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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Thirty-eighth report

World Health Organization
Geneva

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WHO Expert Committee on Specifications for Pharmaceutical Preparations

Geneva, 10–14 March 2003

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1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 10 to 14 March 2003. Dr A. Asamoa-Baah, Executive Director, Health Technology and Pharmaceuticals, welcomed the Committee members and other participants on behalf of the Director-General, Dr Gro Harlem Brundtland.

In his opening remarks Dr Asamoa-Baah explained that since the last meeting of the Committee there had been more evidence of the globalization and harmonization of specifications for pharmaceutical preparations in general, and for pharmaceuticals used in the treatment of HIV, tuberculosis and malaria, in particular. He indicated that WHO was committed to helping to ensure the quality of pharmaceuticals and to treating HIV, tuberculosis and malaria. He added that although some patients were fortunate in having easy access to drugs, others were less so. However, there was cause for optimism with the creation of alliances to finance measures to fight HIV, tuberculosis and malaria. Dr Asamoa-Baah also highlighted the problem of counterfeit medicines which appeared to be greater than had originally been feared, and he emphasized the necessity for more heed to be paid to this problem. The issue of quality and safety of pharmaceuticals required appropriate attention.

The Committee was briefed on the WHO strategy for medicines and its focus on increasing access to quality medicines. He mentioned that the 20th century had been a period during which medical advancement had led to improved life expectancy, but that there was a gap between potential and reality due to lack of access to quality medicines. The Committee was also informed of the nomination of Dr J.W. Lee from the Republic of Korea, to replace Dr Brundtland as the Director-General of WHO. Dr Lee had been involved in the vaccine programme and will assume his new position in July 2003. His nomination coincided with the forthcoming period of consolidation which should result in better links between policy decisions and implementation of WHO activities. Medicine was a priority area in terms of support, developing pharmacopoeial standards and programmes focused on AIDS, tuberculosis and malaria. The Committee was assured of the commitment of the Essential Drugs and Medicines Policy Department to assuring quality medicines, from starting materials to the distribution of finished drugs to procurement agencies.

The WHO Strategy for Medicines laid out the basic aims from 2000 to 2003. Currently the strategy was being updated and comments sought on the main objectives, i.e. access and affordability, quality and safety,

rational use and policy development, which will put norms and standards in place to accomplish these objectives.

The Committee was informed about the wide range of activities undertaken by the Quality Assurance and Safety: Medicines (QSM) team. They were told of the need to continue work relating to the quality of medicines at WHO and to run activities in parallel so that there would be more rapid benefits at country level. Positive changes had already been seen but there was still much to be accomplished. Counterfeiting continued to be a major problem. The next International Conference of Drug Regulatory Authorities (ICDRA) scheduled for 2004 in Madrid, Spain would include a pre-conference meeting on counterfeit drugs which would be open to relevant parties. The Committee was informed about the new activities related to the model quality assurance for procurement and to pragmatic approaches in setting priorities. The safety of certain drugs was also a concern and required investigation. There had been increasing collaboration in the area of quality assurance of medicines within the Health Technology and Pharmaceuticals Cluster, with other clusters in WHO and with outside partners.

2. General Policy

2.1 Tenth International Conference of Drug Regulatory Authorities, China, Hong Kong, Special Administrative Region

Conference reports and recommendations made to the countries and to WHO were made available to the Committee. The Committee was informed that the next ICDRA would be held in Madrid, Spain in 2004, when a special session dedicated to pharmacopoeias had been proposed. In addition a pre-conference meeting on counterfeit drugs was planned.

2.2 Side meeting to the tenth International Conference of Drug Regulatory Authorities

The Committee was provided with the meeting report of the ICDRA side meeting entitled "Pharmacopoeial specifications — need for a worldwide approach?" dated 24 June 2002. The following recommendations were made during that meeting:

1. to hold an international meeting for those involved in the development of pharmacopoeial specifications;
2. to include the topic of pharmacopoeias on the agenda of the forthcoming ICDRA;

3. to encourage international harmonization efforts by WHO to develop common specifications and international reference standards, with special focus on medicines for which no pharmacopoeial monographs currently exist, e.g. new drug entities and combinations or priority disease programmes of major health impact;
4. to make every effort to help combat counterfeit drugs;
5. to reinforce the close links between regulatory authorities and pharmacopoeias; and
6. to discuss the importance of impurity profiles and limits at an international level, especially for internationally traded starting materials.

2.3 International Conference on Harmonisation

WHO is an observer to the International Conference on Harmonisation (ICH) and liaises with non-ICH countries by distributing information about ICH Guidelines. The Committee was provided with a paper entitled "The impact of implementation of ICH guidelines in non-ICH countries". This report includes the issues relating to the application of ICH quality documents to generic drugs. The Committee was provided with an update on the new ICH guidelines on impurities and stability testing.

The Committee endorsed the collaboration between WHO and ICH, especially WHO's participation in the working groups related to quality.

2.4 Pharmacopoeial Discussion Group[1]

The Committee was updated on the collaboration between WHO and the Pharmacopoeial Discussion Group (PDG). WHO has participated as an observer at the last three PDG meetings. The next meeting is scheduled to be held in Brussels, Belgium in July 2003.

2.5 Counterfeit drugs

The Committee was informed about the increasing problem of counterfeit drugs. The Committee members stressed the need for a consistent definition of what constitutes a counterfeit drug that would help to assess the real extent of the problem and improve the clarity of case reporting. A working group composed of WHO, pharmaceutical industry associations and Centrale Humanitaire Medico-Pharmaceutique (CHMP), is working to devise solutions to this

[1] The Pharmacopoeial Discussion Group is composed of the United States Pharmacopeia and the European and Japanese Pharmacopoeias, with WHO as an observer.

widespread problem. In addition, a new project in Asian countries is under way to study the situation in the national context. Notwithstanding the difficulties identified, the Committee re-endorsed the recommendation made in its previous report (*1*).

2.6 Traditional medicine

The Committee was presented with a progress report on WHO's work related to herbal medicine and which introduced the WHO Traditional Medicines Strategy: 2002–2005 for which the four major objectives are:

— framing policy;
— enhancing safety/efficacy/quality;
— ensuring access; and
— promoting rational use.

Several new technical documents on herbal medicines had been produced and had been circulated for comments before their finalization, while other finalized documents had been translated into various languages.

The Committee noted that in some countries herbal medicinal products were considered as food or as dietary supplements and their regulation might therefore be different from that of normal pharmaceutical products.

Members offered their support for the implementation of the new guidance documents the subjects of which included safety monitoring and quality assurance.

The Committee was informed that resolution EB 111.R12 on traditional medicine had been recommended by the one-hundred and eleventh session of the WHO Executive Board for adoption at the fifty-sixth World Health Assembly in May 2003.

The Committee commended the good work undertaken by WHO in this area and encouraged its continuation.

2.7 Malaria

The Committee was updated on the progress of the Roll Back Malaria programme and was informed that the past year had seen a rapid emergence of resistance to antimalarials and suggested that one-drug therapy might no longer be appropriate. It was reported that in 2000–2001 increased resistance to common antimalarials used in monotherapy had been recognized; WHO had therefore recom-

mended the use of combination drugs as more appropriate. However, quality standards for these combinations might not exist in the public domain. It had therefore been recommended by experts on malaria that the development of specifications for quality control should be expedited. The Committee expressed concern that fixed-dose combination drug products were more complicated to manufacture and analyse. In some cases the information available about their safety, efficacy and quality was inadequate. The Committee was also concerned about the results of a study undertaken in the sub-Saharan region that reported on the distribution of substandard quality and counterfeit antimalarial products.

The Committee urged the WHO Secretariat to address these pertinent issues.

2.8 Biologicals

The Committee was informed about a current joint effort with QSM in the area of vaccines to assess the capacity of some national regulatory agencies and to identify their needs. One of the major deficiencies identified so far in the assessment had been in the area of postmarket surveillance monitoring. Another example of collaboration with the Expert Committee on Biological Standardization was its technical advice to the International Nonproprietary Names Programme.

