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data and test results).

11.61 An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.

11.62 Preliminary API expiry or retest dates can be based on pilot-scale batches if:

— the pilot batches employ a method of manufacture and a procedure that simulates the final process to be used on a commercial manufacturing scale; and
— the quality of the API represents the material to be made on a commercial scale.

11.63 A representative sample should be taken for the purpose of performing a retest.

11.7 Reserve/retention samples

11.70 The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing.

11.71 Appropriately identified reserve samples of each batch of API should be retained for one year after the expiry date assigned by the manufacturer to the batch, or for three years after distribution of the batch, whichever is the longer. For APIs with retest dates, similar reserve samples should be retained for three years after the batch has been completely distributed by the manufacturer.

11.72 The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

12. Validation

12.1 Validation policy

12.10 The company's overall policy, intentions and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems and personnel responsible for design, review, approval and documentation of each validation phase, should be documented.

12.11 The critical parameters and attributes should normally be identified during the development stage or from historical data and the ranges necessary for the reproducible operation should be defined. This should include:

— defining the API in terms of its critical product attributes;
— identifying process parameters that could affect the critical quality attributes of the API;
— determining the range for each critical process parameter expected to be used during routine manufacturing and process control.

12.12 Validation should extend to those operations determined to be critical to the quality and purity of the API.

12.2 Validation documentation

12.20 A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.

12.21 The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective or concurrent) and the number of process runs.

12.22 A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

12.23 Any variations from the validation protocol should be documented with appropriate justification.

12.3 Qualification

12.30 Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

— design qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose;
— installation qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements;
— operational qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges;
— performance qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

12.4 Approaches to process validation

12.40 Process validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

12.41 There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These three approaches and their applicability are outlined below.

12.42 Prospective validation should normally be performed for all API processes as defined in section 12.1.3. Prospective validation performed on an API process should be completed before the commercial distribution of the FPP manufactured from that API.

12.43 Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API

batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in FPPs for commercial distribution based on thorough monitoring and testing of the API batches.

12.44 An exception can be made for retrospective validation for well-established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities or the production process. This validation approach may be used where:

(1) Critical quality attributes and critical process parameters have been identified.
(2) Appropriate in-process acceptance criteria and controls have been established.
(3) There have not been significant process or product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability.
(4) Impurity profiles have been established for the existing API.

12.45 Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

12.5 Process validation programme

12.50 The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g. complex API processes or API processes with prolonged completion times). Generally, for retrospective validation, data from 10 to 30 consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.

12.51 Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.

12.52 Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to or better than historical data and, where applicable, the profile determined

during process development or for batches used for pivotal clinical and toxicological studies.

12.6 Periodic review of validated systems

12.60 Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

12.7 Cleaning validation

12.70 Cleaning procedures should normally be validated. In general cleaning validation should be directed to those situations or process steps where contamination or carry-over of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.

12.71 Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity and stability.

12.72 The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labelled.

12.73 Sampling should include swabbing, rinsing or alternative methods (e.g. direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g. inner surfaces of hoses, transfer pipes, reactor tanks with small ports for handling toxic materials and small intricate equipment such as micronizers and microfluidizers).

12.74 Validated analytical methods with the sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable

level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable and verifiable and be based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological or physiological activity of the API or its most deleterious component.

12.75 Equipment cleaning or sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g. non-sterile APIs used to manufacture sterile products).

12.76 Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise remain undetected by sampling and/or analysis.

12.8 Validation of analytical methods

12.80 Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

12.81 Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.

12.82 Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.

12.83 Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

13. Change control

13.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.

13.11 Written procedures should cover the identification, documentation, appropriate review, and approval of changes in raw materials, specifications,

analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials and computer software.

13.12 Any proposals for relevant changes to GMP should be drafted, reviewed and approved by the appropriate organizational units and reviewed and approved by the quality unit(s).

13.13 The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on their nature and extent and the effects these changes may have on the process. Scientific judgement should be used to determine what additional testing and validation studies are appropriate to justify a change in a validated process.

13.14 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

13.15 After the change has been implemented there should be an evaluation of the first batches produced or tested under the change.

13.16 The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability programme and/or can be added to the stability monitoring programme.

13.17 Manufacturers of the current dosage form should be notified of changes from established production and process control procedures that can impact the quality of the API.

14. Rejection and reuse of materials

14.1 Rejection

14.10 Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

14.2 Reprocessing

14.20 Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g. distillation, filtration,

chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches it should be included as part of the standard manufacturing process.

14.21 Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

14.22 Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely affected due to the potential formation of by-products and overreacted materials.

14.3 Reworking

14.30 Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for non-conformance should be performed.

14.31 Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.

14.32 Procedures should provide for comparing the impurity profile of each reworked batch with batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

14.4 Recovery of materials and solvents

14.40 Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

14.41 Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or comingling with other approved materials.

14.42 Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

14.43 The use of recovered solvents, mother liquors and other recovered materials should be adequately documented.

14.5 Returns

14.50 Returned intermediates or APIs should be identified as such and quarantined.

14.51 If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return, or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked or destroyed, as appropriate.

14.52 Records of returned intermediates or APIs should be maintained. For each return, documentation should include:

— name and address of the consignee;
— intermediate or API, batch number and quantity returned;
— reason for return; and
— use or disposal of the returned intermediate or API.

15. Complaints and recalls

15.10 All quality-related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

15.11 Complaint records should include:

— name and address of complainant;
— name (and, where appropriate, title) and telephone number of person submitting the complaint;
— nature of the complaint (including name and batch number of the API);
— date the complaint was received;
— action initially taken (including dates and identity of person taking the action);
— any follow-up action taken;
— response provided to the originator of complaint (including date on which the response was sent); and
— final decision on intermediate or API batch or lot.

15.12 Records of complaints should be retained in order to evaluate trends, product-related frequencies and severity with a view to taking additional, and if appropriate, immediate corrective action.

15.13 There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.

15.14 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall and how the recalled material should be treated.

15.15 In the event of a serious or potentially life-threatening situation, local, national and/or international authorities should be informed and their advice sought.

16. Contract manufacturers (including laboratories)

16.10 All contract manufacturers (including laboratories) should comply with GMP defined in this guide. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

16.11 Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations taking place at the contract sites.

16.12 There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.

16.13 The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.

16.14 Where subcontracting is allowed 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.

16.15 Manufacturing and laboratory records should be kept at the site where the activity takes place and be readily available.

16.16 Changes in the process, equipment, test methods, specifications or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

17. Agents, brokers, traders, distributors, repackers and relabellers

17.1 Applicability

17.10 This section applies to any party other than the original manufacturer who may trade and/or take possession of, repack, relabel, manipulate, distribute or store an API or intermediate.

17.11 All agents, brokers, traders, distributors, repackers and relabellers should comply with GMP as defined in this guide.

17.2 Traceability of distributed APIs and intermediates

17.20 Agents, brokers, traders, distributors, repackers or relabellers should maintain complete traceability of the APIs and intermediates that they distribute. Documents that should be retained and available should include:

— identity of original manufacturer;
— address of original manufacturer;
— purchase orders;
— bills of lading (transportation documentation);
— receipt documents;
— name or designation of API or intermediate;
— manufacturer's batch number;
— transportation and distribution records;
— all authentic certificates of analysis, including those of the original manufacturer; and
— retest or expiry date.

17.3 Quality management

17.30 Agents, brokers, traders, distributors, repackers or relabellers should establish, document and implement an effective system of managing quality, as specified in section 2.

17.4 Repackaging, relabelling and holding of APIs and intermediates

17.40 Repackaging, relabelling and holding of APIs and intermediates should be performed under appropriate GMP controls as stipulated in this guide, to avoid mix-ups and loss of API or intermediate identity or purity.

17.41 Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

17.5 Stability

17.50 Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the manufacturer of the API or intermediate.

17.6 Transfer of information

17.60 Agents, brokers, distributors, repackers or relabellers should transfer all quality or regulatory information received from the manufacturer

of an API or intermediate to the customer, and from the customer to the manufacturer of the API or intermediate.

17.61 The agent, broker, trader, distributor, repacker or relabeller who supplies the API or intermediate to the customer should provide the name of the original manufacturer of the API or intermediate and the batch number(s) supplied.

17.62 The agent should also provide the identity of the manufacturer of the original API or intermediate to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original manufacturer of the API or intermediate. (In this context "authorized" refers to authorized by the manufacturer.)

17.63 The specific guidance for certificates of analysis included in section 11.4 should be met.

17.7 Handling of complaints and recalls

17.70 Agents, brokers, traders, distributors, repackers or relabellers should maintain records of complaints and recalls as specified in section 15 for all complaints and recalls that come to their attention.

17.71 If the situation warrants, the agents, brokers, traders, distributors, repackers or relabellers should review the complaint with the manufacturer of the original API or intermediate to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.

17.72 Where a complaint is referred to the original manufacturer of the API or intermediate, the record maintained by the agents, brokers, traders, distributors, repackers or relabellers should include any response received from the original manufacturer of the API or intermediate (including date and information provided).

17.8 Handling of returns

17.80 Returns should be handled as specified in section 14.5.3. The agents, brokers, traders, distributors, repackers or relabellers should maintain documentation of returned APIs and intermediates.

18. Specific guidance for APIs manufactured by cell culture/fermentation[2]

18.1 General

18.10 Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for "classical" processes for production of small molecules and for processes using recombinant and non-recombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

18.11 The term "biotechnological process" (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.

18.12 The term "classical fermentation" refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g. irradiation or chemical mutagenesis) to produce APIs. APIs produced by "classical fermentation" are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.

18.13 Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral

[2] This section has been referred to the Expert Committee on Biological Standardization for discussion and consideration. Reproduced here but currently not adopted by the aforementioned Expert Committee.

contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

18.14 Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or API quality. While this guide starts at the cell culture/fermentation step, prior steps (e.g. cell banking) should be performed under appropriate process controls. This guide covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

18.15 Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring should depend on the step in production and the production conditions (open, closed or contained systems).

18.16 In general, process controls should take into account:

— maintenance of the working cell bank (where appropriate);
— proper inoculation and expansion of the culture;
— control of the critical operating parameters during fermentation/cell culture;
— monitoring of the process for cell growth, viability (for most cell culture processes) and productivity where appropriate;
— harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality;
— monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production; and
— viral safety concerns as described in ICH Guideline Q5A (*2*)..

18.17 Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

18.2 Cell bank maintenance and record keeping

18.20 Access to cell banks should be limited to authorized personnel.

18.21 Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.

18.22 Records of the use of the vials from the cell banks and storage conditions should be maintained.

18.23 Where appropriate, cell banks should be periodically monitored to determine suitability for use.

18.24 See ICH Guideline Q5D (*3*) for a more complete discussion of cell banking.

18.3 Cell culture/fermentation

18.30 Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

18.31 Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.

18.32 Personnel should be appropriately gowned and take special precautions handling the cultures.

18.33 Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.

18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilized.

18.35 Culture media should be sterilized before use when appropriate to protect the quality of the API.

18.36 There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

18.37 Records of contamination events should be maintained.

18.38 Shared (multiproduct) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

18.4 Harvesting, isolation and purification

18.40 Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment and areas designed to minimize the risk of contamination.

18.41 Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.

18.42 All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

18.43 If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

18. 44 Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

18.5 Viral removal/inactivation steps

18.50 See the ICH Guideline Q5A (*2*) for more specific information.

18.51 Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.

18.52 Appropriate precautions should be taken to prevent potential viral contamination from pre-viral to post-viral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.

18.53 The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carry-over (e.g. through equipment or environment) from previous steps.

19. APIs for use in clinical trials

19.1 General

19.10 Not all the controls in the previous sections of this guide are appropriate for the manufacture of a new API for investigational use during

its development. Section 19 provides specific guidance unique to these circumstances.

19.11 The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the pharmaceutical product incorporating the API. Process and test procedures should be flexible to allow for changes to be made as knowledge of the process increases and clinical testing of a pharmaceutical product progresses from the preclinical stages through the clinical stages. Once pharmaceutical development reaches the stage where the API is produced for use in pharmaceutical products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

19.2 Quality

19.20 Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism for the approval of each batch.

19.21 A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.

19.22 Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.

19.23 Quality measures should include a system for testing of raw materials, packaging materials, intermediates and APIs.

19.24 Process and quality problems should be evaluated.

19.25 Labelling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

19.3 Equipment and facilities

19.30 During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use.

19.31 Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

19.4 Control of raw materials

19.40 Raw materials used in production of APIs for use in clinical trials should be evaluated by testing or be received with a supplier's analysis and

subjected to identity testing. When a material is considered hazardous a supplier's analysis should suffice.

19.41 In some instances the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e. use testing) rather than on analytical testing alone.

19.5 Production

19.50 The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records or by other appropriate means. These documents should include information on the use of production materials, equipment, processing and scientific observations.

19.51 Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

19.6 Validation

19.60 Process validation for the production of APIs for use in clinical trials is normally inappropriate where a single API batch is produced or where process changes during development of an API make batch replication difficult or inexact. The combination of controls, calibration and, where appropriate, equipment qualification assures quality of the API during this development phase.

19.61 Process validation should be conducted in accordance with section 12 when batches are produced for commercial use, even when such batches are produced on a pilot scale or small scale.

19.7 Changes

19.70 Changes are expected during development as knowledge is gained and the production is scaled up. Every change in the production, specifications or test procedures should be adequately recorded.

19.8 Laboratory controls

19.80 While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated they should be scientifically sound.

19.81 A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination or discontinuation of an application.

19.82 Expiry and retest dating as defined in section 11.6 applies to existing APIs used in clinical trials. For new APIs section 11.6 does not normally apply in early stages of clinical trials.