2.9 Risk related to transmissible spongiform encephalopathy

The Committee was informed of the results of the WHO consultation held in February 2003 on transmissible spongiform encephalopathy (TSE) and indicated that the main concerns with this disease were its transmission from animals to humans and possibly from human to human. There were links between variant Creutzfeldt-Jakob disease (vCJD) and bovine spongiform encephalopathy (BSE). There had been fewer cases of BSE reported in recent years in the United Kingdom as a result of precautionary measures, whereas in the rest of Europe and other parts of the world the trend was increasing, although on a much smaller scale. It is not yet known if the current situation will continue. Products of ruminant origin of interest to the Committee were gelatin, bovine blood derivatives, tallow derivatives, milk and milk derivatives (lactose) and amino acids. In addition to measures already taken, the Committee re-emphasized the need to continue to raise awareness of the possible risk associated with these products through publication of guidelines, inclusion of requirements in pharmacopoeias, and improving the traceability of products. The

possibility of applying WHO's rapid alert system to starting materials had also been discussed.

2.10 Bioequivalence

The Committee was presented with the first results on comparative dissolution testing studies, using in vitro testing under conditions that may be used to indicate bioequivalence. The subjects of discussion included bioequivalence studies for fixed-dose combination products; the difficulty in conducting bioequivalence studies in some countries; the need for proper guidance; and the possibility of phasing in bioequivalence requirements for certain drugs or of waiving in vivo bioequivalence requirements for some dosage forms (e.g. liquids) based on existing knowledge.

The Committee acknowledged the good guidance provided by WHO and the need to apply a risk analysis-based approach in the field of bioequivalence. Future work should include the review and update of current guidance, noting that in vitro dissolution testing could be considered as an indicator of possible bioequivalence problems.

Bioequivalence is significant only if compliance with good manufacturing practices and sourcing of active pharmaceutical ingredients (API) are well controlled. The Committee endorsed the need for a review and an update of the existing WHO guidelines on bioequivalence.

3. Quality control — specifications and tests

3.1 *The International Pharmacopoeia*

Volume 5 of the third edition of *The International Pharmacopoeia* is now available. The Committee was informed that revision of some of the general methods of *The International Pharmacopoeia* described in other volumes, as well as the development of new methods, are needed. It is intended that the amendments made to previous volumes will be incorporated in an updated version, to be made available in CD-ROM format.

The Committee endorsed the recommendation and assured WHO of their continued support and willingness to participate in this exercise.

3.2 Dissolution test requirements

The work on "In vitro dissolution testing methods for oral immediate-release drug products containing Biopharmaceutical Classification

Scheme (BCS) class I drugs", was presented to the Committee. The methods include a recommended test procedure for inclusion in *The International Pharmacopoeia*.

The Committee praised this work. It recommended that the document be circulated for comments and for validation of the proposed methods prior to its adoption.

3.3 Specifications for radiopharmaceuticals

The representative of the International Atomic Energy Agency (IAEA) presented an update of the joint effort of WHO and the IAEA in radiopharmaceuticals, as well as a draft report of the consultation on monographs and specifications for radiopharmaceuticals held in Geneva on 16–17 December 2002. It was reported that the expert group had recommended that the general methods as contained in the third edition of Volume 1 of *The International Pharmacopoeia* be replaced with the revised version.

The Committee endorsed the recommendation and also recommended that work commence on the specific monographs.

3.4 Quality specifications for antituberculosis drugs

The Committee was presented with a status report on work undertaken on methods for conducting screening tests and specifications for antituberculosis drugs that were currently being developed and validated entitled "Quality specifications for antituberculosis drugs".

The Committee recommended that this work should continue.

3.5 Quality specifications for antimalarials

The Committee received a status report on work carried out on screening test methods and specifications for antimalarials that were currently being developed and validated entitled "Quality specifications for antimalarials". Reference was made to Volume 5 of the third edition of *The International Pharmacopoeia* where it was indicated that International Chemical Reference Substances were required for these tests. These were being developed by the WHO Collaborating Centre for Chemical Reference Substances in Sweden. During the discussion, questions were raised about the issue of different strengths of the same medicine being recommended and leading to irrational drug therapy. This issue will be referred to the Roll Back Malaria programme.

The Committee commended the availability and quality of the monographs on antimalarials published in Volume 5 of *The International Pharmacopoeia* and recommended that the work be continued (see also section 2).

3.6 Pharmacopoeial monographs on antiretrovirals

The Committee was provided with a document entitled "Quality specifications for antiretrovirals" which described work being carried out on the development of specifications of certain antiretroviral drugs. This project was developed as a result of a recommendation made by the Expert Committee at its thirty-seventh meeting, and of the tremendous political pressure to make quality antiretroviral agents more readily available to disadvantaged HIV-positive persons. It was indicated that when these monographs become available they should be widely distributed for further consultation and validation.

The Committee expressed its support for the work and asked to be kept informed of its progress and results.

3.7 Quality control — specifications for excipients

The Committee was informed of the work in progress by the Pharmacopoeial Discussion Group (PDG) on harmonizing specifications for excipients. The discussion that followed highlighted the fact that some excipients were of a potentially high-risk nature. It was agreed to accept the offer of the PDG to publish monographs on those excipients harmonized to date in the next volume of *The International Pharmacopoeia*. It was further recommended that WHO should indicate differences in tests where they exist, in order to facilitate a better understanding of the harmonized monographs.

4. Quality control — International Reference Materials

4.1 International Chemical Reference Substances

The reports of the WHO Collaborating Centre for Chemical Reference Substances for 2001 and for 2002 were presented to the Committee.

It was reported that, despite staffing problems, the Centre continued to meet the demand for reference standards. Questions were raised on the absence of expiry dates on the reference substances supplied. During the discussion it was emphasized that reference substances were monitored by the issuing laboratory. The Committee acknowl-

edged the opinion of the EDQM representative who clarified that auditors using ISO 17025 had agreed to consider the practice of not giving expiry dates as acceptable. General guidelines for the establishment, maintenance and distribution of chemical reference substances can be found in the Thirty-fifth report of the Expert Committee on Specifications for Pharmaceutical Preparations (*2*).

The report for 2001 was accepted and the Committee expressed its appreciation of the support given by Apoteket in providing these reference standards at a minimal cost. Any further comments received on the Centre's report within the deadline will be forwarded to the Centre for appropriate action.

The Centre's report for 2002 was circulated for distribution and further comments. A document was presented to the Committee and a proposal made to disestablish some 13 of these standards as they are no longer required or requested. In addition, it was recommended that where the reference substances had either been disestablished (e.g. biological reference materials), or were subject to international customs controls, that monographs in *The International Pharmacopoeia* be revised.

It was noted that because there would be a delay between the disestablishment of reference standards and publication of the new monographs, the old standards should be temporarily retained. The proposals were accepted.

The Centre for International Chemical Reference Substances can be contacted at the following address:

WHO Collaborating Centre for Chemical Reference Substances
Apoteket AB
Produktion & Laboratorier
Centrallaboratoriet, ACL
Prismavägen 2
SE-141 75 Kungens Kurva, Sweden
Fax: + 46 8 740 60 40 or e-mail: who.apl@apoteket.se

The International Reference Materials available from the Centre, including both International Chemical Reference Substances (ICRS) and International Infrared (IR) Reference Spectra, are listed in Annex 1.

4.2 International Infrared Reference Spectra

To promote a more efficient process for the review and adoption of pending and future IR Spectra, it was proposed to take advantage of

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new technology such as e-mail to transmit spectra. Only contentious spectra would be discussed at meetings. The proposal was endorsed and the Committee acknowledged the contribution of the WHO Collaborating Centre for International Infrared Reference Spectra, Zurich, Switzerland. Members expressed their appreciation to the Swiss Federal Institute of Technology for providing the resources necessary for the activities of the Centre.

5. Quality control — national laboratories

5.1 Equipment for model quality control laboratories

The Committee was informed that the document providing information on the cost of equipment for model quality control laboratories entitled "Cost estimate of equipment for model quality control laboratories" was being revised to include the technical specifications for each item of equipment as requested by the Expert Committee at its thirty-seventh meeting.

5.2 External quality assurance assessment scheme

Two documents and the summary report from the European Directorate for the Quality of Medicines were presented to the Committee. It was noted that 36 laboratories, i.e. six in each WHO Region, randomly numbered in each report, had participated in this second phase of the external quality assessment scheme.

The Committee noted that this was a valuable exercise providing insight into the realities of the proficiency of drug quality control laboratories. It was also seen as a tool to help laboratories to improve their performance by serving as a benchmarking exercise.

The Committee expressed its appreciation of the work done and recommended continuation of these efforts. It was further recommended that the names of participating laboratories be included in the list of acknowledgements of the Expert Committee report.

6. Quality assurance — good manufacturing practices

6.1 Excipients

The Committee was informed of the efforts made by various parties in the area of good manufacturing practices (GMP) for excipients.

However, the Committee saw no need to revise the current version of the WHO supplementary GMP for excipients as it was found to be satisfactory in its present form (*3*).

6.2 Heating, ventilation and air conditioning

The Committee was provided with the first draft of the supplementary guidelines on GMP for heating, ventilation and air conditioning (HVAC) systems. The document will enter the consultation process and be included in the agenda of the next meeting of the Expert Committee.

The Committee commended WHO for its work on this subject.

6.3 Herbal medicinal products

The Committee was informed that a process for the revision of the WHO supplementary guidelines for the manufacture of herbal medicinal products had been initiated (*4*). A modified version of the guidelines would be submitted to the Expert Committee at its next meeting. Although some concerns about validation requirements were expressed, the Committee recommended the retention of the validation requirements as an important part of quality assurance of drugs. It also stressed the importance of proper packaging and labelling for these products.

6.4 Validation

The Committee was informed that a new WHO text for a supplementary GMP guideline on validation had been prepared and circulated for comments. A modified version would be submitted to the Expert Committee at its next meeting.

6.5 Water for pharmaceutical use

The Committee was informed that the supplementary GMP text on water for pharmaceutical use was being distributed for comments. The document had been written in a format different to that of the usual GMP texts. The Committee recommended that the document be separated into two parts: a general section and a section on GMP.

7. Quality assurance — inspection

7.1 Strengthening of Pharmaceutical Manufacturing Inspection project and development of training modules for inspectors

A presentation on the Strengthening of Pharmaceutical Manufacturing Inspection (SPMI) project and on the new training modules recently developed for inspectors was made to the Committee.

The aim of the SPMI project was to consolidate and extend upon the achievements of the first project entitled: "Promoting of the Implementation of GMP" (1998–2000) and to focus on strengthening the pharmaceutical manufacturing inspectorates by developing networks and using the CD-ROM of WHO basic training modules on GMP. A total of 240 participants from 47 countries had undergone the training and about 5800 copies of the CD-ROM had been distributed. The materials had been translated into Spanish by the WHO Regional Office for the Americas/Pan American Health Organization (PAHO) and into Chinese by the State Drug Administration (SDA), China. The Spanish version had been utilized by PAHO in the Region of the Americas, where 571 individuals had received training. The SDA had run five training courses during 2002.

Supplementary training modules on the subject of "Validation", "Water for pharmaceutical use" and "Air handling systems" had also been developed and were almost ready for distribution.

The efforts undertaken with the SPMI project may assist in providing a consistent application of the requirements in the inspection process. The Committee acknowledged that the project would assist in strengthening and improving the inspection process. Members commended the WHO project staff for their initiative and their success in raising the awareness of GMP around the world.

8. Quality assurance — distribution and trade-related

8.1 Good trade and distribution practices for pharmaceutical starting materials

The Committee was informed that a number of incidents involving diethylene glycol had resulted in a World Health Assembly resolution (WHA52.19) which had triggered the preparation of the GTDP and of the recommendations on good trade and distribution practices for pharmaceutical starting materials. The Committee was informed that the new guidelines, which focused on GMP and good storage

practices (GSP) related to activities, such as repackaging and relabelling, involved in the distribution of starting materials, had been widely circulated and the resulting comments incorporated. It was recognized that the implementation of this guidance could also assist in reducing the occurrence of counterfeit drugs. After discussion the Committee recommended the adoption of this guidance (Annex 2) with some minor additions reflecting the outcome of the discussions.

8.2 WHO Pharmaceutical Starting Materials Certification Scheme for use in international commerce

The Committee considered the new WHO Pharmaceutical Starting Materials Certification Scheme (SMACS) for which two model certificates were proposed: one for issue by national authorities and the other for completion by manufacturers of starting materials. The concept of this scheme was presented and discussed during the tenth ICDRA as suggested by the Expert Committee at its thirty-sixth meeting.

After a discussion about the implementation of the minimum requirements by the relevant authorities, it was suggested that the scheme should be reviewed after a pilot phase. Additionally, QSM should develop training materials on this subject. The Committee members supported the proposal and adopted the document for submission to the World Health Assembly (Annex 3).

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

The Committee was briefed on the implementation of the scheme in which about 140 members were participating. The Committee was also briefed on the recommendations made at the ICDRA in 1999 on the issue of certificates.

The Committee was informed of some cases where WHO-type certificates were issued:

— by authorities that did not meet the conditions specified in the WHO guidelines for the implementation of the scheme;
— for manufacturers not meeting WHO GMP standards; or
— by authorities that were not party to the scheme.

The issue of differences in the implementation of GMP requirements was also raised. The Committee suggested that every effort should be made to ensure the credibility of the certification scheme which was based on self-assessment by the participating country.

The Committee agreed that a small working group be formed to discuss the current status of the certification scheme, and recommended further measures to improve its effectiveness for presentation to the next Expert Committee meeting.

9. Quality assurance — risk analysis

9.1 New approach to inspections and manufacture

Documents related to the use of parametric release and a risk analysis approach for the inspection process were provided for the Committee's information and discussion. It was noted that the principle of risk analysis was being used in a variety of settings and could possibly be used by drug regulatory authorities, especially those with limited resources.

The Committee considered the approach to have value and recommended that the issue be reconsidered in the future.

10. Quality assurance — drug supply

10.1 Pre-qualification of manufacturers for the procurement and sourcing of pharmaceutical products

The Committee was informed of the background and progress of the WHO procedure for the pre-qualification of suppliers and pharmaceutical products (*5*).

The purpose of this procedure was to verify that pharmaceutical products and manufacturers met the specifications and standards set by WHO. As an additional benefit, those manufacturers that adopt this programme would serve as an example to others because the manufacturers that did adopt it would receive international recognition. The Committee emphasized the need for preserving the confidentiality of information and for selecting competent inspectors and evaluators.

The Committee discussed issues related to the inspection of sites per product rather than a global GMP inspection, to donations of drugs that might not be subject to inspection, and to confidentiality. The Committee noted that pre-qualification for vaccines was handled by another department in WHO and the focus of the project discussed here was on medicines used in treating HIV/AIDS, tuberculosis and malaria.

The Committee noted that drug regulatory authorities would also benefit as inspections were carried out by teams of inspectors, including those from the Pharmaceutical Inspection Co-operation Scheme (PIC/S), signatories, WHO staff and local representatives from the drug regulatory authority inspectorates of the countries involved.

The Committee commended the good work in developing the documents discussed below and acknowledged the need for a pre-qualification programme.

10.2 Pre-qualification of quality control laboratories

A draft procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations Agencies was presented to the Committee. Suggestions for additions to the document were made (e.g. a standard operation procedure document describing the infrastructure of the laboratories, etc.). The Expert Committee suggested that laboratories that were accepted following this suggested procedure could also be used by other countries for the same activities. It was recommended that certification under ISO 17025 should be taken into consideration when laboratories were assessed by WHO.

The Committee accepted, in principle, the text as a working document. Suggestions made would be taken into consideration by the Secretariat and a revised version would be distributed by e-mail for approval (the final document will be published as an annex) (Annex 4).

Guidelines for drafting a laboratory information file were presented to the Committee. The Committee accepted, in principle, the document as a working document. Suggestions made would be taken into consideration by the Secretariat and a revised version would be distributed by e-mail for approval (the final document will be published as an annex) (Annex 5).

10.3 Pre-qualification of procurement agencies

The draft procedure for assessing the acceptability, in principle, of procurement agencies for use by United Nations Agencies was presented to the Committee and discussed.