19.9 Documentation

19.90 A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

19.91 The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.

19.92 A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination or discontinuation of an application.

20. Glossary

acceptance criteria

Numerical limits, ranges or other suitable measures for acceptance of test results.

active pharmaceutical ingredient (API) (or pharmaceutical substance)

Any substance or mixture of substances intended to be used in the manufacture of a finished pharmaceutical product (FPP) and that, when used in the production of a pharmaceutical product, becomes an active ingredient of the pharmaceutical product. 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.

API starting material

A raw material, intermediate or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house. API starting materials normally have defined chemical properties and structure.

batch (or lot)

A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case

of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

batch number (or lot number)

A unique combination of numbers, letters and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

bioburden

The level and type (e.g. objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

calibration

The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

computer system

A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions.

computerized system

A process or operation integrated with a computer system.

contamination

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

contract manufacturer

A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

critical

Describes a process step, process condition, test requirement or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

cross-contamination

Contamination of a material or product with another material or product.

deviation

Departure from an approved instruction or established standard.

expiry date (or expiration date)

The date placed on the container or labels of an API designating the time during which the API is expected to remain within established shelf-life specifications if stored under defined conditions and after which it should not be used.

finished pharmaceutical product (FPP)

ICH: The dosage form in the final immediate packaging intended for marketing (reference Q1A (*4*)).

WHO: 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.

impurity

Any component present in the intermediate or API that is not the desired entity.

impurity profile

A description of the identified and unidentified impurities present in an API.

in-process control (or process control)

Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

intermediate

A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated.

(*Note*: this guide only addresses those intermediates produced after the point that the company has defined as the point at which the production of the API begins.)

lot

See Batch.

lot number

See Batch number.

manufacture

All operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and related controls.

material

A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs and packaging and labelling materials.

mother liquor

The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API and/or impurities. It may be used for further processing.

packaging material

Any material intended to protect an intermediate or API during storage and transport.

pharmaceutical substance

See Active pharmaceutical ingredient.

procedure

A documented description of the operations to be performed, the precautions to be taken and measures to be applied, directly or indirectly related to the manufacture of an intermediate or API.

process aids

Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid or activated carbon).

process control

See In-process control.

production

All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

qualification

Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

quality assurance (QA)

The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

quality control (QC)

Checking or testing that specifications are met.

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 materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

raw material

A general term used to denote starting materials, reagents and solvents intended for use in the production of intermediates or APIs.

reference standard, primary

A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be:

— obtained from an officially recognized source;
— prepared by independent synthesis;
— obtained from existing production material of high purity; or
— prepared by further purification of existing production material.

reference standard, secondary

A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

reprocessing

Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g. distillation, filtration, chromatography or milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process and not to be reprocessing.

retest date

The date when a material should be re-examined to ensure that it is still suitable for use.

reworking

Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g. recrystallizing with a different solvent).

signature (signed)

See Signed.

signed (signature)

The record of the individual who performed a particular action or review. This record can be in the form of initials, full handwritten signature, personal seal or an authenticated and secure electronic signature.

solvent

An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

specification

A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

validation

A documented programme that provides a high degree of assurance that a specific process, method or system will consistently produce a result meeting predetermined acceptance criteria.

validation protocol

A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters and operating ranges, product characteristics, sampling, test data to be collected, number of validation runs and acceptable test results.

yield, expected

The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot-scale or manufacturing data.

yield, theoretical

The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

References

1. *ICH Harmonised Tripartite Guideline: Specifications: test procedures and acceptance criteria for biotechnological/biological products Q6B*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1999.
2. *ICH Harmonised Tripartite Guideline: Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin Q5A*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1999.
3. *ICH Harmonised Tripartite Guideline: Derivation and characterisation of cell substrates used for production of biotechnological/biological products Q5D*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1997.
4. *ICH Harmonised Tripartite Guideline: Stability testing of new drug substances and products Q1A*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2003.

Appendix 1

List of references for related WHO guidelines

Distribution

(http://www.who.int/medicines/areas/quality_safety/quality_assurance/distribution/en/)

Good trade and distribution practices for pharmaceutical starting materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report.* Geneva, World Health Organization, 2003, Annex 2 (WHO Technical Report Series, No. 917).

WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report.* Geneva, World Health Organization, 2003, Annex 3 (WHO Technical Report Series, No. 917).

Guide to good storage practices for pharmaceuticals In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report.* Geneva, World Health Organization, 2003, Annex 9 (WHO Technical Report Series, No. 908).

Production

(http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html)

Good Manufacturing Practices for Pharmaceutical Products: Main Principles. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report.* Geneva, World Health Organization, 2003, Annex 4 (WHO Technical Report Series, No. 908).

Good manufacturing practices: requirement for the sampling of starting materials (amendment). In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report.* Geneva, World Health Organization, 2005, Annex 2 (WHO Technical Report Series, No. 929).

Sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002, Annex 6 (WHO Technical Report Series, No. 902).

Investigational pharmaceutical products for clinical trials in humans. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations.*

Thirty-fourth report. Geneva, World Health Organization, 1996, Annex 7 (WHO Technical Report Series, No. 863).

Herbal medicinal products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report.* Geneva, World Health Organization, 2006, Annex 3 (WHO Technical Report Series, No. 937).

Water for pharmaceutical use. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report.* Geneva, World Health Organization, 2005, Annex 3 (WHO Technical Report Series, No. 929).

Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report.* Geneva, World Health Organization, 2006, Annex 2 (WHO Technical Report Series, No. 937).

Validation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report.* Geneva, World Health Organization, 2006, Annex 4 (WHO Technical Report Series, No. 937).

Quality control

(http://www.who.int/medicines/areas/quality_safety/quality_assurance/control/en/index.html)

The International Pharmacopoeia (Ph. Int.) — Fourth Edition + First Supplement. Geneva, World Health Organization, 2006.

General guidelines for the establishment, maintenance and distribution of chemical reference substances. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report.* Geneva, World Health Organization, 2007, Annex 3 (WHO Technical Report Series, No. 943).

Considerations for requesting analyses of drug samples. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002, Annex 4 (WHO Technical Report Series, No. 902).

Model certificate of analysis. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002, Annex 10 (WHO Technical Report Series, No. 902).

Related regulatory standards

(http://www.who.int/medicines/areas/quality_safety/quality_assurance/regulatory_standards/en/)

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, Annex 2 (WHO Technical Report Series, No. 953).

Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report.* Geneva, World Health Organization, 2009, Annex 4 (WHO Technical Report Series, No. 953).

Guidelines on active pharmaceutical ingredient master file procedure. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-second report.* Geneva, World Health Organization, 2008, Annex 4 (WHO Technical Report Series, No. 948).

Guidance on variations to a prequalified product dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report.* Geneva, World Health Organization, 2007, Annex 6 (WHO Technical Report Series, No. 943).

WHO guidelines for sampling of pharmaceutical products and related materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report.* Geneva, World Health Organization, 2005, Annex 4 (WHO Technical Report Series, No. 929).

Appendix 2

General notes: additional clarifications and explanations

2.1.1 The intent of this clause is that senior management of the API manufacturer has the responsibility to ensure that there is an effective quality management system in place and that all employees are made aware of their roles and responsibilities in assuring the quality of the API(s) produced.

2.3 The intent of this clause is to specify the roles and responsibilities that should apply to production activities and, in particular, that these responsibilities should not be delegated to non-production personnel within the company or to any persons outside the company.

5.2.1 This clause requires a written standard operating procedure (SOP) covering the maintenance of equipment. Important information to specify in this SOP should include:

— who is responsible for coordinating equipment maintenance activities (usually production management or engineering management);
— a provision that a schedule of planned preventive maintenance of equipment should be available (a useful reference is *ISPE Good Practice Guide: Maintenance. May 2009*) (*1*);
— a statement of the necessity to follow proper change control procedures where non-routine repairs, or modifications, replacements or other activities, are required.

7.1.2 There is an expectation that suppliers of critical materials should be subject to on-site audits as part of the company's supplier qualification programme.

7.2.1 There is an expectation that upon receipt and before acceptance of materials, each container or grouping of containers of materials should be examined visually for correct labelling, including correlation between the name used by the supplier and the in-house name. If these names are different, both names should be recorded and verified against a previously approved list of synonyms and checked by a scientifically qualified person.

7.3.1 This clause requires that at least one test be performed to verify the identity of each batch of material received. For clarification, one test for identity may not be sufficient in the majority of cases as this is dependent on various aspects, including supplier qualification.

11.7.3 For clarification, the reserve sample should be stored in a packaging system designed to give maximum protection of the API against change over time, e.g. a glass bottle with tightly fitted cap.

17. Refer to WHO GTDP *(2)* and WHO GMP for excipients *(3)*.

18. See footnote on p. 174.

API starting material

As discussed in this document the introduction of the API starting material into the manufacturing process is where the requirements of GMP commence.

The API starting material itself needs to be proposed and justified by the manufacturer and accepted as such by assessors. This justification should be documented and be available for review by WHO GMP inspectors.

The API starting material should be fully characterized according to identity and purity. In addition, the steps prior to the step where the API starting material appears, which may involve "starting materials for synthesis", should be available in he form of a flow chart.

In general, the starting materials for synthesis should:

— be a synthetic precursor one or more synthetic steps prior to the final API intermediate;
— be a well characterized, isolated and purified substance with a fully elucidated structure;
— have well defined specifications which include one or more specific identity tests, and tests and limits for potency, specified and unspecified impurities and total impurities.

References

1. International Society for Pharmaceutical Engineering. *ISPE good practice guide: maintenance*. 2009 (http://www.ispe.org/cs/ispe_good_practice_guides_section/ispe_good_practice_guides).
2. Good trade and distribution practices for pharmaceutical starting materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report.* Geneva, World Health Organization, 2003, Annex 2 (WHO Technical Report Series, No. 917) (http://www.who.int/medicines/areas/quality_safety/quality_assurance/distribution/en/index.html).
3. WHO GMP for excipients In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report*. Geneva, World Health Organization, 1999, Annex 5 (WHO Technical Report Series, No. 885) (http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html); and in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2,* 2nd updated ed., *Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007.

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Annex 3

WHO good manufacturing practices for pharmaceutical products containing hazardous substances

1. Introduction
2. General
3. Glossary
4. Risk assessment
5. Product protection
6. Personal protection equipment and breathing air systems
7. Environmental protection
8. Facility layout
9. Air-handling systems
10. Air-handling units
11. Safe change filter housings
12. Personnel decontamination systems
13. Effluent treatment
14. Maintenance
15. Qualification and validation

References

1. Introduction

1.1 These guidelines set out good practices applicable to facilities handling pharmaceutical products (including active pharmaceutical ingredients (APIs)) that contain hazardous substances such as certain hormones, steroids or cytotoxins. They do not replace national legislation for protection of the environment and personnel. Other WHO guides to good manufacturing practices (GMP) and regulations need to be observed in addition to the workers' safety criteria (*1–4*).

1.2 These guidelines are to be read in conjunction with other WHO GMP guidelines with respect to building finishes and general services installations, among others. See the reference list for relevant publications which serve as additional background material. The primary focus of these guidelines is on the air-conditioning and ventilation systems of the facility; however, the document also provides some guidance on personnel protection.

1.3 The areas to which this document applies include all zones where the handling of products could lead to cross-contamination, exposure of personnel, or discharge to the environment. This includes research and development facilities, and the sites of API manufacturing and storage and of finished product manufacturing.

1.4 Where possible products should be manufactured in closed systems.

2. General

2.1 Facilities should be designed and operated in accordance with the main GMP principles, as follows:

— to ensure quality of product;
— to protect the operators from possible harmful effects of products containing hazardous substances; and
— to protect the environment from contamination and thereby protect the public from possible harmful effects of products containing hazardous substances.

2.2 The production of certain products containing hazardous substances should generally be conducted in separate, dedicated, self-contained facilities.

These *self-contained facilities* may be in the same building as another facility but should be separated by a physical barrier and have, e.g. separate entrances, staff facilities and air-handling systems. The extent of the separation from adjacent facilities and sharing of common services should be determined by risk assessment.

2.3 In general these manufacturing facilities should be regarded as containment facilities.

2.4 The effective operation of a facility may require the combination of some or all of the following aspects:

— appropriate facility design and layout, with the emphasis on safely containing the materials being handled. Manufacturing processes using closed systems or barrier technology enhance operator and product protection;
— manufacturing process controls including adherence to standard operating procedures (SOPs);
— appropriately designed environmental control systems (ECS) or heating, ventilation and air-conditioning (HVAC);
— extraction systems;
— personal protective equipment (PPE);
— appropriate degowning and decontamination procedures;
— industrial hygiene (monitoring staff exposure levels);
— medical surveillance (monitoring staff exposure levels); and
— administrative controls.

3. Glossary

The definitions given below apply to terms used in these guidelines. They may have a different meaning in other contexts.

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.

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.

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 (this can be a personnel airlock (PAL) or a material airlock (MAL)).

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.

barrier technology

A system designed to segregate people from the product, contain contaminants or segregate two areas, which could be a barrier isolator (BI) or a restricted access barrier system (RABS):

- A BI is a unit supplied with high-efficiency particulate air (HEPA) filtered air that provides uncompromised continuous isolation of its interior from the external environment, including surrounding clean room air and personnel.
- A RABS is a type of barrier system that reduces or eliminates interventions into the critical zone. In practice, its level of contamination control is less than that of a barrier isolator.

clean room

A room or 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.

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.

cross-contamination

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

environmental control system (ECS)

Environmental control system, also referred to as heating, ventilation and air-conditioning (HVAC).

facility

The built environment within which the clean area installation and associated controlled environments operate together with their supporting infrastructure.

hazardous substance or product

A product or substance that may present a substantial risk of injury, to health or to the environment.

heating, ventilation and air-conditioning (HVAC)

Heating, ventilation and air-conditioning, also referred to as environmental control system (ECS).

high efficiency particulate air (HEPA) filter

High efficiency particulate air filter.

ISO 14644

International standard relating to the design, classification and testing of clean environments (*5*).

laminar airflow (LAF)

A rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (modern standards no longer refer to laminar flow, but have adopted the term unidirectional airflow).

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.

occupational exposure level (OEL)

Airborne concentration of substances that will not result in adverse effects to most healthy workers, exposed for 8 hours/day, 40 hours/week.

operating range

The range of validated critical parameters within which acceptable products can be manufactured.

personal protective equipment (PPE)

The necessary garments and equipment required to protect the operator in the workplace.

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

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.

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.

unidirectional airflow (UDAF)

A rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines.

validation

The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

4. Risk assessment

4.1 Not all products containing hazardous substances are equally potent and risk assessments should be carried out to determine the potential hazards to operators and to the environment. The risk assessment should also determine which phases of the product production and control cycles, from manufacture of the API to distribution of the finished product, would fall under the requirements of these guidelines. Risk assessments applicable to the environment should include airborne contamination as well as liquid effluent contamination.

4.2 Assuming that the risk assessment determines that the products or materials being handled pose a risk to the operators and/or the public and/or the environment, the guidelines to be followed for the design and operation of the facility should be as detailed in this document.

4.3 The toxicological data available, such as permissible occupational exposure levels (OEL) for the product, should be taken into account when conducting the risk assessment.

4.4 The risk assessment should take into account the national or international occupational health and safety requirements for OELs in the work environment.

5. Product protection

5.1 The requirement for producing quality products, with respect to protection from contamination and cross-contamination, clean room class of air, temperature and humidity should be as for other pharmaceutical products. These requirements are covered in other WHO GMP guidelines.

6. Personal protection equipment and breathing air systems

6.1 The fundamental design principle for a facility and its production equipment is to provide product containment and operator protection. Should the facility and equipment design not provide adequate product containment, operator protection should be provided. If facility and equipment design are adequate, a spillage or non-routine incident could cause a hazardous situation, in which case PPE should be available. Unless otherwise specified in the material safety data sheet, operators should be protected from exposure with an appropriate method, such as by wearing:

— flash-spun, high-density polyethylene fibre material suits or impervious washable protective suits. Integral hoods may be required depending on the respirator type used;
— flash-spun, high-density polyethylene fibre material shoes, lower leg covers or cleanable boots;
— suitable single-use, disposable gloves. Double gloves should be worn where direct active contact with the product cannot be avoided. Gloves should be taped or sealed on to the protective suit sleeves; and
— respirator eye and face protection with associated breathing air systems.

6.2 Where breathing air systems are used, these should be provided to supply safe breathing air to the operators to prevent them from inhaling air from within the facility. Personnel should be appropriately trained and assessed in the use of these systems before they can enter the area. The breathing air systems should comprise a protective face mask, which should form an integral part of a protective suit. The breathing air systems could be any of the systems described below:

- a central air supply system which connects to the operator's face mask by means of flexible hoses and quick coupling sockets, also called an airline respirator (AR). The air connection should incorporate a one-way air system to prevent contaminated air entering the face mask during connection or disconnection. The air supply should be treated to ensure a temperature and level of humidity that are comfortable for the operator. The air source could be a high pressure fan or an air compressor. If an air compressor is used, it should be of the oil-free type or have suitable oil removal filters fitted;
- a self-contained breathing apparatus (SCBA) or powered air purifying respirator (PAPR) that is securely attached to the operator's belt and connects to the operator's face mask. This system draws air from the room in which the operator is working and the air supply is delivered to the face mask by means of a battery-driven fan. The AR provides superior protection to the PAPR apparatus;
- for zones with lower contamination levels, a half-mask high efficiency particulate air filter (HEPA) cartridge respirator of N95-type paper filter mask may be acceptable.

6.3 The selection of the respirator type is based on the relationship between the accepted OEL and the respirator-certified protection factor (PF).

6.4 The air supplies should be filtered through a final filter, which should be a HEPA filter rated as an H13 filter according to EN 1822 (European Norm). The supply of breathing air into the face mask and/or protective suit should result in the interior of the mask and suit being at a positive pressure relative to the facility environment.

6.5 Central breathing air supply systems should have a 100% back-up system in the event of the main system failing. This could be in the form of a gas bottle system with at least 5 minutes supply. Changeover from the normal supply to the back-up supply should be automatic. The system should have a monitoring system and send alarm signals to a permanently manned location in the following situations:

— failure of main air supply;
— temperature out of specification (OOS);
— humidity OOS;
— carbon dioxide (CO2) OOS;
— carbon monoxide (CO) OOS; and
— sulfur dioxide (SO2) OOS.

6.6 Breathing air should be filtered by means of pre-filters, coalescing filters and final filters to have the minimum air quality specifications of ISO 8573-1 3-9-1 and EN 12021:1999.

6.7 Where air is delivered through a central system the piping should not cause any contamination to be liberated into the air stream. Stainless steel piping is preferred. The final filters should be as close as possible to the operator connection points. The operator hose connection to the air supply should be a dedicated connection specific to the breathing air system (to avoid inadvertent connection to a different gas system).

7. Environmental protection

7.1 Due to the hazardous nature of the products being handled in the facility, neither the product nor its residues should be allowed to escape into the atmosphere or to be discharged directly to normal drainage systems.

7.2 The external atmosphere and the public in the vicinity of the facility should be protected from possible harm from hazardous substances.

7.3 If liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain.

7.4 Exhaust air filtration to ensure environmental protection is discussed in section 11.

8. Facility layout

8.1 The premises should be designed and constructed to prevent the ingress or egress of contaminants. In drawing up the facility design, attention should be paid to the level of containment provided by the equipment.

8.2 The link between the interior and exterior of the premises should be through airlocks (PAL and/or MAL), changing rooms, pass boxes, pass-through hatches, decontamination devices, etc. These entry and exit doors for materials and personnel should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time.

8.3 The changing rooms should have an arrangement with a step-over-bench. The facilities on the exit side should incorporate showers for the operators.

8.4 The premises should be laid out and designed so as to facilitate the required pressure cascades and containment.

8.5 The premises (and equipment) should be appropriately designed and installed to facilitate cleaning and decontamination.

8.6 The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) to ensure that the designation and conditions of use of all the rooms are correctly shown.

8.7 The flow of people and products should be clearly marked on the layouts and plans.

8.8 The activities carried out in the vicinity of the site should be indicated.

8.9 Plans should describe the ventilation systems, indicating inlets and outlets, in relation to other facility air inlet and outlet points.

8.10 The facility should be a well-sealed structure with no air leakage through ceilings, cracks or service areas.

8.11 Areas of the facility where exposed product presents a risk should be maintained at a negative air pressure relative to the environment.

9. Air-handling systems

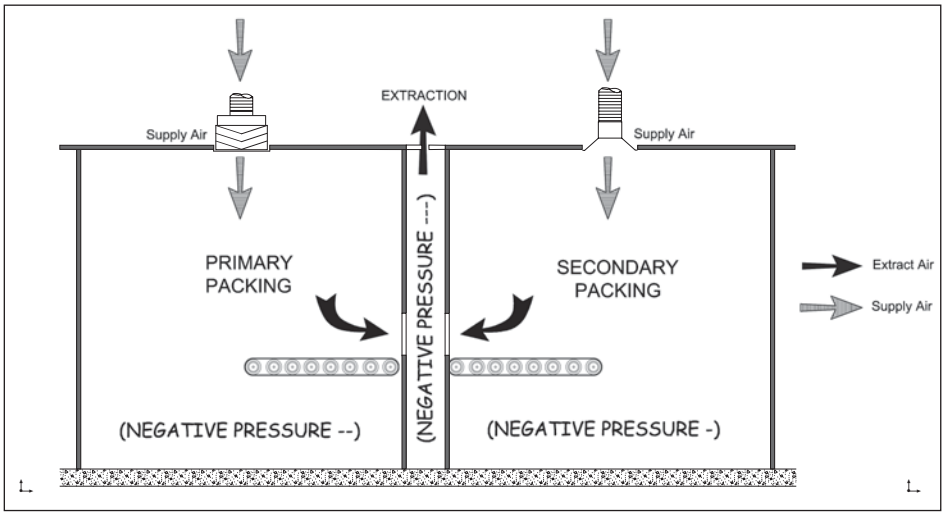
9.1 The HVAC system should be appropriately designed, installed and maintained to ensure protection of product, personnel and the environment.

9.2 The principles of airflow direction, air filtration standards, temperature, humidity and related parameters should comply with the minimum requirements as set out in Annex 2 of the fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2006 (*2*).

9.3 Facilities and premises dealing with hazardous substances should have the following basic air-handling characteristics:

- There should be no direct venting of air to the outside.
- Air-conditioning or ventilation should result in a negative pressure relative to the outside. Air pressure differentials should be such that there is no uncontrolled flow of air between the work area and the external environment.
- Appropriate air pressure alarm systems should be provided to warn of any pressure cascade reversal or loss of design pressure status. The appropriate design, alert and action limits should be in place. System redundancies should be in place to respond appropriately to pressure cascade failure.
- The starting and stopping of the supply and exhaust air fan should be synchronized such that the premises remain at a negative pressure during start-up and shut-down.
- The air pressure cascade within the facility, although negative relative to the environment, should comply with normal pharmaceutical pressure cascade requirements with regards to product protection, dust containment and personnel protection.
- Visual indication of the status of room pressures should be provided in each room.
- Air should be exhausted to the outside through HEPA filters and not be recirculated except to the same area, and provided that a further HEPA filtration stage is applied to the return air. Where HEPA filters are

Figure 1
Typical airflow pattern for contaminant



mentioned in these guidelines, this refers to HEPA filters with a minimum rating of H13 according to EN 1822.

- Where possible, single-pass air-handling systems with no recirculation should be provided.
- Exhaust air or return air should be filtered through a safe-change or bag-in-bag-out filter housing. The filter housing should contain pre-filters and HEPA filters, both of which should be removable with the safe bagging system.
- Changing rooms should be supplied with air filtered to the same standard as that for the work area they serve.
- Airlocks, pass-through hatches, etc., should have supply and extract air to provide the necessary air pressure cascade and containment. The final, or containment perimeter, airlock or pass-through hatch bordering on an external or non-GMP area should be at a positive pressure relative to the environment, to prevent the ingress of contaminants to the facility.
- If the facility provides insufficient containment, and operators' garments are contaminated with dust, the operators leaving the containment area should pass through a decontamination system, e.g. air showers or a mist shower system, to assist with removing or controlling dust particles on their garments. Operators should follow this route before de-gowning to use the ablutions or canteen facilities. All garments leaving the facility for laundering should be safely bagged. Appropriate means for protecting laundry staff and prevention of contamination of other garments from non-hazardous facilities should be in place.

9.4 If required, appropriate measures should be taken to prevent airflow from the primary packing area (through the conveyor "mouse hole") to the secondary packing area.

Note: This could be overcome by having a pass-through chamber over the "mouse hole", which is maintained at a negative pressure to both primary and secondary packing. This typical arrangement is illustrated in Figure 1. This principle can be applied to other situations where containment from two sides is required.

9.5 Where possible, HEPA filters in the supply air system should be terminally mounted to provide protection against back-flow cross-contamination in the event of a failure in the supply airflow.

9.6 In some cases consideration can be given to the use of biosafety cabinets, isolation systems or glove boxes as a means for containment and operator protection.

9.7 There should be a system description including schematic drawings detailing the filters and their specifications, the number of air changes per hour, pressure gradients, clean room classes and related specifications. These should be available for inspection.

9.8 There should be an indication of pressure gradients that are monitored by means of digital or analogue pressure indicators.

9.9 Consideration should be given to providing an emergency power supply, e.g. diesel generators, to ensure that safe operation of the premises and systems can be maintained at all times.

10. Air-handling units

10.1 The air-handling units (AHUs) supplying air to the facility should conform to AHU requirements as detailed in *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials* (*1*) and *Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* (*2*) and the filtration should be consistent with the zone concepts and product protection required.

10.2 The decision to use return air or recirculated air should be made on the basis of a risk assessment.

10.3 Where a full fresh-air or single-pass system is used, an energy recovery wheel could be considered. In such cases, there should not be any potential for air leakage between the supply air and exhaust air as it passes through the wheel. 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. (Alternatives to the energy recovery wheel, such as crossover plate heat exchangers, heat pipes and water coil heat exchangers, may be used.)

10.4 Risk management principles should be applied to address the potential of cross-contamination where energy wheels are used.

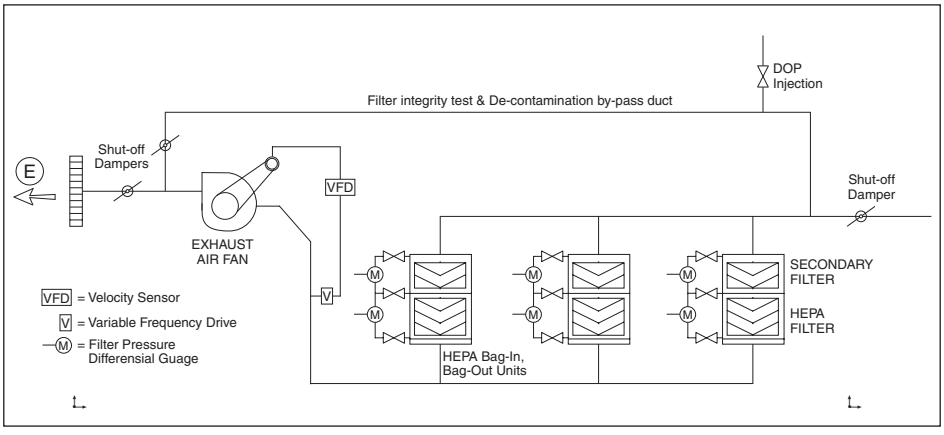
10.5 If return air is to be recirculated it should pass through a safe change filtration system before being introduced back into the supply AHU. The return air fan could form part of the AHU; however, the safe change filter should be a dedicated unit. With this arrangement the return air passes through two sets of HEPA filters in series, i.e. the return air filters in the safe change housing and the supply air HEPA filters. The supply air HEPA filters could either be located in the AHU or terminally located at the supply diffusers, depending on the clean room classification of the facility.