Comments were made on the content of the next version of the document, i.e. to include the definition of the term procurement agency, and address the issues of complaint handling, recalls and traceability of the product after distribution, to protect against diversion.

The Committee accepted, in principle, the document as a working document. Suggestions made would be taken into consideration by the Secretariat and a revised version would be distributed by e-mail for approval (the final document will be published as an annex) (Annex 6).

Guidelines for drafting a procurement agency information file were presented to the Committee and discussed. Suggestions were made for the inclusion of additional information to be submitted on requirements regarding personnel and storage requirements.

The Committee accepted, in principle, the document as a working document. Suggestions made would be taken into consideration by the Secretariat and a revised version would be distributed by e-mail for approval (the final document will be published as an annex) (Annex 7).

Draft interim guidelines for the assessment of a procurement agency were presented to the Committee and discussed. These interim guidelines would be used during the transition period until the final document (model quality assurance system) becomes available.

The Committee suggested that the checklist should be considered as basic, some of the criteria be considered as essential, and others should be classed as desirable or expected. The outcome should be monitored to assess its impact on the delivery of quality drugs.

The Committee accepted the document, in principle, as a working document. Suggestions made would be taken into consideration by the Secretariat and a revised version would be distributed by e-mail for approval (the final document will be published as an annex) (Annex 8).

The second draft of a model quality assurance system for pre-qualification, procurement, storage and distribution of pharmaceutical products was considered by the Committee. The Committee was informed about the background that led to the development of this document and received an explanation of the urgent need for this document to be finalized. The Committee was also informed that many comments on the document had already been received and that these were being processed by the Secretariat.

When reviewing the document, the Committee stressed the need to involve the drug regulatory authorities in the approval process and recommended that the role of the regulatory authority be clearly defined in the text. As guidelines related to quality assurance are not always respected, the Committee recommended that the document

should urge countries to ensure that all pertinent activities be performed in accordance with the relevant guidelines. The issues of bioequivalence, storage conditions and delivery were also raised in the discussion, reflecting their importance for the assurance of drug quality.

The Committee accepted the document, in principle, as a model that could be assessed and modified as necessary. It was further agreed that the Secretariat should produce a revised version, taking into consideration the comments made during the discussion. The Committee agreed, on the basis of urgency, to make the revised text available for use as an interim text. As it was anticipated that the document would be finalized before the end of 2003, it was further agreed that it would subsequently be presented for inclusion in the report of the next meeting of the Expert Committee.

10.4 Pre-qualification procedure for procurement of HIV/AIDS drugs

The Committee was informed of WHO's pilot project, being conducted in conjunction with the United Nations Children's Fund (UNICEF), the Joint United Nations Programme on HIV/AIDS (UNAIDS), the United Nations Population Fund (UNFPA) and with the support of the World Bank, to test the system for the prequalification of suppliers of HIV/AIDS drugs. This included:

— dossier evaluation;
— samples for analysis; and
— manufacturing site inspection.

Only manufacturers of dosage forms were subject to inspection under this programme (the manufacturers of active pharmaceutical ingredients were not to be inspected at this time, but the possibility of such inspections being required in the future was not to be excluded). The Committee was briefed on the number of quality defects found in the course of this project and recommended that all possible efforts should be made to ensure budgetary support for its continuation.

11. International Nonproprietary Names programme

The Committee was presented with a progress report of the work carried out since the previous meeting of the Expert Committee. The International Nonproprietary Names (INN) cumulative list was now available on CD-ROM and on a database that would facilitate searches. It was also planned to have applications submitted over the

Internet as well as further computerized processes to facilitate publication preparation. The link with the updated pharmacopoeial database, which is a compilation of monographs available in major pharmacopoeias, was also mentioned.

The Committee was informed of the workplan, progress and future challenges of this programme. The Committee was also informed that priority continued to be given to upgrading the database architecture and functionality.

The Committee noted that a small panel of experts had been formed to advise on issues relating to compounds in the area of biologicals in close collaboration with the Expert Committee on Biological Standardization.

The Committee was also informed of the plans for naming excipients. The Committee endorsed this plan because the consistent naming of excipients would be useful for the GTDP effort.

The Committee was informed about a proposed revision of "The procedure for the selection of recommended INNs for pharmaceutical substances" which was under discussion by the Executive Board.

The Committee commended the close collaboration with the WHO Expert Committee on Biological Standardization as well as the success of the INN programme, and encouraged their continued effort.

12. Miscellaneous

12.1 Launch of *The International Pharmacopoeia*, Volume 5

The new volume of *The International Pharmacopoeia* was presented to the Committee. This document includes 72 new monographs, 15 of which are for antimalarials, and contains monographs for artemisinin derivatives and their dosage forms for finished products. It was noted that no other pharmacopoeia had such complete monographs for this type of drug. In addition, a number of new test methods and general requirements were included in this volume. The Committee highly commended the good work that had resulted in the new volume.

12.2 Global Alliance for Quality of Pharmaceuticals

The Committee was provided with an update of the plans to launch a Global Alliance for Quality of Pharmaceuticals. There was evidence to show that problems related to the quality assurance of pharmaceuticals persisted. This applied especially to the growing problem world-

wide of the production, distribution and sale of counterfeit, spurious and substandard pharmaceutical products. In addition to being a waste of money for the people who buy them, counterfeit and substandard drugs prolonged treatment periods, exacerbated the conditions being treated, led to increased drug resistance and could even cause death.

A recommendation was made at the last ICDRA that WHO should work with other partners to address these problems jointly. Partnership was initially envisaged with PIC/S, the International Pharmaceutical Federation (FIP) and national pharmacopoeias. The objectives of the Alliance would be to:

— increase awareness of the importance of the quality, safety and efficacy of medicines through advocacy and promotion;
— promote assistance to countries to improve their access to good quality medicines;
— promote measures to eliminate the manufacture, distribution and sale of poor quality medicines with special focus on those used in the treatment of life-threatening conditions; and
— promote cooperation between international and national organizations to improve the quality of medicines.

There were presently a number of participants, but there is a possibility of others joining in the future.

The Committee was in favour of WHO's efforts to establish a Global Alliance for the Quality of Pharmaceuticals in response to challenges relating to the quality of medicines.

12.3 WHO Medicines Strategy 2004–2007

The Committee was presented with the new proposed framework for the WHO Medicines Strategy 2004–2007 on which comments were being sought by 15 May 2003. The document outlined the policy aspects, the challenges envisaged, measures to meet these challenges and benchmarks for the assessment of achievement. It was emphasized that although there had been some broad consultations with various stakeholders in drafting the document, it was still in its initial consultation phase, and could benefit from input by Committee members.

In discussing the documents, the Committee felt that it would have been easier and more beneficial to compare the objectives and expected outcomes of the 2004–2007 plan with those from 2000–2003. This would have enabled its members to assess to what extent the

objectives of the old plan had been met; this knowledge could then have been used as a measure for the potential success of the new plan. It was also felt that although provision for training was made in the document, greater emphasis on the development of human resources would be desirable, particularly for personnel in community pharmacies in rural areas, such as chemical vendors, and for personnel involved in GMP and GTDP. Members felt that although patent protection could be an incentive to research and development of new drugs for target diseases, its considerable cost could also be a stumbling block to making drugs available more cheaply to vulnerable groups, and to future research on treatments for HIV/AIDS, tuberculosis and malaria in developing countries.

Notwithstanding the questions raised, the members were unanimous in accepting the document as a good working draft. The Committee recommended that the WHO Secretariat should take the suggestions into consideration and re-circulate the revised document for further study.

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Annex 1
Lists of available International Chemical Reference Substances and International Infrared Reference Spectra

1. International Chemical Reference Substances

International Chemical Reference Substances (ICRS) are established upon the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are supplied primarily for use in physical and chemical tests and assays described in the specifications for quality control of drugs published in *The International Pharmacopoeia* or proposed in draft monographs. The International Chemical Reference Substances are mainly intended to be used as primary standards to calibrate secondary standards.

Directions for use and the analytical data required for the tests specified in *The International Pharmacopoeia* are given in the certificates enclosed with the substances when distributed.