10.6 The starting and stopping of the supply and exhaust air fans, and associated system ventilation fans, should be synchronized such that the premises retain their design pressure and flow relationships during start-up and shut-down. Processing should stop when the fans are not running. This fan interlock sequence should also apply if any fan should fail, to ensure that there is no airflow reversal in the system.

11. Safe change filter housings

11.1 Safe change or bag-in-bag-out filter housings should be suitably designed to provide operator protection and to prevent dust from the filters entering the atmosphere when filters are changed.

Figure 2
Safe change filter bypass arrangement



11.2 The final filters on the safe change unit should be HEPA filters with at least an H13 classification according to EN 1822 filter standards. For dusty return, air pre-filtration may also be required to prolong the life of the HEPA filters. The pre-filtration filters should also be removable through the bag-in-bag-out method.

11.3 For exhaust systems where the discharge contaminant is considered particularly hazardous, two banks of HEPA filters in series should be considered to provide additional protection should the first filter fail.

11.4 All filter banks should be provided with pressure differential indication gauges to indicate the filter dust loading and remaining lifespan of the filters. Connection to these gauges should be copper or stainless steel and not plastic tubing, which could perish causing a contamination hazard. The tube connections on the filter casing should be provided with stopcocks, for safe removal or calibration of gauges.

11.5 Monitoring of filters should be done at regular intervals to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in ambient contamination.

11.6 Computer-based data monitoring systems may be installed to monitor filter condition.

11.7 Filter pressure gauges should be marked with the clean filter resistance and the change-out filter resistance.

11.8 Installed filter leakage tests should be performed in accordance with ISO 14644-3. Injection ports (upstream) and access ports (downstream) should, therefore, be provided for this purpose.

11.9 The exhaust air fan on a safe change filter system should be located after the filters so that the filter housing is maintained at a negative pressure. This poses a difficulty when carrying out filter integrity tests, and for this reason a bypass damper system should be provided, as illustrated in Figure 2, so that air can be circulated through the HEPA filters, while the scanning ports are open. Alternatively an independent booster fan system can be used, with appropriate shut-off dampers.

11.10 The bypass arrangement as shown in Figure 2 also permits decontamination of the filters by means of circulation of a sanitizing agent.

11.11 All exhaust systems from the facility, including dust extraction systems, vacuum system exhaust, fluid bed drier exhaust and coating pan exhaust, should be passed through safe change filter housings before being exhausted to the atmosphere.

11.12 All exhaust points outside the building should be located as far as possible from air entry points, and exit points should be at a high level to minimize the possibility of re-entrainment of exhaust air. Dominant and seasonal wind directions should be taken into account when positioning exhaust and supply points.

11.13 Where excessively dust-laden air is handled, a dust collector or bag house should be considered, with the dust collector being located in an enclosed room maintained at a negative pressure. Access control, maintenance staff, personal protection equipment (PPE) and breathing air systems should then be provided to protect the operators during removal of dust from the collector bins.

11.14 Portable vacuum cleaners and portable dust collectors should be fitted with H13 HEPA filters. These types of units should be emptied and cleaned in a room which is under negative pressure relative to the environment. Personnel should be provided with suitable PPE.

11.15 Records of the safe disposal of all contaminated filters and dust should be kept.

12. Personnel decontamination systems

12.1 If required, a means of preventing contaminants from leaving the facility on the garments of personnel should be provided. This could be in the form of an air shower; mist shower, water shower or appropriate device.

12.2 An air shower comprises an airlock where high velocity air is supplied through air nozzles (e.g. from the sides of the airlock) in order to dislodge dust particles. Air extraction grilles (e.g. at low level) should draw the air away and return it to the filtration system. Some air showers may also incorporate a vertical unidirectional airflow section at the exit end, to flush contaminants away.

Note: When air showers are used these should be correctly designed to effectively extract dust.

Air filtration of the supply air and return or exhaust air should comply with the same filtration standards as used in the manufacturing facility. Normally the fan should be activated by opening the door as the operator enters the shower, with a timing device on the exit door interlock to allow sufficient time for the decontamination process to be effective.

12.3 Flushing devices similar to air or mist showers for personnel could be used at material exits to assist with removing contaminants.

12.4 Wet mist or fog decontamination systems for operators can be employed for deactivating contaminants on the operator's garments, or

causing contaminants to adhere to the garments so that they are not easily liberated.

12.5 Personnel should change into clean garments after having taken a shower.

13. Effluent treatment

13.1 Liquid and solid waste effluent should be handled in such a manner as not to present a risk of contamination to the product, personnel or to the environment.

13.2 All effluent should be disposed of in a safe manner, and the means of disposal should be documented. Where external contractors are used for effluent disposal they should have certification authorizing them to handle and treat hazardous products.

14. Maintenance

14.1 The efficient and safe operation of a facility handling hazardous materials is reliant on regular maintenance being carried out, to ensure that all parameters remain within specified tolerances. See *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials* (*1*) *or* WHO Technical Report Series, No. 937, Annex 2, section 8.3 (*2*) for further details on maintenance.

15. Qualification and validation

15.1 System qualification and validation should be carried out as described in other WHO guidelines.

References

1. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2,* 2nd updated ed. *Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007.
2. Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006, Annex 2 (WHO Technical Report Series, No. 937).
3. *Health Canada: Laboratory biosafety guidelines*, 3rd ed. Ottawa, Health Canada, 2004.
4. WHO good manufacturing practices for sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report*. Geneva, World Health Organization, 2010, Annex 4 (WHO Technical Report Series, No. 957).
5. ISO: International Standard. *Clean rooms and associated controlled environments. ISO 14644*. Geneva, International Organization for Standardization.

WHO Technical Report Series, No. 957, 2010

Annex 4

WHO good manufacturing practices for sterile pharmaceutical products

Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations in its thirty-sixth report in 1999 adopted *WHO good manufacturing practices for sterile pharmaceutical products* (WHO Technical Report Series, No. 902, 2002, Annex 6) (http://whqlibdoc.who.int/trs/WHO_TRS_902.pdf); and published in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2.* 2nd updated ed. *Good manufacturing practices and inspection* (2007) (*1*).

Following implementation of these WHO good manufacturing practices (GMP) within the context of the WHO Prequalification Programme, a proposal for revision is being submitted to take into consideration new developments. The proposal for revision of the above-mentioned guidance is being made to bring the WHO GMP into line with International Standardization Organization standard ISO 14644-1 (*2*) and recent practices of the United States (*3*), Japan (*4*), the European Union (*5*) and the Pharmaceutical Inspection Co-operation Scheme.

- New chapters on Isolator technology and Blow/fill/seal technology have been added to the document.
- The chapter on Finishing of sterile products has been amended and provisions have been given for capping of vials.
- The chapter entitled Manufacture of sterile preparations has been amended and provisions have been given for clean room and clean-air device monitoring.

Implementation of these new practices may need to be undertaken for certain parts using a step-wise approach, especially the part relating to the provision for capping in a clean or sterile environment, as this is currently not implemented in most industries.

On the basis of the above, the following text is proposed to replace the previously published guidance.

WHO good manufacturing practices for sterile pharmaceutical products

1. General considerations
2. Quality control
3. Sanitation
4. Manufacture of sterile preparations
5. Sterilization
6. Terminal sterilization
7. Aseptic processing and sterilization by filtration
8. Isolator technology
9. Blow/fill/seal technology
10. Personnel
11. Premises
12. Equipment
13. Finishing of sterile products

References

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).

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 (*6*) 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 (*7*).

4.6 Clean room and clean-air device classification

4.6.1 Clean rooms and clean-air devices should be classified in accordance with ISO 14644 (*2, 6–9*).

4.6.1.1 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 concentration

	Maximum permitted number of particles per m³ greater than or equal to the tabulated size			
	At rest[a]		**In operation[b]**	
Grade	0.5 µm	5.0µm	0.5 µm	5.0µm
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, 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 considered particle size and the method for evaluation of the data collected. For classification of grade A zones (at rest and operational) and grade B zones (at rest), the minimum sample volume is based on the ISO 5 limit for the number of particles ≥ 0.5 µm (3520). Similarly, for classification of grade B (operational), grade C (at rest and operational), and grade D (at rest), the minimum sample volume is based on the class limits for particles ≥ 0.5 µm shown in Table 1.

For classification purposes in grade A zones, a minimum sample volume of 1 m³ 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. There should not be less than 3 sample locations per room.

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 (*8*) provides information on testing to demonstrate continued compliance with the assigned cleanliness classification.

4.7 Clean room and clean-air device monitoring

4.7.1 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.

4.7.2 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.

4.7.3 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.

4.7.4 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.

4.7.5 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.

4.7.6 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) (*6*).

4.7.7 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.

4.7.8 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.

4.7.9 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.

4.7.10 Examples of operations to be carried out in the various grades are given in Table 2 (see also sections 4.14–4.22).

Table 2
Examples of operations to be carried out in the various grades

Grade	Examples of operations for terminally sterilized products (see sections 4.14–4.17)
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 4.18–4.22)
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 the cleanliness 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 levels 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 levels, 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 (*10*).

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 process.

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 to be 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 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 (*10*).

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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Annex 5

WHO good distribution practices for pharmaceutical products

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References

1. Introduction

Distribution is an important activity in the integrated supply-chain management of pharmaceutical products. Various people and entities are generally responsible for the handling, storage and distribution of such products. In some cases, however, a person or entity is only involved in and responsible for certain elements of the distribution process. The objective of these guidelines is to assist in ensuring the quality and identity of pharmaceutical products during all aspects of the distribution process. These aspects include, but are not limited to, procurement, purchasing, storage, distribution, transportation, repackaging, relabelling, documentation and record-keeping practices.

The storage, sale and distribution of pharmaceutical products are often carried out by various companies, institutions and individuals. This document sets out appropriate steps to assist in fulfilling the responsibilities involved in the different aspects of the distribution process within the supply chain and to avoid the introduction of counterfeits into the marketplace via the distribution chain. The relevant sections should be considered by various participants as applicable to the particular role that they play in the distribution of pharmaceutical products.

The nature of the risks involved is likely to be similar to that for risks encountered in the manufacturing environment, e.g. mix-ups, adulteration, contamination and cross-contamination. When the distribution chain is interrupted by manufacturing steps such as repackaging and relabelling, the principles of good manufacturing practices (GMP) should be applied to these processes.

Counterfeit pharmaceutical products are a real threat to public health and safety. Consequently, it is essential to protect the pharmaceutical supply chain against the penetration of such products. Weak points in the distribution processes of pharmaceutical products provide an avenue for counterfeit as well as illegally imported, stolen and substandard medicines to enter the supply chain. This is a concern in both developed and developing countries. The methods by which such products enter the supply chain have become increasingly complex and have resulted in the development of thriving secondary and grey markets throughout the world. The involvement of unauthorized entities in the distribution and sale of pharmaceutical products is a particular concern. Only a joint approach including all parties involved in the supply chain can be successful in the fight against counterfeit pharmaceutical products and, therefore, all parties active in the market should take an active part in collaborative activities.

Different models for the distribution of pharmaceutical products are used in different countries and sometimes within the same country, for example,

in the public and the private sector. These guidelines are intended to be applicable to all persons and outlets involved in any aspect of the distribution of pharmaceutical products from the premises of the manufacturer of the product to the person dispensing or providing pharmaceutical products directly to a patient or his or her agent. This includes all parties involved in trade and distribution of medicines, pharmaceutical manufacturers, including the manufacturers of finished products and pharmaceutical wholesalers as well as other parties such as brokers, suppliers, distributors, logistics providers, traders, transport companies and forwarding agents and their employees.

The relevant sections of these guidelines should also be considered for implementation by, among others, governments, regulatory bodies, international procurement organizations, donor agencies and certifying bodies, as well as all parties involved in any aspect of the trade and distribution of pharmaceutical products, including health care workers. The guidelines can also be used as a tool in the prevention of the distribution of counterfeit pharmaceutical products. It should, however, be noted that these are general guidelines which may be adapted to suit the prevailing situations and conditions in individual countries. National or regional guidelines may be developed to meet specific needs and situations in a particular region or country.

To maintain the original quality of pharmaceutical products, every party active in the distribution chain has to comply with the applicable legislation and regulations. Every activity in the distribution of pharmaceutical products should be carried out according to the principles of GMP, good storage practice (GSP) and good distribution practice (GDP) as applicable. These guidelines do not deal with all aspects of the standards for the storage of pharmaceuticals which are covered in the *WHO guide to good storage practices for pharmaceuticals* (*1*). The dispensing to patients is addressed in the WHO good pharmacy practice (GPP) guide (*2*). These guidelines should also be read in conjunction with other WHO guidelines *(3–6)*.

2. Scope of the document

This document lays down guidelines for the distribution of pharmaceutical products. Depending on the national and regional legislation on pharmaceuticals, these guidelines may apply equally to products for human and for veterinary use. The guidelines thus cover products for which a prescription is required by the patient, products which may be provided to a patient without a prescription, biologicals and vaccines. Although medical devices are not included in the definition of pharmaceutical products for the purposes of this document, the main principles established in this document may also be used where applicable for medical devices.