International Chemical Reference Substances may also be used in tests and assays not described in *The International Pharmacopoeia*. However, the responsibility for assessing the suitability of the substances then rests with the user or with the pharmacopoeia commission or other authority that has prescribed the use of these substances.

It is generally recommended that the substances should be stored protected from light and moisture and preferably at a temperature of about +5 °C. When special storage conditions are required, this is stated on the label or in the certificate. It is recommended that the user purchase only an amount sufficient for immediate use.

The stability of the International Chemical Reference Substances kept at the Collaborating Centre is monitored by regular re-examination and any material that has deteriorated is replaced by new batches when necessary. Lists giving control numbers for the current batches are issued in the annual reports from the Centre and new yearly lists may also be obtained on request.

Ordering information

Orders for the International Chemical Reference Substances should be sent to:

Table 1
Available International Chemical Reference Substances

Catalogue number	Reference substance	Package size	Control number
9930375	*p*-acetamidobenzalazine	25 mg	290042
9930202	acetazolamide	100 mg	186128
9930204	allopurinol	100 mg	287049
9930206	amidotrizoic acid	100 mg	196205
9930191	2-amino-5-nitrothiazole	25 mg	186131
9930194	3-aminopyrazole-4-carboxamide hemisulfate	100 mg	172050
9930193	3-amino-2,4,6-triiodobenzoic acid	100 mg	196206
9930208	amitriptyline hydrochloride	100 mg	181101
9930209	amodiaquine hydrochloride	200 mg	192160
9930210	amphotericin B	400 mg	191153
9930211	ampicillin (anhydrous)	200 mg	390001
9930212	ampicillin sodium	200 mg	388002
9930213	ampicillin trihydrate	200 mg	274003
9930214	anhydrotetracycline hydrochloride	25 mg	180096
9930215	atropine sulfate	100 mg	183111
9930216	azathioprine	100 mg	172060
9930218	bacitracin zinc	200 mg	192174
9930219	beclometasone dipropionate	200 mg	192175
9930220	bendazol hydrochloride	100 mg	173066
9930223	benzobarbital	100 mg	172051
9930224	benzylamine sulfate	100 mg	172052
9930225	benzylpenicillin potassium	200 mg	180099
9930226	benzylpenicillin sodium	200 mg	280047
9930227	bephenium hydroxynaphthoate	100 mg	183112
9930228	betamethasone	100 mg	183113
9930229	betamethasone sodium phosphate	100 mg	196203
9930230	betamethasone valerate	100 mg	190145
9930231	betanidine sulfate	100 mg	172053
9930233	bupivacaine hydrochloride	100 mg	289054
9930234	caffeine	100 mg	181102
9930236	calcium folinate (leucovorin calcium)	100 mg	194188
9930237	captopril	100 mg	197214
9930238	captopril disulfide	25 mg	198216
9930239	carbamazepine	100 mg	189143
9930240	carbenicillin monosodium	200 mg	383043
9930241	chloramphenicol	200 mg	486004
9930242	chloramphenicol palmitate	1 g	286072
9930243	chloramphenicol palmitate (polymorph A)	200 mg	175073
9930199	5-chloro-2-methylaminobenzophenone	100 mg	172061
9930245	chloroquine sulfate	200 mg	195201
9930190	2-(4-chloro-3-sulfamoylbenzoyl)benzoic acid	50 mg	181106
9930246	chlorphenamine hydrogen maleate	100 mg	182109
9930247	chlorpromazine hydrochloride	100 mg	178080
9930248	chlortalidone	100 mg	183114
9930249	chlortetracycline hydrochloride	200 mg	187138
9930250	cimetidine	100 mg	190150

Table 1 *(continued)*

Catalogue number	Reference substance	Package size	Control number
9930256	ciprofloxacin hydrochloride	400 mg	197210
9930252	ciprofloxacin by-compound A	20 mg	198220
9930253	ciprofloxacin desfluoro-compound	20 mg	198219
9930254	ciprofloxacin ethylenediamine-compound	20 mg	198218
9930255	ciprofloxacin fluoroquinolonic acid	20 mg	198217
9930258	cisplatin	100 mg	197207
9930259	clomifene citrate	100 mg	187136
	clomifene citrate *Z*-isomer *see* zuclomifene		
9930261	cloxacillin sodium	200 mg	274005
9930262	colecalciferol (vitamin D_3)	500 mg	190146
9930263	cortisone acetate	100 mg	167006
9930265	dapsone	100 mg	183115
9930266	desoxycortone acetate	100 mg	167007
9930267	dexamethasone	100 mg	388008
9930268	dexamethasone acetate	100 mg	288009
9930269	dexamethasone phosphoric acid	100 mg	192161
9930270	dexamethasone sodium phosphate	100 mg	192158
9930281	diazepam	100 mg	172062
9930282	diazoxide	100 mg	181103
9930283	dicloxacillin sodium	200 mg	174071
9930284	dicolinium iodide	100 mg	172055
9930285	dicoumarol	100 mg	178077
9930287	diethylcarbamazine dihydrogen citrate	100 mg	181100
9930288	digitoxin	100 mg	277010
9930289	digoxin	100 mg	587011
9930290	dopamine hydrochloride	100 mg	192159
9930292	doxorubicin hydrochloride	100 mg	196202
9930294	emetine hydrochloride	100 mg	187134
9930197	4-epianhydrotetracycline hydrochloride	25 mg	288097
9930198	4-epitetracycline hydrochloride	25 mg	293098
9930295	ergocalciferol (vitamin D_2)	500 mg	190147
9930296	ergometrine hydrogen maleate	50 mg	277012
9930297	ergotamine tartrate	50 mg	385013
9930298	erythromycin	250 mg	191154
9930299	erythromycin B	150 mg	194186
9930300	erythromycin C	25 mg	194187
9930301	estradiol benzoate	100 mg	167014
9930302	estrone	100 mg	279015
9930303	etacrynic acid	100 mg	281056
9930304	ethambutol hydrochloride	100 mg	179081
9930305	ethinylestradiol	100 mg	301016
9930306	ethisterone	100 mg	167017
9930307	ethosuximide	100 mg	179088
9930308	etocarlide	100 mg	172057
9930309	flucloxacillin sodium	200 mg	195194
9930310	flucytosine	100 mg	184121

Catalogue number	Reference substance	Package size	Control number
9930311	fludrocortisone acetate	200 mg	195199
9930312	fluorouracil	100 mg	184122
9930313	fluphenazine decanoate dihydrochloride	100 mg	182107
9930314	fluphenazine enantate dihydrochloride	100 mg	182108
9930315	fluphenazine hydrochloride	100 mg	176076
9930316	folic acid	100 mg	388019
9930195	3-formylrifamycin	200 mg	202149
9930355	framycetin sulfate (neomycin B sulfate)	200 mg	193178
9930318	furosemide	100 mg	171044
9930319	gentamicin sulfate	100 mg	194183
9930322	griseofulvin	200 mg	280040
9930323	haloperidol	100 mg	172063
9930324	hydrochlorothiazide	100 mg	179087
9930325	hydrocortisone	100 mg	283020
9930326	hydrocortisone acetate	100 mg	280021
9930327	hydrocortisone sodium succinate	200 mg	194184
9930188	(–)-3-(4-hydroxy-3-methoxyphenyl)-2-hydrazino-2-methylalanine (3-*O*-methylcarbidopa)	25 mg	193180
9930189	(–)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine (3-*O*-methylmethyldopa)	25 mg	179085
9930328	ibuprofen	100 mg	183117
9930329	imipramine hydrochloride	100 mg	172064
9930330	indometacin	100 mg	178078
9930370	*o*-iodohippuric acid	100 mg	171045
9930331	isoniazid	100 mg	185124
9930332	kanamycin monosulfate	12 mg	197211
9930333	lanatoside C	100 mg	281022
9930334	levodopa	100 mg	295065
9930335	levonorgestrel	200 mg	194182
9930336	levothyroxine sodium	100 mg	189144
9930337	lidocaine	100 mg	181104
9930338	lidocaine hydrochloride	100 mg	181105
9930339	liothyronine sodium	50 mg	193179
9930340	loperamide hydrochloride	100 mg	194185
9930341	mebendazole	200 mg	195195
	Melting point reference substances		
9930217	azobenzene (69 °C)	1 g	192168
9930438	vanillin (83 °C)	1 g	299169
9930222	benzil (96 °C)	4 g	294170
9930201	acetanilide (116 °C)	1 g	297171
9930380	phenacetin (136 °C)	1 g	297172
9930221	benzanilide (165 °C)	4 g	192173
9930422	sulfanilamide (166 °C)	1 g	192162