The document does not specifically cover GMP aspects of finished products in bulk, distribution of labels or packaging, as these aspects are considered to be covered by other guidelines (*3*).

The principles for the distribution of starting materials (active pharmaceutical ingredients (APIs) and excipients) are also not covered here. These are laid down in the WHO guidance *Good trade and distribution practices for pharmaceutical starting materials (7).*

3. Glossary

The definitions provided below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents.

agreement

Arrangement undertaken by and legally binding on parties.

auditing

An independent and objective activity designed to add value and improve an organization's operations by helping the organization to accomplish its objectives by using a systematic, disciplined approach to evaluate and improve the effectiveness of risk management, control and governance processes.

batch

A defined quantity of pharmaceutical products processed in a single process or series of processes so that it is expected to be homogeneous.

batch number

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

consignment

The quantity of pharmaceutical products 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 pharmaceutical products belonging to more than one batch.

container

The material employed in the packaging of a pharmaceutical product. Containers include primary, secondary and transportation containers.

Containers are referred to as primary if they are intended to be in direct contact with the product. Secondary containers are not intended to be in direct contact with the product.

contamination

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

contract

Business agreement for the supply of goods or performance of work at a specified price.

counterfeit pharmaceutical product

A pharmaceutical product which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products, and counterfeit pharmaceutical products may include products with the correct ingredients, with the wrong ingredients, without active ingredients, with an incorrect quantity of active ingredient or with fake packaging.

cross-contamination

Contamination of a starting material, intermediate product or finished pharmaceutical product with another starting material or product during production, storage and transportation.

distribution

The procuring, purchasing, holding, storing, selling, supplying, importing, exporting, or movement of pharmaceutical products, with the exception of the dispensing or providing pharmaceutical products directly to a patient or his or her agent.

expiry date

The date given on the individual container (usually on the label) of a pharmaceutical product up to and including the date on which the product is expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture.

first expiry/first out (FEFO)

A distribution procedure that ensures that the stock with the earliest expiry date is distributed and/or used before an identical stock item with a later expiry date is distributed and/or used.

forwarding agent

A person or entity engaged in providing, either directly or indirectly, any service concerned with clearing and forwarding operations in any manner to any other person and includes a consignment agent.

good distribution practices (GDP)

That part of quality assurance that ensures that the quality of a pharmaceutical product is maintained by means of adequate control of the numerous activities which occur during the distribution process as well as providing a tool to secure the distribution system from counterfeits, unapproved, illegally imported, stolen, counterfeit, substandard, adulterated, and/or misbranded pharmaceutical products.

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.

good pharmacy practice (GPP)

The practice of pharmacy aimed at providing and promoting the best use of medicines and other health care services and products, by patients and members of the public. It requires that the welfare of the patient is the pharmacist's prime concern at all times.

good storage practices (GSP)

That part of quality assurance that ensures that the quality of pharmaceutical products is maintained by means of adequate control throughout the storage thereof.

good trade and distribution practices (GTDP)

That part of quality assurance that ensures that the quality of pharmaceutical products is maintained by means of adequate control throughout the numerous activities which occur during the trade and the distribution process.

importation

The act of bringing or causing any goods to be brought into a customs territory (national territory, excluding any free zone).

intermediate product

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

labelling

Process of identifying a pharmaceutical product including the following information, as appropriate: name of the product; active ingredient(s),

type and amount; batch number; expiry date; special storage conditions or handling precautions; directions for use, warnings and precautions; names and addresses of the manufacturer and/or the supplier.

manufacture

All operations of purchase of materials and products, production, packaging, labelling, quality control, release, storage and distribution of pharmaceutical products, and the related controls.

marketing authorization

A legal document issued by the competent medicines regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INNs or national generic names where they exist), the shelf-life and storage conditions, and packaging characteristics. It specifies the information on which authorization is based (e.g. "The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence"). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization.

Once a product has been given marketing authorization, it is included on a list of authorized products — the register — and is often said to be "registered" or to "have registration". Market authorization may occasionally also be referred to as a "licence" or "product licence".

pedigree

A complete record that traces the ownership of and transactions relating to a pharmaceutical product as it is distributed through the supply chain.

pharmaceutical product

Any product intended for human use, or veterinary product intended for administration to food-producing animals, presented in its finished dosage form, which 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.

product recall

A process for withdrawing or removing a pharmaceutical product from the pharmaceutical distribution chain because of defects in the product, complaints of serious adverse reactions to the product and/or concerns

that the product is or may be counterfeit. The recall might be initiated by the manufacturer, importer, wholesaler, distributor or a responsible agency.

quality assurance

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.

quality system

An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product (or services) will satisfy given requirements for quality.

quarantine

The status of pharmaceutical products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

sampling

Operations designed to obtain a representative portion of a pharmaceutical product, based on an appropriate statistical procedure, for a defined purpose, e.g. acceptance of consignments or batch release.

shelf-life

The period of time during which a pharmaceutical product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch.

standard operating procedure (SOP)

An authorized, written procedure giving instructions for performing operations not necessarily specific to a given product but of a more general nature (e.g. equipment operation, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection).

storage

The storing of pharmaceutical products up to the point of use.

supplier

A person or entity engaged in the activity of providing products and/or services.

transit

The period during which pharmaceutical products are in the process of being carried, conveyed, or transported across, over or through a passage or route to reach the destination.

vehicles

Trucks, vans, buses, minibuses, cars, trailers, aircraft, railway carriages, boats and other means which are used to convey pharmaceutical products.

4. General principles

4.1 All parties involved in the distribution of pharmaceutical products have a responsibility to ensure that the quality of pharmaceutical products and the integrity of the distribution chain is maintained throughout the distribution process from the site of the manufacturer to the entity responsible for dispensing or providing the product to the patient or his or her agent.

4.2 The principles of GDP should be included in national legislation and guidelines for the distribution of pharmaceutical products, in a country or region as applicable, as a means of establishing minimum standards.

4.3 The principles of GDP are applicable both to pharmaceutical products moving forward in the distribution chain from the manufacturer to the entity responsible for dispensing or providing pharmaceutical products to the patient and to products which are moving backwards in the chain, for example, as a result of the return or recall thereof.

4.4 The principles of GDP should also be adhered to in the case of pharmaceutical products which are donated.

4.5 All entities involved in the distribution process should apply due diligence with adherence to the principles of GDP, for example, in procedures relating to traceability and in recognition of security risks.

4.6 There should be collaboration between all parties including governments, customs agencies, law enforcement agencies, regulatory authorities, manufacturers, distributors and entities responsible for the supply of pharmaceutical products to patients to ensure the quality and safety of pharmaceutical products and prevent the exposure of patients to counterfeit pharmaceutical products.

5. Regulation of the distribution of pharmaceutical products

5.1 National legislation should be in place to regulate the activities of persons or entities involved in the distribution of pharmaceutical products.

5.2 The distributor or the organization to which the distributor belongs should be an entity that is appropriately authorized in terms of applicable legislation to perform the function(s) that it intends to perform. The distributor or the organization to which it belongs should be held accountable for the activities that it performs which relate to the distribution of pharmaceutical products.

5.3 Only persons or entities which are authorized to do so and/or which hold the appropriate licence should be entitled to import or export pharmaceutical products.

5.4 Distributors or their agents may only distribute a pharmaceutical product within or to a country or territory if a marketing authorization or similar authorization has been granted, which allows the use of that pharmaceutical product in that country or territory.

5.5 Holders of an authorization to distribute pharmaceutical products should obtain their supplies of pharmaceutical products only from persons or entities which are in possession of the applicable authorization to sell or supply such products to a distributor.

5.6 Distributors or their agents should supply pharmaceutical products only to persons or entities which are themselves authorized to acquire such products either in terms of an authorization to act as a distributor or to sell or supply products directly to a patient or to his or her agent.

5.7 Some duties and responsibilities may be delegated or contracted out to suitably designated persons or entities as authorized and as necessary. Duties and responsibilities may only be delegated to entities which are suitably authorized in line with the national legislation. Duties and responsibilities should be specified in a written agreement. There should be no gaps or unexplained overlaps with regard to the application of GDP. These delegated and contracted out activities should be documented in agreements or contracts. There should be a periodic audit of such activities with regard to application of GDP.

5.8 If a distributor or his or her agent subcontracts an activity to another entity, the person or entity to whom the activity is subcontracted must be appropriately authorized to perform the subcontracted activity and should uphold the same standards as the distributor.

5.9 The sale of pharmaceutical products via the Internet should be limited to registered and authorized mail-order pharmacies or other authorized entities.

6. Organization and management

6.1 There should be an adequate organizational structure for each entity defined with the aid of an organizational chart. The responsibility, authority and interrelationships of all personnel should be clearly indicated.

6.2 Duties and responsibilities should be clearly defined and understood by the individuals concerned and recorded as written job descriptions. Certain activities may require special attention, such as the supervision of performance of activities, in accordance with local legislation. At every level of the supply chain, employees should be fully informed and trained in their duties and responsibilities.

6.3 A designated person should be appointed within the organization, who has defined authority and responsibility for ensuring that a quality system is implemented and maintained.

6.4 Managerial and technical personnel must have the authority and resources needed to carry out their duties and to set up and maintain a quality system, as well as to identify and correct deviations from the established quality system (see section 8).

6.5 The responsibilities placed on any one individual should not be so extensive as to present any risk to product quality.

6.6 There should be arrangements in place to ensure that management and personnel are not subject to commercial, political, financial and other pressures or conflict of interest that may have an adverse effect on the quality of service provided or on the integrity of pharmaceutical products.

6.7 Safety procedures relating to all relevant aspects including the safety of personnel and property, environmental protection and product integrity, should be in place.

7. Personnel

7.1 All personnel involved in distribution activities should be trained and qualified in the requirements of GDP, as applicable. Training should be based on written standard operating procedures (SOPs). Personnel should receive initial and continuing training relevant to their tasks, and be assessed as applicable, in accordance with a written training programme. In addition, training of the personnel should include the topic of product security, as well as aspects of product identification, the detection of counterfeits and the avoidance of counterfeits entering the supply chain. A record of all training, which includes details of subjects covered and participants trained, should be kept.

7.2 Key personnel involved in the distribution of pharmaceutical products should have the ability and experience appropriate to their responsibility for ensuring that pharmaceutical products are distributed properly.

7.3 There should be an adequate number of competent personnel involved in all stages of the distribution of pharmaceutical products in order to ensure that the quality of the product is maintained.

7.4 National regulations relating to the qualifications and experience of personnel should be adhered to.

7.5 Personnel dealing with hazardous pharmaceutical products (such as highly active materials, radioactive materials, narcotics, and other hazardous, environmentally sensitive and/or dangerous pharmaceutical products, as well as products presenting special risks of abuse, fire or explosion) should be given specific training.

7.6 Personnel involved in the distribution of pharmaceutical products should wear garments suitable for the activities that they perform. Personnel dealing with hazardous pharmaceutical products, including products containing materials that are highly active, toxic, infectious or sensitizing, should be provided with protective garments as necessary.

7.7 Appropriate procedures relating to personnel hygiene, relevant to the activities to be carried out, should be established and observed. Such procedures should cover health, hygiene and clothing of personnel.

7.8 Procedures and conditions of employment for employees, including contract and temporary staff, and other personnel having access to pharmaceutical products must be designed and administered to assist in minimizing the possibility of such products coming into the possession of unauthorized persons or entities.

7.9 Codes of practice and punitive procedures should be in place to prevent and address situations where persons involved in the distribution of pharmaceutical products are suspected of, or found to be implicated in, any activities relating to the misappropriation, tampering, diversion or counterfeiting of any product.

8. Quality system

8.1 Within an organization, quality assurance serves as a management tool. There should be a documented quality policy describing the overall intentions and requirements of the distributor regarding quality, as formally expressed and authorized by management.

8.2 The quality system should include an appropriate organizational structure, procedure, processes and resources and systematic actions necessary to ensure adequate confidence that a product or service and its documentation will satisfy given requirements for quality. The totality of these actions is described as the quality system.

8.3 The quality system should include provisions to ensure that the holder of the marketing authorization, entity identified on the label (if different from the manufacturer), the appropriate national and/or international

regulatory bodies, as well as other relevant competent authorities, would be informed immediately in a case of confirmed or suspected counterfeiting of a pharmaceutical product. Such products should be stored in a secure, segregated area and clearly identified to prevent further distribution or sale.

8.4 Where electronic commerce (e-commerce) is used, i.e. electronic means are used for any of the distribution steps, defined procedures and adequate systems should be in place to ensure traceability and confidence in the quality of the pharmaceutical products concerned. Electronic transactions (including those conducted via the Internet), relating to the distribution of pharmaceutical products, should be performed only by authorized persons or entities.

8.5 Authorized procurement and release procedures for all administrative and technical operations performed should be in place to ensure that appropriate pharmaceutical products are sourced only from approved suppliers and distributed by approved entities. The approval should come from the competent authority of the individual country where the legal entity is registered.

8.6 Inspection, auditing and certification of compliance with a quality system (such as the applicable International Standardization Organization (ISO) series, or national or international guidelines) by external bodies is recommended. Such certification should not, however, be seen as a substitute for compliance with these GDP guidelines and the applicable principles of GMP relating to pharmaceutical products.

8.7 If measures to ensure the integrity of the pharmaceutical products in transit are in place, they should be managed properly. For example, if seal control programmes for transit shipment are used, numbers should be issued in a tracked and sequential manner, the integrity of seals should be monitored and numbers verified during transit and upon receipt. Written procedures should be in place for use in situations where pharmaceutical products are suspected of being or are found to be counterfeit.

8.8 Distributors should from time to time conduct risk assessments to assess potential risks to the quality and integrity of pharmaceutical products. The quality system should be developed and implemented to address any potential risks identified. The quality system should be reviewed and revised periodically to address new risks identified during a risk assessment.

Traceability of pharmaceutical products

8.9 Regulations should foster a safe, transparent and secure distribution system which includes product traceability throughout the supply chain. This is a shared responsibility among the parties involved. There should be

procedures in place to ensure document traceability of products received and distributed, to facilitate product recall.

8.10 All parties involved in the supply chain should be identifiable, depending on the type of product and on national policies and legislation.

8.11 Measures should be in place to ensure that pharmaceutical products have documentation that can be used to permit traceability of the products throughout distribution channels from the manufacturer/importer to the entity responsible for selling or supplying the product to the patient or his or her agent (see also 14.2). Records including expiry dates and batch numbers may be part of a secure distribution documentation enabling traceability.

8.12 Ideally there should be a procedure in place for the creation and maintenance of a pedigree for pharmaceutical products.

Provision should be made for a visual and/or analytical identification of potential counterfeit products. The procedure to be followed when a suspected product is identified should include provisions for notification, as appropriate, of the holder of the marketing authorization, entity identified on the label (if different from the manufacturer), the appropriate national and/or international regulatory bodies, as well as other relevant competent authorities (see also section 19).

8.13 A suitable and, to the extent possible, internationally compatible product coding, identification system should be in place and developed in collaboration with the various parties involved in the supply chain. While it is understood that a differentiated approach may be necessary for different products and regions, pedigree and/or track-and-trace technologies provide possible options to ensure traceability.

9. Premises, warehousing and storage

9.1 Good storage practices (GSP) are applicable in all circumstances where pharmaceutical products are stored and throughout the distribution process. For additional guidance relating to the general principles of storage of pharmaceutical products, refer to the *WHO guide to good storage practices for pharmaceuticals* (*1*).

Storage areas

9.2 Precautions must be taken to prevent unauthorized persons from entering storage areas. Employees should comply with the company policies to maintain a safe, secure and efficient working environment.

9.3 Storage areas should be of sufficient capacity to allow the orderly storage of the various categories of pharmaceutical products, namely commercial

and non-commercial products, products in quarantine, and released, rejected, returned or recalled products as well as those suspected to be counterfeits.

9.4 Storage areas should be designed or adapted to ensure appropriate and good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Pharmaceutical products should be stored off the floor and suitably spaced to permit cleaning and inspection. Pallets should be kept in a good state of cleanliness and repair.

9.5 Storage areas should be clean and free from accumulated waste and vermin. Organizations in charge of distribution must ensure that premises and storage areas are cleaned regularly. There should also be a written programme for pest control. The pest control agents used should be safe and there should be no risk of contamination of pharmaceutical products. There should be appropriate procedures for the clean-up of any spillage to ensure complete removal of any risk of contamination.

9.6 If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination. Adequate cleaning procedures should be in place for the sampling areas.

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

9.8 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and access restricted to authorized personnel. Any system replacing physical quarantine should provide equivalent security. For example, computerized systems can be used, provided that they are validated to demonstrate security of access.

9.9 Physical or other equivalent validated (e.g. electronic) segregation should be provided for the storage of rejected, expired, recalled or returned products and suspected counterfeits. The products and the areas concerned should be appropriately identified.

9.10 Unless there is an appropriate alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned, recalled or suspected counterfeit pharmaceutical products, separate storage areas should be assigned for their temporary storage until a decision as to their future has been made.

9.11 Radioactive materials, narcotics and other hazardous, sensitive and/or dangerous pharmaceutical products, as well as products presenting special risks of abuse, fire or explosion (e.g. combustible or flammable liquids and solids and pressurized gases) should be stored in a dedicated area(s) that is subject to appropriate additional safety and security measures.

9.12 Pharmaceutical products should be handled and stored in such a manner as to prevent contamination, mix-ups and cross-contamination.

9.13 A system should be in place to ensure that the pharmaceutical products due to expire first are sold and/or distributed first (first expiry/first out (FEFO)). Exceptions may be permitted as appropriate, provided that adequate controls are in place to prevent the distribution of expired products.

9.14 Broken or damaged items should be withdrawn from usable stock and stored separately.

9.15 Storage areas should be provided with adequate lighting to enable all operations to be carried out accurately and safely.

Storage conditions and stock control

9.16 Storage and handling conditions should comply with applicable national and local regulations (*8*).

9.17 Storage conditions for pharmaceutical products should be in compliance with the recommendations of the manufacturer.

9.18 Facilities should be available for the storage of all pharmaceutical products under appropriate conditions (e.g. environmentally controlled when necessary). Records should be maintained of these conditions if they are critical for the maintenance of the characteristics of the pharmaceutical product stored.

9.19 Records of temperature monitoring data should be available for review. There should be defined intervals for checking temperature. The equipment used for monitoring should be checked at suitable predetermined intervals and the results of such checks should be recorded and retained. All monitoring records should be kept for at least the shelf-life of the stored pharmaceutical product plus one year, or as required by national legislation. Temperature mapping should show uniformity of the temperature across the storage facility. It is recommended that temperature monitors be located in areas that are most likely to show fluctuations.

9.20 Equipment used for monitoring of storage conditions should also be calibrated at defined intervals.

9.21 Periodic stock reconciliation should be performed by comparing the actual and recorded stocks. This should be done at defined intervals.

9.22 Stock discrepancies should be investigated in accordance with a specified procedure to check that there have been no inadvertent mix-ups, incorrect issues and receipts, thefts and/or misappropriations of

pharmaceutical products. Documentation relating to the investigation should be kept for a predetermined period.

10. Vehicles and equipment

10.1 Vehicles and equipment used to distribute, store or handle pharmaceutical products should be suitable for their purpose and appropriately equipped to prevent exposure of the products to conditions that could affect their stability and packaging integrity, and to prevent contamination of any kind.

10.2 The design and use of vehicles and equipment must aim to minimize the risk of errors and permit effective cleaning and/or maintenance to avoid contamination, build-up of dust or dirt and/or any adverse effect on the quality of the pharmaceutical products being distributed.

10.3 Where feasible, consideration should be given to adding technology, such as global positioning system (GPS) electronic tracking devices and engine-kill buttons to vehicles, which would enhance the security of pharmaceutical products while in the vehicle.

10.4 Dedicated vehicles and equipment should be used, where possible, when handling pharmaceutical products.

10.5 Where non-dedicated vehicles and equipment are used, procedures should be in place to ensure that the quality of the pharmaceutical product will not be compromised. Appropriate cleaning should be performed, checked and recorded.

10.6 Procedures should be in place to ensure that the integrity of the products is not compromised during transportation.

10.7 Where third-party carriers are used, distributors should develop written agreements with carriers to ensure that appropriate measures are taken to safeguard pharmaceutical products, including maintaining appropriate documentation and records. Such agreements should be in line with national and regional regulatory requirements.

10.8 Defective vehicles and equipment should not be used and should either be labelled as such or removed from service.

10.9 There should be procedures in place for the operation and maintenance of all vehicles and equipment involved in the distribution process, including cleaning and safety precautions.

10.10 Vehicles, containers and equipment should be kept clean and dry and free from accumulated waste. Organizations in charge of distribution must ensure that vehicles used are cleaned regularly.

10.11 Vehicles, containers and equipment should be kept free from rodents, vermin, birds and other pests. There should be written programmes and records for such pest control. The cleaning and fumigation agents used should not have any adverse effect on product quality.

10.12 Equipment chosen and used for the cleaning of vehicles should not constitute a source of contamination. Agents used for the cleaning of vehicles should be approved by management.

10.13 Special attention should be paid to the design, use, cleaning and maintenance of all equipment used for the handling of pharmaceutical products which are not in a protective shipping carton or case.

10.14 Where special storage conditions (e.g. temperature and/or relative humidity), different from, or limiting, the expected environmental conditions, are required during transportation, these should be provided, checked, monitored and recorded. All monitoring records should be kept for a minimum of the shelf-life of the product distributed plus one year, or as required by national legislation. Records of monitoring data should be made available for inspection by the regulatory or other oversight body.

10.15 Equipment used for monitoring conditions, e.g. temperature and humidity, within vehicles and containers should be calibrated at regular intervals.

10.16 Vehicles and containers should be of sufficient capacity to allow orderly storage of the various categories of pharmaceutical products during transportation.

10.17 Where possible, mechanisms should be available to allow for the segregation during transit of rejected, recalled and returned pharmaceutical products as well as those suspected of being counterfeits. Such goods should be securely packaged, clearly labelled, and be accompanied by appropriate supporting documentation.

10.18 Measures should be in place to prevent unauthorized persons from entering and/or tampering with vehicles and/or equipment, as well as to prevent the theft or misappropriation thereof.

11. Shipment containers and container labelling

11.1 Pharmaceutical products should be stored and distributed in shipment containers that have no adverse effect on the quality of the products, and that offer adequate protection from external influences, including contamination.

11.2 Shipping containers should bear labels providing sufficient information on handling and storage conditions and precautions to ensure

that the products are properly handled and secure at all times. The shipment container should enable identification of the container's contents and source.

11.3 The need for any special transport and/or storage conditions should be stated on the shipment container label. If a pharmaceutical product is intended for transfer to areas outside the control of the manufacturer's products management system, the name and address of the manufacturer, special transport conditions and any special legal requirements, including safety symbols, should also be included on the container label.

11.4 Normally, internationally and/or nationally accepted abbreviations, names or codes should be used in the labelling of shipment containers.

11.5 Special care should be taken when using dry ice in shipment containers. In addition to safety issues it must be ensured that the pharmaceutical product does not come into contact with the dry ice, as it may have an adverse effect on the quality of the product.

11.6 Written procedures should be available for the handling of damaged and/or broken shipment containers. Particular attention should be paid to those containing potentially toxic and hazardous products.

12. Dispatch and receipt

12.1 Pharmaceutical products should only be sold and/or distributed to persons or entities that are authorized to acquire such products in accordance with the applicable national, regional and international legislation. Written proof of such authority must be obtained prior to the distribution of products to such persons or entities.

12.2 Prior to the dispatch of the pharmaceutical products, the supplier should ensure that the person or entity, e.g. the contract acceptor for transportation of the pharmaceutical products, is aware of the pharmaceutical products to be distributed and complies with the appropriate storage and transport conditions.

12.3 The dispatch and transportation of pharmaceutical products should be undertaken only after the receipt of a valid delivery order or material replenishment plan, which should be documented.

12.4 Written procedures for the dispatch of pharmaceutical products should be established. Such procedures should take into account the nature of the product as well as any special precautions to be observed. Pharmaceutical products under quarantine will require release for dispatch by the person responsible for quality (see 6.3).

12.5 Records for the dispatch of pharmaceutical products should be prepared and should include at least the following information:

— date of dispatch;
— complete business name and address (no acronyms), type of entity responsible for the transportation, telephone number and names of contact persons;
— complete business name, address (no acronyms), and status of the addressee (e.g. retail pharmacy, hospital or community clinic);
— a description of the products including, e.g. name, dosage form and strength (if applicable);
— quantity of the products, i.e. number of containers and quantity per container (if applicable);
— applicable transport and storage conditions;
— a unique number to allow identification of the delivery order; and
— assigned batch number and expiry date (where not possible at dispatch, this information should at least be kept at receipt to facilitate traceability).

12.6 Records of dispatch should contain enough information to enable traceability of the pharmaceutical product. Such records should facilitate the recall of a batch of a product, if necessary, as well as the investigation of counterfeit or potentially counterfeit pharmaceutical products.

12.7 In addition, the assigned batch number and expiry date of pharmaceutical products should be recorded at the point of receipt to facilitate traceability.

12.8 Methods of transportation, including vehicles to be used, should be selected with care, and local conditions should be considered, including the climate and any seasonal variations experienced. Delivery of products requiring controlled temperatures should be in accordance with the applicable storage and transport conditions.

12.9 Delivery schedules should be established and routes planned, taking local needs and conditions into account. Such schedules and plans should be realistic and systematic. Security risks should also be taken into account when planning the schedules and routes of the delivery.

12.10 Care should be taken to ensure that the volume of pharmaceutical products ordered does not exceed the capacity of storage facilities at the destination.

12.11 Vehicles and containers should be loaded carefully and systematically, where applicable on a first-out/last-in basis, to save time when unloading, prevent physical damage and reduce security risks. Extra care should be taken during loading and unloading of cartons to avoid damage.

12.12 Pharmaceutical products should not be supplied or received after their expiry date, or so close to the expiry date that this date is likely to be reached before the products are used by the consumer.

12.13 Incoming shipments should be examined to verify the integrity of the container/closure system, ensure that tamper-evident packaging features are intact, and that labelling appears intact.

13. Transportation and products in transit

13.1 Products and shipment containers should be secured to prevent or provide evidence of unauthorized access. Vehicles and operators should be provided with additional security, as appropriate, to prevent theft and other misappropriation of products during transportation.

13.2 Product shipments should be secured and include the appropriate documentation to facilitate identification and verification of compliance with regulatory requirements. Policies and procedures should be followed by all persons involved in the transportation, to secure pharmaceutical products.

13.3 The people responsible for the transportation of pharmaceutical products should be informed about all relevant conditions for storage and transportation. These requirements should be adhered to throughout transportation and at any intermediate storage stages.

13.4 Pharmaceutical products should be stored and transported in accordance with procedures such that:

- The identity of the product is not lost.
- The product does not contaminate and is not contaminated by other products.
- Adequate precautions are taken against spillage, breakage, misappropriation and theft.
- Appropriate environmental conditions are maintained, e.g. using cold chain for thermolabile products.

13.5 The required storage conditions for pharmaceutical products should be maintained within acceptable limits during transportation. If a deviation has been noticed during transportation by the person or entity responsible for transportation, this should be reported to the distributor and recipient. In cases where the recipient notices the deviation, it should be reported to the distributor. Where necessary, the manufacturer of the pharmaceutical product should be contacted for information about appropriate steps to be taken.