Table 1 *(continued)*

Catalogue number	Reference substance	Package size	Control number
9930423	sulfapyridine (193 °C)	4 g	192163
9930286	dicyanodiamide (210 °C)	1 g	192164
9930411	saccharin (229 °C)	1 g	192165
9930235	caffeine (237 °C)	1 g	299166
9930382	phenolphthalein (263 °C)	1 g	299167
9930343	metazide	100 mg	172058
9930344	methaqualone	100 mg	173069
9930345	methotrexate	100 mg	194193
9930346	methyldopa	100 mg	179084
9930347	methyltestosterone	100 mg	167023
9930348	meticillin sodium	200 mg	274024
9930350	metronidazole	100 mg	183118
9930351	nafcillin sodium	200 mg	272025
9930354	neamine hydrochloride (neomycin A hydrochloride)	0.5 mg	193177
	neomycin B sulfate *see* framycetin sulfate		
9930356	neostigmine metilsulfate	100 mg	187135
9930357	nicotinamide	100 mg	200090
9930358	nicotinic acid	100 mg	179091
9930359	nifurtimox	100 mg	194189
9930360	niridazole	200 mg	186129
9930361	niridazole-chlorethylcarboxamide	25 mg	186130
9930366	norethisterone	100 mg	186132
9930367	norethisterone acetate	100 mg	185123
9930369	nystatin	200 mg	300152
9930371	ouabain	100 mg	283026
9930372	oxacillin sodium	200 mg	382027
9930373	oxytetracycline dihydrate	200 mg	189142
9930374	oxytetracycline hydrochloride	200 mg	189141
9930376	papaverine hydrochloride	100 mg	185127
9930377	paracetamol	100 mg	195198
9930378	paromomycin sulfate	75 mg	195197
9930381	pheneticillin potassium	200 mg	167028
9930383	phenoxymethylpenicillin	200 mg	179082
9930384	phenoxymethylpenicillin calcium	200 mg	179083
9930385	phenoxymethylpenicillin potassium	200 mg	176075
9930387	phenytoin	100 mg	179089
9930388	piperazine adipate	100 mg	197212
9930389	piperazine citrate	100 mg	197213
9930390	praziquantel	100 mg	194191
9930391	prednisolone	100 mg	389029
9930392	prednisolone acetate	100 mg	289030
9930393	prednisolone hemisuccinate	200 mg	195196
9930394	prednisolone sodium phosphate	200 mg	194190
9930395	prednisone	100 mg	167031
9930396	prednisone acetate	100 mg	169032
9930397	probenecid	100 mg	192156

Catalogue number	Reference substance	Package size	Control number
9930398	procaine hydrochloride	100 mg	183119
9930399	procarbazine hydrochloride	100 mg	184120
9930400	progesterone	100 mg	167033
9930401	propicillin potassium	200 mg	274034
9930402	propranolol hydrochloride	100 mg	187139
9930403	propylthiouracil	100 mg	185126
9930404	pyrantel embonate (pyrantel pamoate)	500 mg	192157
9930405	pyridostigmine bromide	100 mg	182110
9930406	reserpine	100 mg	186133
9930407	retinol acetate (solution)	5 caps[a]	898038
9930408	riboflavin	250 mg	382035
9930409	rifampicin	300 mg	191151
9930410	rifampicin quinone	200 mg	202148
9930412	sodium amidotrizoate	100 mg	198221
9930413	sodium cromoglicate	100 mg	188140
9930415	spectinomycin hydrochloride	200 mg	193176
9930416	streptomycin sulfate	100 mg	197215
9930417	sulfacetamide	100 mg	196200
9930419	sulfamethoxazole	100 mg	179092
9930420	sulfamethoxypyridazine	100 mg	178079
9930421	sulfanilamide	100 mg	179094
9930424	sulfasalazine	100 mg	191155
9930425	tamoxifen citrate	100 mg	196208
9930426	tamoxifen citrate *E*-isomer	10 mg	196209
9930427	testosterone enantate	200 mg	194192
9930428	testosterone propionate	100 mg	167036
9930429	tetracycline hydrochloride	200 mg	180095
9930430	thioacetazone	100 mg	171046
9930196	4,4′-thiodianiline	50 mg	183116
	thyroxine sodium *see* levothyroxine sodium		
9930431	tolbutamide	100 mg	179086
9930432	tolnaftate	100 mg	176074
9930433	toluene-2-sulfonamide	100 mg	196204
9930434	trimethadione	200 mg	185125
9930435	trimethoprim	100 mg	179093
9930436	trimethylguanidine sulfate	100 mg	172059
9930440	vincristine sulfate	9.7 mg/vial	193181
	Vitamin A acetate (solution) *see* retinol acetate (solution)		
9930439	warfarin	100 mg	168041
9930260	zuclomifene	50 mg	187137

[a] About 8 mg in 230 mg oil per capsule

WHO Collaborating Centre for Chemical Reference Substances
Apoteket AB
Produktion & Laboratorier
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Prismavägen 2
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International Chemical Reference Substances are supplied only in the standard packages indicated in the following list.

2. International Infrared Reference Spectra

The WHO Collaborating Centre for Chemical Reference Substances is able to supply 69 International Infrared Reference Spectra.

Orders should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteket AB
Produktion & Laboratorier
Centrallaboratoriet, ACL
Prismavägen 2
SE-141 75 Kungens Kurva, Sweden
Fax: +46 8 740 60 40
or e-mail: who.apl@apoteket.se

The following International Infrared Reference Spectra are currently available from the Centre:

aceclidine salicylate
acetazolamide
allopurinol

amiloride hydrochloride
amitriptyline hydrochloride
ampicillin trihydrate

beclometasone dipropionate
benzylpenicillin potassium
biperiden

biperiden hydrochloride
bupivacaine hydrochloride

caffeine (anhydrous)
calcium folinate
carbidopa
chlorphenamine hydrogen maleate

clofazimine
cloxacillin sodium
colchicine
cytarabine

dexamethasone
dexamethasone acetate, monohydrate
dextromethorphan hydrobromide
diazepam

erythromycin ethylsuccinate
erythromycin stearate
etacrynic acid

furosemide

gallamine triethiodide

haloperidol

ibuprofen
imipramine hydrochloride

lidocaine
lidocaine hydrochloride

metronidazole

niclosamide
nicotinamide

oxamniquine

papaverine hydrochloride
phenobarbital
phenoxymethylpenicillin calcium
phenytoin

salbutamol
salbutamol sulfate
sulfadimidine

tiabendazole
trihexyphenidyl hydrochloride

valproic acid

dicolinium iodide
dicoumarol
diethylcarbamazine dihydrogen citrate
diphenoxylate hydrochloride

ethionamide
ethosuximide

glibenclamide

hydrochlorothiazide

indometacin
isoniazid

lindane

miconazole nitrate

noscapine

primaquine phosphate
propylthiouracil
protionamide
pyrimethamine

sulfadoxine
sulfamethoxazole
sulfamethoxypyridazine

trimethoprim

verapamil hydrochloride

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Annex 2
Good trade and distribution practices for pharmaceutical starting materials

Introductory note

The storage, trade and distribution of pharmaceutical starting materials are activities that are not only carried out by companies that manufacture pharmaceutical starting materials. The nature of the risks is generally the same as that of those encountered in the manufacturing environment, e.g. mix-ups and cross-contamination. Therefore, there are aspects in trading and distribution where the implementation of good manufacturing practice (GMP) would be beneficial. These include, but are not limited to, packaging, repackag-

ing, labelling, relabelling, storage, distribution and documentation and record-keeping practices.