13.6 Where special conditions are required during transportation that are different from or limit the given environmental conditions (e.g. temperature and humidity) these should be provided by the manufacturer on the labels, monitored and recorded.

13.7 Written procedures should be in place for investigating and dealing with any failure to comply with storage requirements, e.g. temperature deviations.

13.8 Transportation and storage of pharmaceutical products containing hazardous substances, such as toxic, radioactive material, and other dangerous pharmaceutical products presenting special risks of abuse, fire or explosion (e.g. combustible or flammable liquids, solids and pressurized gases) should be stored in safe, dedicated and secure areas, and transported in safe, suitably designed, secured containers and vehicles. In addition, the requirements of applicable international agreements and national legislation should be met.

13.9 Products containing narcotics and other dependence-producing substances should be transported in safe and secure containers and vehicles and be stored in safe and secure areas.

In addition, applicable international agreements and national legislation should be complied with.

13.10 Spillages should be cleaned up as soon as possible to prevent possible contamination, cross-contamination and hazards. Written procedures should be in place for the handling of such occurrences.

13.11 Physical or other equivalent (e.g. electronic) segregation should be provided for the storage and distribution during transit of rejected, expired, recalled or returned pharmaceutical products and suspected counterfeits. The products should be appropriately identified, securely packaged, clearly labelled and be accompanied by appropriate supporting documentation.

13.12 The interiors of vehicles and containers should remain clean and dry while pharmaceutical products are in transit.

13.13 Packaging materials and shipment containers should be of suitable design to prevent damage of pharmaceutical products during transport. Seal control programmes should be in place and managed properly.

13.14 Drivers of vehicles should identify themselves and present appropriate documentation to demonstrate that they are authorized to transport the load.

13.15 Damage to containers and any other event or problem that occurs during transit must be recorded and reported to the relevant department, entity or authority, and investigated.

13.16 Pharmaceutical products in transit must be accompanied by the appropriate documentation.

14. Documentation

14.1 Written instructions and records which document all activities relating to the distribution of pharmaceutical products, including all applicable receipts and issues (invoices) should be available. Records should be kept for seven years, unless otherwise specified in national or regional regulations.

14.2 Distributors should keep records of all pharmaceutical products received. Records should contain at least the following information:
— date;
— name of the pharmaceutical product;
— quantity received, or supplied; and
— name and address of the supplier.

14.3 Procedures should be established and maintained for the preparation, review, approval, use of and control of changes to all documents relating to the distribution process. Procedures must be in place for both internally generated documents and those from external sources.

14.4 Documents, and in particular instructions and procedures relating to any activity that could have an impact on the quality of pharmaceutical products, should be designed, completed, reviewed and distributed with care.

14.5 The title, nature and purpose of each document should be clearly stated. The contents of documents should be clear and unambiguous. Documents should be laid out in an orderly fashion and be easy to check.

14.6 All documents should be completed, approved, signed (as required) and dated by an appropriate authorized person(s) and should not be changed without the necessary authorization.

14.7 The nature, content and retention of documentation relating to the distribution of pharmaceutical products and any investigations conducted and action taken, should comply with national legislative requirements. Where such requirements are not in place, the documents should be retained for at least one year after the expiry date of the product concerned.

14.8 The distributor must establish and maintain procedures for the identification, collection, indexing, retrieval, storage, maintenance, disposal of and access to all applicable documentation.

14.9 All records must be readily retrievable, and be stored and retained using facilities that are safeguarded against unauthorized modification, damage, deterioration and/or loss of documentation.

14.10 Documents should be reviewed regularly and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version.

14.11 Mechanisms should exist to allow for transfer of information, including quality or regulatory information, between a manufacturer and a customer, as well as the transfer of information to the relevant regulatory authority as required.

14.12 Records relating to storage of pharmaceutical products should be kept and be readily available upon request in accordance with the *WHO guidelines on good storage practice for pharmaceuticals* (*1*).

14.13 Permanent records, written or electronic, should exist for each stored product indicating recommended storage conditions, any precautions to be observed and retest dates. Pharmacopoeial requirements and current national regulations concerning labels and containers should be respected at all times.

14.14 Procedures should be in place for temperature mapping, security services to prevent theft or tampering with goods at the storage facilities, destruction of unsaleable or unusable stocks and on retention of the records.

14.15 Where the records are generated and kept in electronic form, back ups should be maintained to prevent any accidental data loss.

15. Repackaging and relabelling

15.1 Repackaging and relabelling of pharmaceutical products should be limited, as these practices may represent a risk to the safety and security of the supply chain.

15.2 Where they do occur, they should only be performed by entities appropriately authorized to do so and in compliance with the applicable national, regional and international guidelines, i.e. in accordance with GMP principles.

15.3 In the event of repackaging by companies other than the original manufacturer, these operations should result in at least equivalent means of identification and authentication of the products.

15.4 Procedures should be in place for the secure disposal of original packaging.

16. Complaints

16.1 There should be a written procedure in place for the handling of complaints. A distinction should be made between complaints about a product or its packaging and those relating to distribution. In the case of a complaint about the quality of a product or its packaging, the original manufacturer and/or marketing authorization holder should be informed as soon as possible.

16.2 All complaints and other information concerning potentially defective and potentially counterfeit pharmaceutical products should be reviewed carefully according to written procedures describing the action to be taken, including the need to consider a recall where appropriate.

16.3 Any complaint concerning a material defect should be recorded and thoroughly investigated to identify the origin or reason for the complaint (e.g. repackaging procedure or original manufacturing process).

16.4 If a defect relating to a pharmaceutical product is discovered or suspected, consideration should be given to whether other batches of the product should also be checked.

16.5 Where necessary, appropriate follow-up action should be taken after investigation and evaluation of the complaint. There should be a system in place to ensure that the complaint, the response received from the original product manufacturer, or the results of the investigation of the complaint, are shared with all the relevant parties.

16.6 Product quality problems or suspected cases of counterfeit products should be documented and the information shared with the appropriate national and/or regional regulatory authorities.

17. Recalls

17.1 There should be a system, which includes a written procedure, to effectively and promptly recall pharmaceutical products known or suspected to be defective or counterfeit, with a designated person(s) responsible for recalls. The system should comply with the guidance issued by the national or regional regulatory authority. This procedure should be checked regularly and updated as necessary.

17.2 The original manufacturer and/or marketing authorization holder should be informed in the event of a recall. Where a recall is instituted by an entity other than the original manufacturer and/or marketing authorization holder, consultation with the original manufacturer and/or marketing authorization holder should, where possible, take place before the recall is instituted.

Information on a recall should be shared with the appropriate national or regional regulatory authority. If a recall of the original product is necessary because of a counterfeited product which is not easily distinguishable from the original product, the manufacturer of the original product and the relevant health authority should be informed.

17.3 The effectiveness of the arrangements for recalls should be evaluated at regular intervals. All recalled pharmaceutical products should be stored in a secure, segregated area pending appropriate action.

17.4 Recalled pharmaceutical products should be segregated during transit and clearly labelled as recalled products. Where segregation in transit is not possible, such goods must be securely packaged, clearly labelled, and be accompanied by appropriate documentation.

17.5 The particular storage conditions applicable to a pharmaceutical product which is subject to recall should be maintained during storage and transit until such time as a decision has been made regarding the fate of the product in question.

17.6 All customers and competent authorities of all countries to which a given pharmaceutical product may have been distributed should be informed promptly of any intention to recall the product because it is, or is suspected to be, defective or counterfeit.

17.7 All records should be readily available to the designated person(s) responsible for recalls. These records should contain sufficient information on pharmaceutical products supplied to customers (including exported products).

17.8 The progress of a recall process should be recorded and a final report issued, which includes a reconciliation between delivered and recovered quantities of products.

17.9 When necessary emergency recall procedures should be implemented.

18. Returned products

18.1 A distributor should receive pharmaceutical product returns or exchanges pursuant to the terms and conditions of the agreement between the distributor and the recipient. Both distributors and recipients should be accountable for administering their returns process and ensuring that the aspects of this operation are secure and do not permit the entry of counterfeit products.

18.2 The necessary assessment and decision regarding the disposition of such products must be made by a suitably authorized person. The nature of the product returned to the distributor, any special storage conditions required, 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 a pharmaceutical product, it should not be considered suitable for reissue or reuse

18.3 Provision should be made for the appropriate and safe transport of returned products in accordance with the relevant storage and other requirements.

18.4 Rejected pharmaceutical products and those returned to a distributor should be appropriately identified and handled in accordance with a procedure which involves at least:

— the physical segregation of such pharmaceutical products in quarantine in a dedicated area; or
— other equivalent (e.g. electronic) segregation.

This is to avoid confusion and prevent distribution until a decision has been taken with regard to their disposition. The particular storage conditions applicable to a pharmaceutical product which is rejected or returned should be maintained during storage and transit until such time as a decision has been made regarding the product in question.

18.5 Provision should be made for the appropriate and safe transport of rejected pharmaceutical products prior to their disposal.

18.6 Destruction of pharmaceutical products should be done in accordance with international, national and local requirements regarding disposal of such products, and with due consideration to protection of the environment.

18.7 Records of all returned, rejected and/or destroyed pharmaceutical products should be kept for a predetermined period.

19. Counterfeit pharmaceutical products

19.1 Counterfeit pharmaceutical products found in the distribution chain should be kept apart from other pharmaceutical products to avoid any confusion. They should be clearly labelled as not for sale and national regulatory authorities and the holder of the marketing authorization for the original product should be informed immediately.

19.2 The sale and distribution of a suspected counterfeit pharmaceutical product should be suspended and the national regulatory authority notified without delay.

19.3 Upon confirmation of the product being counterfeit a formal decision should be taken on its disposal, ensuring that it does not re-enter the market, and the decision recorded.

20. Importation

20.1 Consideration should be given to the *WHO guidelines on import procedures for pharmaceutical products (6)*. The following aspects should be given particular attention.

20.2 The number of ports of entry in a country for the handling of imports of pharmaceutical products should be limited by appropriate legislation. Such ports could be designated by the state.

20.3 The chosen port(s) of entry should be those most appropriately located and best equipped to handle imports of pharmaceutical products.

20.4 At the port of entry, consignments of pharmaceutical products should be stored under suitable conditions for as short a time as possible.

20.5 All reasonable steps should be taken by importers to ensure that products are not mishandled or exposed to adverse storage conditions at wharves or airports.

20.6 Where necessary, persons with pharmaceutical training should be involved with the customs procedures or should be readily contactable.

20.7 The *WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce* should be used to provide data regarding quality assessment of imported pharmaceutical products.

20.8 Customs, enforcement agencies and regulatory agencies responsible for supervision of pharmaceutical products should establish means for cooperation and information exchange in order to prevent importation of counterfeit pharmaceutical products.

21. Contract activities

21.1 Any activity relating to the distribution of a pharmaceutical product which is delegated to another person or entity should be performed by parties appropriately authorized for that function and in accordance with the terms of a written contract.

21.2 The contract should define the responsibilities of each party including observance of the principles of GDP and relevant warranty clauses. It should also include responsibilities of the contractor for measures to avoid the entry of counterfeit medicines into the distribution chain, such as by suitable training programmes.

21.3 All contract accepters should comply with the requirements in these guidelines.

21.4 Subcontracting may be permissible, under certain conditions and subject to the written approval of the contract giver; however, the subcontractors should be authorized for the function.

21.5 Contract accepters should be audited periodically.

22. Self-inspection

22.1 The quality system should include self-inspections. These should be conducted to monitor implementation and compliance with the principles of GDP and, if necessary, to trigger corrective and preventive measures.

22.2 Self-inspections should be conducted in an independent and detailed way by a designated, competent person.

22.3 The results of all self-inspections should be recorded. Reports should contain all observations made during the inspection and, where applicable, proposals for corrective measures. There should be an effective follow-up programme. Management should evaluate the inspection report and the records of any corrective actions taken.

References

1. WHO guide to good storage practices for pharmaceuticals. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report.* Geneva, World Health Organization, 2003, Annex 9 (WHO Technical Report Series, No. 908).
2. WHO good pharmacy practice in community and hospital pharmacy settings. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report.* Geneva, World Health Organization, 1999, Annex 7 (WHO Technical Report Series, No. 885).
3. WHO good manufacturing practices. In: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Good manufacturing practices and inspection, Vol. 2,* 2nd updated ed. Geneva, World Health Organization, 2007.
4. Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996, Annex 10 (WHO Technical Report Series, No. 863).
5. WHO pharmaceutical starting materials certification scheme (SMACS). In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report.* Geneva, World Health Organization, 2004, Annex 3 (Technical Report Series, No. 917).
6. Guidelines on import procedures for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996, Annex 12 (WHO Technical Report Series, No. 863).
7. Good trade and distribution practices for pharmaceutical starting materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report.* Geneva, World Health Organization, 2004, Annex 2 (WHO Technical Report Series, No. 917).
8. 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, Annex 2 (WHO Technical Report Series, No. 953) (http://www.who.int/medicines/areas/quality_safety/quality_assurance/regulatory_standards/en/index.html).

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Annex 6

Guidelines on the requalification of prequalified dossiers

1. Introduction

2. Requalification of prequalified dossiers

Appendix 1
Summary of key product information

Appendix 2
Variations to the product

1. Introduction

In accordance with the provisions set out in section 12 (Maintenance of prequalification status) of the *Procedure for prequalification of pharmaceutical products*[1], holders of WHO-prequalified products should submit a quality review 5 years from the date of prequalification of the product, or when requested to do so by WHO Prequalification (whichever date is earlier).

Section 12 of the above-mentioned guidelines states that:

> WHO will furthermore arrange for the products and manufacturing sites included in the list to be re-evaluated at regular intervals. If, as a result of this re-evaluation, it is found that a product and/or specified manufacturing site no longer complies with the WHO-recommended standards, such products and manufacturing sites will be removed from the list. Failure of a manufacturer or applicant to participate in the re-evaluation procedure will also lead to removal from the list.
>
> Re-evaluation, including re-inspections of manufacturing sites and contract research organizations (CROs), will be done at regular intervals, based on risk assessment, but at least once every 5 years.
>
> Re-evaluation, including re-inspections, shall also be performed:

[1] Procedure for prequalification of pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report.* Geneva, World Health Organization, 2009, Annex 4 (WHO Technical Report Series, No. 953) (http://www.who.int/medicines/publications/pharmprep/pdf_trs953.pdf#page=145).

- if any fraud or omissions by the applicant, manufacturer(s) of a finished pharmaceutical product (FPP) or active pharmaceutical ingredient (API), or CROs in the initial assessment procedure or during the follow-up activities, becomes 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.

Requalification will be applicable to multisource FPPs (generics) where the full dossiers have been submitted, assessed and prequalified by WHO. Renewal of marketing authorization for products that have been listed by WHO based on approval by a stringent regulatory agency[2] (SRA) remains the responsibility of the relevant SRA.

2. Requalification of prequalified dossiers

The objective of this quality review submission is to enable WHO to requalify the product based on an assessment of the data and information submitted by the holder of a prequalified product, which includes verification of the acceptability of the product and its conformity to current norms and standards, and assessment of consistency of the quality of the prequalified FPPs, and its manufacturing process(es) over the identified period.

The holder of a prequalified product should submit the following documents electronically (in pdf format and in also in WinWord where indicated):

- A covering letter, which should contain a clear statement by the responsible person submitting the quality review, indicating that the information submitted is true and correct.
- Summary of key product information (as per Appendix 1).
- Variations to the product (as per Appendix 2).
- A pharmaceutical quality information form (PQIF)[3], completed in WinWord format. It should reflect the requirements of current prequalification guidelines and should also take into account technical and

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[2] 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 Swiss Medic, Health Canada and World Health Organization (WHO) (as 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 (as may be updated from time to time).

[3] Presentation of pharmaceutical quality information. In: *Guidance for submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis*. Annex 8 (http://apps.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc).

scientific progress. The API and FPP specifications should be provided in tabulated format, comparing the specifications at prequalification and at the time of the requalification submission.

- Copies of the current API and FPP specifications, duly signed and dated, including the test methods. The specifications should indicate the reference number, version number, effective date and change history if any.

A product quality review may be submitted as supportive documentation. It may also be requested by WHO.

Appendix 1

Summary of key product information

This section compares key information on the FPP at the time of prequalification and at the time of the submission for requalification. Table A1.1 should be completed by the holder of the prequalified product. Include remarks as a footnote to Table A1.1, where deemed necessary, to clarify the information provided.

Table A1.1
Summary of key product information

Item	Prequalified dossier	Current data[a]
Product number (e.g. HA001)		
INN, strength and pharmaceutical form		
Applicant (name, physical address and contact numbers)		
Manufacturing site(s) of FPP, with physical address (including unit and block numbers) and contact numbers (list separately if different steps are performed by different sites, e.g. packaging, quality control)		
Batch size(s) of FPP		
Product description (visual appearance)		
Primary and secondary packaging material(s) and pack size(s)		
Storage conditions of FPP		
Shelf-life of FPP		
FPP specification(s) reference number and/or version[b]		
Manufacturer(s) of API(s), with physical address (including unit and block numbers) and contact numbers (list each API separately)		
Number/version of each APIMF associated with the FPP		
Storage conditions of API		
Retest period of API(s)		
API specification(s) reference number and/or version (for each API)[b]		
All commitments and their outcomes		

INN, international nonproprietary name; FPP, finished pharmaceutical product; API, active pharmaceutical ingredient; APIMF, active pharmaceutical ingredient master file.

[a] If there has been no update of the dossier then indicate "N/A" (not applicable).

[b] According to the latest editions of *The International Pharmacopoeia* (Ph.Int.), the European Pharmacopoeia (Ph.Eur), the British Pharmacopoeia (BP) and/or the United States Pharmacopeia (USP). Where in-house specifications have been approved and there is now a monograph in any of the internationally-recognized pharmacopoeias (Ph.Int., Ph.Eur, BP, or USP), the specifications should be updated to comply with the new monograph or demonstrated to be at least equivalent. In the case that no compendial monograph exists, the applicant should ensure that the approved in-house specifications are updated, through the variation process, to reflect the requirements of current prequalification guidelines and to take into account technical and scientific progress (e.g. current ICH guidelines, general chapters of the Ph.Int.). Each new version of the documents should allow traceability to the prequalified dossier and approved variations.

Appendix 2

Variations to the product

The holder of the prequalified product should submit a review, in tabular format, of any minor and/or major changes (including those pending) to the initially prequalified product or to the terms of the initially prequalified dossier. Table A2.1 should be completed by the holder of the prequalified product.

Table A2.1

Information on variations to the prequalified product

Reference no.	Date of submission	Date of approval/ rejection and reference number of the letter	Date of implementation
Major changes			
Description of the change, e.g. change in the primary packaging site of a sterile product			
Minor changes			
Description of the change according to the PQ variation guide			

Add as many rows as necessary.

Note. Requests for variations should have been submitted in accordance with WHO's Guidance on variations to a prequalified product dossier[4].

[4] WHO Guidance on variations to a prequalified product dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007, Annex 6 (WHO Technical Report Series, No. 943) (http://apps.who.int/prequal/info_general/documents/TRS943/TRS943.pdf#page=121).

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Annex 7

Guidelines for the preparation of a contract research organization master file

Background

1. General information
2. Quality management system of the contract research organization
3. Personnel
4. Ethics committee
5. Computer systems
6. Equipment and instruments
7. Documentation
8. Safety monitoring
9. Investigational medicinal products and comparator products
10. Pathology
11. Bioanalytical laboratory
12. Biostatistics
13. Study volunteers
14. Other information

Background

A contract research organization master file (CROMF) is a document prepared by the contract research organization (CRO) containing specific and factual information about the CRO and the conduct of clinical studies as well as the analyses of samples and related operations (including clinical trials, clinical data management, pharmacokinetics and statistical analysis and regulatory affairs) carried out at the named site. If only some of the operations referred to below are carried out at the site, the master file (MF) needs to be presented only for those operations.

In a case where a CRO is responsible for activities pertaining only to bioanalytical procedures, then only sections in the CROMF relating to these should be described. Other sections may be marked as "not applicable".

Where a CRO performs various activities, separate sections could be prepared for the different units, e.g. clinical pharmacology unit (CPU) and bioanalytical laboratory (BAL).

A CROMF provides information on the policies, approach and general activities of a CRO. It is not trial-specific as trial-specific data are submitted in a product dossier. It serves as general information to regulators and can be used during preparation for inspections by regulatory inspectors in addition to the trial-specific data and information submitted for assessment. It also provides an overview of the organization's approach to good clinical practices (GCP), good laboratory practices (GLP) and other guidelines pertaining to its activities.

A CROMF should be submitted to the national medicines regulatory authority (NMRA) where such a document is requested. It should be succinct and as far as possible not exceed 25 A4 pages (where appropriate, supportive documentation may be appended).

An updated CROMF should be submitted when requested by the NMRA, or if significant changes have been implemented by the CRO.

1. General information

1.1 Name and exact address of the CRO, including telephone, fax, 24-hour telephone numbers and e-mail address

1.2 Short description of the CRO (including size, location, number of beds, layout and plan, areas for handling samples and waste)

1.3 Activities as licensed/authorized by the national authority

1.4 Inspections and approvals

1.4.1 Inspections/approvals/accreditations by any regulatory agency

1.4.2 Audits of subcontractors

1.5 Type of studies (and indications, where appropriate) performed on site (a list of projects conducted at this site may be provided)

1.6 Provisions for insurance

1.6.1 Number of employees engaged in studies, quality, storage and distribution

1.7 Contract services employed

1.7.1 Use of outside scientific, analytical or other technical assistance in relation to studies and analysis (e.g. clinical laboratory, bioanalytical laboratory, X-ray facilities and caterers)

1.7.2 Services outsourced, e.g. contracts with tertiary care hospital for handling of medical emergencies, ambulance facility, nutrition, biomedical waste, chemical waste, caterers, pest control and pathology laboratory

2. Quality management system of the contract research organization

(Short description including, e.g. responsibilities of the quality assurance unit. A list of quality system documents can be included)

2.1 Organization chart including the arrangements for quality assurance

2.2 Internal audits and self inspection

2.3 Corrective and preventive action plans (CAPA)

3. Personnel

(A brief description can be presented in tabular format)

3.1 Qualifications, experience and responsibilities of key personnel as applicable

3.1.1 project manager

3.1.2 principal investigator

3.1.3 analytical investigator

3.1.4 biostatistician

3.1.5 clinical research associates

3.1.6 data manager

3.1.7 monitor

3.1.8 the study director(s)

3.1.9 person responsible for quality assurance

3.2 Training of personnel:

3.2.1 training policy and procedure (brief description)

3.2.2 training records

4. Ethics committee

4.1 Constitution and relation to CRO

4.2 Procedures including review and approval of protocols

5. Computer systems

(Short description)

5.1 Hardware

5.2 Software (and version number) used (e.g. in the bioanalytical laboratory, in pharmacokinetic and statistical analysis) and change control procedure

5.3 Data management systems (include a procedural flow chart and a brief description of query generation and resolution)

5.4. Security procedures

5.5 Electronic exchange of confidential information

5.6 Brief description of validation programme

5.7 Back-up and storage of electronic data

6. Equipment and instruments

6.1 Brief description of major equipment and instruments (a list of equipment is not required)

6.2 Qualification, maintenance and calibration programme, including the temperature recording systems

7. Documentation

7.1 Briefly describe document management systems

7.2 Project work flow including quality assurance and control process

7.3 Preparation of protocols

7.4 Preparation of informed consent forms and subject information forms

7.5 Preparation of report forms

7.6 Preparation of final report

8. Safety monitoring

(Brief description)

Adverse drug reaction reporting procedure

Provisions made for emergencies, including protocols and equipment available

9. Investigational medicinal products and comparator products

(Brief description)

9.1 Acquisition, storage, handling, sampling and disposal

9.2 Pharmacy and dispensing

10. Pathology

10.1 Biological sample collection and storage

10.2 Handling and analysis of biological samples

11. Bioanalytical laboratory

(Brief description)

11.1 Method development and validation

11.2 Reference standard materials used for preparation of calibration standards and quality control samples

11.3 Biological matrix storage, and handling of matrix samples

11.4 Analysis of unknown samples

11.5 Preparation and labelling of reagents

11.6 Storage of samples

11.7 Stability procedures

11.8 Waste management

12. Biostatistics

12.1 Data processing and analysis

12.2 Data management

13. Study volunteers

13.1 Procedure for recruitment

13.2 Collecting information on volunteers (e.g. databank), while confidentiality is maintained

13.3 Procedure for obtaining informed consent

14. Other information

14.1 Power supply system — uninterrupted power supply and generator availability and capacity

14.2 Brief description of any other activities performed on site by the CRO

14.3 Any other information which the CRO may feel it appropriate to add

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The International Pharmacopoeia, fourth edition.
Volume 1: general notices; monographs for pharmaceutical substances (A–O)
Volume 2: monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents.
2006 (1500 pages), also available in CD-ROM format and online
First supplement: general notices; monographs for pharmaceutical substances; monographs for dosage forms; general and specific monographs; methods of analysis; International Chemical Reference Substances; International Infrared Reference Spectra; reagents, test solutions and volumetric solutions.
2008 (309 pages), also available in CD-ROM format and online

Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms
1998 (94 pages)

Basic tests for pharmaceutical dosage forms
1991 (134 pages)

Quality Assurance of Pharmaceuticals: a compendium of guidelines and related materials
Volume 1: 1997 (244 pages)
Volume 2: good manufacturing practices and inspection.
Second updated edition, 2007 (409 pages)
Also available on: WHO training modules on GMP. A resource and study pack for trainers, 2007 (CD-ROM).

WHO Expert Committee on Specifications for Pharmaceutical Preparations
Forty-third report.
WHO Technical Report Series, No. 953, 2009 (161 pages)

International nonproprietary names (INN) for pharmaceutical substances
Cumulative list no. 13
2010 (available in CD-ROM format only)

The selection and use of essential medicines
Report of the WHO Expert Committee (including the 16th WHO Model List of Essential Medicines and the 2nd WHO Model List for Children).
WHO Technical Report Series, No. 958, 2010 (174 pages)

WHO Expert Committee on Biological Standardization
Fifty-sixth report.
WHO Technical Report Series, No. 941, 2007 (340 pages)

Further information on these and other WHO publications can be obtained from
WHO Press, World Health Organization, 1211 Geneva 27, Switzerland
(tel. +41 22 791 3264; fax: +41 22 791 4857;
e-mail: bookorders@who.int; order online: http://www.who.int/bookorders)

The Expert Committee on Specifications for Pharmaceutical Preparations works towards clear, independent and practical standards and guidelines for the quality assurance of medicines. Standards are developed by the Committee through worldwide consultation and an international consensus-building process. The following new guidelines were adopted and recommended for use: good practices for pharmaceutical quality control laboratories; supplementary guidelines for active pharmaceutical ingredients; good manufacturing practices for pharmaceutical products containing hazardous substances; good manufacturing practices for sterile pharmaceutical products; good distribution practices for pharmaceutical products; guidelines on the requalification of prequalified dossiers: and guidelines for the preparation of a contract research organization master file.

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