WHO is concerned about the quality of materials used for the manufacture of pharmaceutical products because the quality of the pharmaceutical starting materials can be affected by the lack of adequate control of activities including packaging, repackaging, labelling, relabelling, storage and distribution of the materials used in pharmaceutical products.

Packaging, repackaging, labelling, relabelling, storage and distribution are the usual practices of a number of parties involved in the trade and distribution of pharmaceutical starting materials, including traders, brokers and distributors. Other activities include the issuing of Certificates of Analysis. Improper trading practices (e.g. packaging, storage and distribution) can pose a significant risk to the quality of pharmaceutical starting materials. Experience has shown that activities such as repackaging and relabelling, in particular, can increase the risk of contamination, cross-contamination, mix-ups, degradation and changes in physical properties.

To maintain the original quality, all activities such as packaging, labelling and retesting of materials should be carried out according to GMP, good storage practice (GSP) and good trade and distribution practice (GTDP).

This guideline is a stand-alone text. However, there may be some overlap with other guidelines such as those for GMP and GSP.

Scope

These guidelines are applicable to all persons and companies involved in handling pharmaceutical starting materials (i.e. active pharmaceutical ingredients (APIs) and excipients), including the materials removed during the process of pharmaceutical product manufacture. The guidelines apply to all parties involved in trade and distribution, brokers, suppliers, distributors, traders, transport companies, forwarding agents, processors, etc.

All materials designated or intended to be used as pharmaceutical starting materials are covered by these guidelines, from the point at which the starting material is identified or designated as being for pharmaceutical use.

The guidelines apply to every step in the distribution and supply chain.

Persons and companies performing processing activities, such as mixing, micronization, relabelling or repackaging of pharmaceutical starting materials, should also comply with all relevant aspects of GMP.

In addition to this text, the good storage practices for pharmaceuticals are applicable.

General considerations

The objective of the implementation of these guidelines is to ensure the quality and integrity of the starting material and the pharmaceutical product.

The guidelines should be considered and implemented inter alia by suppliers, such as:

— pharmaceutical manufacturers, including manufacturers of intermediate and/or finished products;
— distributors;
— manufacturers of pharmaceutical starting materials;
— brokers; and
— other suppliers.

They are also relevant to:

— governments;
— regulatory bodies;
— international organizations and donor agencies involved in procurement tenders;
— relevant trade organizations;
— certifying bodies; and
— all parties involved in trade and distribution.

Member States should take appropriate measures to ensure the implementation of these guidelines. The guidelines can be used as one tool in the prevention of the trade in counterfeit and substandard medicines.

The importance of quality of the pharmaceutical starting materials used in the manufacture of pharmaceutical products cannot be overemphasized. The marketing authorization dossier for a finished product should normally refer to the use of a pharmaceutical starting material from a specific source(s) in that product. The sourcing, storage, distribution and use of these starting materials are thus a shared responsibility.

The role of the producer, manufacturer, trader, broker or distributor in sharing the responsibility for a quality product is evident. Each must ensure that materials are of the quality required for use in the pharmaceutical industry, as each plays an important part in the manufacture and supply chain to ensure that a quality product is supplied to the patient.

For this reason, materials can only be reclassified from pharmaceutical grade to non-pharmaceutical grade and not from non-pharmaceutical grade to pharmaceutical grade.

Each batch of pharmaceutical starting material should normally be tested by its manufacturer for compliance with its specification. When results are obtained from skip lot testing this should be indicated on the Certificate of Analysis issued by the manufacturer.

Glossary

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

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

agreement
Arrangement undertaken by and legally binding on parties.

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 could be expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced during a fixed time interval.

batch number (or lot number)
A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, the batch records, the certificates of analysis, etc.

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.

certificate of analysis (COA)
A document listing the results of testing a representative sample drawn from the batch to be delivered. A COA should be equivalent to the WHO Model COA (*1*).

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

contract
Business agreement for supply of goods or performance of work at a specified price.

Earliest expiry/first out principle concept (EEFO)
A distribution procedure to ensure that the stock with the earliest expiry date is distributed and/or utilized before an identical stock item with a later expiry date is distributed and/or utilized.

excipient
A substance or compound, other than the active pharmaceutical ingredient and packaging materials, that is intended or designated to be used in the manufacture of a pharmaceutical product.

expiry date
The expiry date displayed on the container of a pharmaceutical starting material is the date up to and including which the pharmaceutical starting material is expected to remain within specification if stored correctly. It is established for every batch by adding the shelf-life to the date of manufacture.

First in/first out principle concept (FIFO)
A distribution procedure to ensure that the oldest stock is distributed and/or utilized before a newer and identical stock item is distributed and/or utilized.

good manufacturing practice (GMP)
That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

homogeneous material
Material of uniform consistency and composition throughout a batch.

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

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

labelling
The action involving the selection of the correct label, with the required information, followed by line-clearance and application of the label.

manufacture
All operations of purchase of materials, production, quality control, release, storage, and distribution of pharmaceutical starting materials, and the related controls.

original manufacturer
Person or company manufacturing a material to the stage at which it is designated as a pharmaceutical starting material.

pharmaceutical starting material
A pharmaceutical starting material is an active pharmaceutical ingredient (API) or an excipient intended or designated for use in the production of a pharmaceutical product.

production
All operations involved in the preparation of a pharmaceutical starting material, from receipt of materials, through processing, packaging

and repackaging, labelling and relabelling, to completion of the finished pharmaceutical starting materials.

quality assurance
A wide-ranging concept covering all matters that individually or collectively influence the quality of a product, including pharmaceutical starting materials. It is the totality of the arrangements made with the object of ensuring that pharmaceutical starting materials and pharmaceutical products are of the quality required for their intended use.

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 starting materials conform to established specifications for identity, strength, purity and other characteristics.

quarantine
The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

recall
A process for withdrawing or removing a pharmaceutical material from the distribution chain because of defects in the materials or complaints of a serious nature. The recall might be initiated by the manufacturer/importer/distributor or a responsible agency.

relabelling
The process of putting a new label on the material (see also *labelling*).

repackaging
The action of changing the packaging of the material.

retest date
The date when a material should be re-examined to ensure that it is still suitable for use.

sampling
Operations designed to obtain a representative portion of a pharmaceutical starting material based on an appropriate statistical procedure, for a defined purpose, e.g. acceptance of consignments, batch release, etc.

skip lot (periodic) testing
The performance of specified tests at release on preselected batches and/or at predetermined intervals, rather than on a batch-to-batch

basis, with the understanding that those batches not tested must still meet all the acceptance criteria established for that product. This represents a less than full schedule of testing and should therefore be justified, presented to, and approved by, the regulatory authority before implementation. When tested, any failure of the starting material to meet the acceptance criteria established for the periodic (skip lot) test should be handled by proper notification of the appropriate regulatory authority (authorities). If these data demonstrate a need to restore routine testing, then batch-by-batch release testing should be reinstated.

supplier
Person or company providing pharmaceutical starting materials on request. Suppliers may be distributors, manufacturers, traders, etc.

validation
The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

1. Quality management

1.1 Within an organization, quality assurance serves as a management tool. In contractual situations quality assurance also serves to generate confidence in the supplier. There should be a documented quality policy describing the overall intentions and direction of the supplier regarding quality, as formally expressed and authorized by management.

1.2 Quality management should include:

— an appropriate infrastructure or "quality system", encompassing the organizational structure, procedures, processes and resources;
— the systematic actions necessary to ensure adequate confidence that a material (or service) and the relevant documentation will satisfy given requirements for quality. (The totality of these actions is termed "quality assurance".); and
— a clear procedure for approving suppliers of pharmaceutical starting materials and services (for details see GMP).

1.3 The system should cover quality assurance principles.

1.4 All parties involved in the manufacture and supply chain must share responsibility for the quality and safety of the materials and products to ensure that they are fit for their intended use.

1.5 The responsibilities placed on any one individual should not be so extensive as to present any risk to quality. In the event of a supplier having a limited number of staff, some duties may be delegated or contracted out to designated persons who are appropriately qualified. There should, however, be no gaps or unexplained overlaps related to the application of GTDP.

1.6 Where electronic commerce (e-commerce) is used, defined procedures and adequate systems should be in place to ensure traceability and confidence in the quality of the material.

1.7 Authorized release procedures should be in place to ensure that material of an appropriate quality is sourced from approved suppliers and released for its intended purpose.

1.8 Inspection and certification of compliance with a quality system (such as applicable International Standards Organization (ISO) series and hazard analysis and critical control point (HACCP)) by external bodies is recommended. However, this should not be seen as a substitute for the implementation of these guidelines or for conforming with pharmaceutical GMP requirements, as applicable.

1.9 A system should be in place for the performance of regular internal audits with the aim of continuous improvement. The findings of the audit and any corrective actions taken should be documented and brought to the attention of the responsible management.

2. Organization and personnel

2.1 There should be an adequate organizational structure and sufficient personnel should be employed to carry out all the tasks for which the supplier is responsible.

2.2 Individual responsibilities should be clearly defined, understood by the individuals concerned and recorded in writing (as job descriptions or in a contract). Certain activities, such as the supervision of performance of activities in accordance with local legislation, may require special attention. Personnel should be suitably qualified and authorized to undertake their duties and responsibilities.

2.3 All personnel should be aware of the principles of GTDP.

2.4 Personnel should receive initial and continuing training relevant to their tasks. All personnel should be motivated to support the establishment and maintenance of quality standards.

2.5 Personnel dealing with hazardous materials (such as highly active, toxic, infectious or sensitizing materials) should be given spe-

cific training and should be provided with the necessary protective equipment.

2.6 Personnel who may be exposed to materials from open containers should maintain good hygiene, have no open wounds and be equipped with an appropriate protective outfit, such as gloves, masks and goggles.

3. Premises

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

3.2 Measures should be in place to prevent unauthorized persons from entering the premises.

3.3 Premises should be designed and equipped so as to afford maximum protection against the entry of insects, rodents or other animals.

3.4 Suitable supporting facilities and utilities (such as air control, lighting and ventilation) should be in place and appropriate to the activities performed.

3.5 There should normally be a separate sampling area for pharmaceutical starting materials in a controlled environment. 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.

4. Warehousing and storage

GSP is applicable in all circumstances in which and all areas where materials are stored.

4.1 There should be authorized procedures describing the activities relating to the receipt, storage and distribution of materials.

4.2 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials.

4.3 Receipt and dispatch bays should be equipped with the means to protect materials from the weather. Reception areas should be

designed and equipped to allow containers of incoming materials to be cleaned before storage if necessary.

4.4 Segregated areas should be provided for the storage of rejected, recalled and returned materials, including those with damaged packaging.

4.5 Segregated areas and materials should be appropriately identified.

4.6 The required storage conditions as specified for the product should be maintained within acceptable limits. The storage areas should be kept clean and dry.

4.7 Where special storage conditions are required (e.g. particular requirements for temperature or humidity) these should be provided, monitored and recorded.

4.8 Highly active materials, narcotics, other dangerous drugs and substances presenting special risks of abuse, fire or explosion should be stored in safe, dedicated and secure areas. In addition international conventions and national legislation may apply.

4.9 Special attention should be given to the design, use, cleaning and maintenance of all equipment for bulk handling and storage, such as tanks and silos.

4.10 Spillages should be cleaned as soon as possible to prevent possible cross-contamination and hazard.

4.11 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, closed containers in enclosed areas, taking into account the relevant national legislation.

4.12 A system should be in place to ensure that those materials due to expire first are sold or distributed first (earliest expiry/first out (EEFO)). Where no expiry dates are specified for the materials, the first in/first out (FIFO) principle should be applied.

4.13 Storage areas should be clean and free from accumulated waste and from vermin. A written sanitation programme should be available, indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas. There should also be a written programme for pest control.

5. Equipment

5.1 Equipment must be located, designed, constructed, adapted, used and maintained to suit the operations to be carried out. Defective equipment should not be used, and should either be removed or labelled as defective. Equipment should be disposed of in such a way as to prevent any misuse.

5.2 The layout, design and use of equipment must aim to minimize the risk of errors and to permit effective cleaning and maintenance to avoid cross-contamination, build-up of dust or dirt and any adverse effect on the quality of materials.

5.3 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

5.4 All services, piping and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases, liquids and other materials.

5.5 Balances and other measuring equipment of an appropriate range and precision should be available and should be calibrated on a scheduled basis.

5.6 Procedures should be in place for the operation and maintenance of equipment. Lubricants and other materials used on surfaces that come into direct contact with the materials should be of the appropriate grade, e.g. food-grade oil.

5.7 Washing and cleaning equipment should be chosen and used such that it cannot be a source of contamination.

5.8 Dedicated equipment should be used where possible when handling and/or processing pharmaceutical starting materials. Where non-dedicated equipment is used, cleaning validation should be performed.

6. Documentation

6.1 Documents, in particular instructions and procedures relating to any activity that might have an impact on the quality of materials, should be designed, completed, reviewed and distributed with care. Documents should be completed, approved, signed and dated by appropriate authorized persons and should not be changed without authorization.

6.2 Documents should have unambiguous contents: their title, nature and purpose should be clearly stated. They should be laid out in an orderly manner and be easy to check.

6.3 Original Certificates of Analysis (COAs) should accompany materials supplied by manufacturers to suppliers. COAs issued by the manufacturer should indicate which results were obtained by testing the original material and which results came from skip lot testing. The use of the Model COA as adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations is recommended (*1*).

6.4 Before any material is sold or distributed, the supplier should ensure that the COAs and results are available and that the results are within the required specifications. Alternatively the customer should be informed without delay of the results as soon as these become available. For each shipment the COA should be forwarded to the pharmaceutical product manufacturer.

6.5 The original manufacturer and intermediaries handling the material should always be traceable and the information available to authorities and end-users, downstream and upstream.

6.6 Mechanisms should exist to allow for transfer of information including the transfer of quality or regulatory information between a manufacturer and a customer, and of information to the regulatory authority upon request.

6.7 Labels applied to containers should be clear, unambiguous, permanently fixed and in the company's agreed format. The information on the label should be indelible.

6.8 Each container should be identified by labelling bearing at least the following information:

— the name of the pharmaceutical starting material, including grade and reference to pharmacopoeias, where relevant;
— if applicable, the International Nonproprietary Names (INNs);
— the amount (weight or volume);
— the batch number assigned by the original manufacturer or the batch number assigned by the repacker, if the material has been repacked and relabelled;
— the retest date or expiry date (where applicable);
— any special storage conditions;
— handling precautions, where necessary;
— identification of the original manufacturing site; and
— name and contact details of the supplier.

6.9 Relevant storage, handling and safety data sheets should be available.

6.10 Records must be kept and must be readily available upon request in accordance with GSP (*2*).

7. Repackaging and relabelling

7.1 Operations, such as combining into a homogeneous batch, repackaging and/or relabelling, are manufacturing processes and their performance should therefore follow GMP.

7.2 Special attention should be given to the following points:

— prevention of contamination, cross-contamination and mix-ups;
— security of stocks of labels, line clearance checks, on-line inspections, destruction of excess batch-printed labels;
— good sanitation and hygiene practices;
— maintaining batch integrity (normally mixing of different batches of the same solid material should not be done);
— as part of batch records, all labels that were removed from the original container during operations, and a sample of the new label, should be kept;
— if more than one batch of labels is used in one operation, samples of each batch should be kept; and
— maintaining product identity and integrity.

7.3 When different batches of a material from the same original manufacturing site are received by a distributor and combined into a homogeneous batch, the conformity of each batch with its specification should be confirmed before it is added.

7.4 Only materials from the same manufacturing site received by a distributor and conforming to the same specifications can be mixed. If different batches of the same material are mixed to form a homogeneous batch it should be defined as a new batch, tested and supplied with a batch certificate of analysis. In such cases the customer should be informed that the material supplied is a mixture of manufacturers' batches. The supplied material must have a certificate of conformity to a specification at date of supply.

7.5 In all cases the original COA of the original manufacturer should be provided. If retesting is done, both the original and the new COA should be provided. The batch referred to on the new COA should be traceable to the original COA.

7.6 Repackaging of materials should be carried out with primary packaging materials for which the quality and suitability have been established to be equal to or better than those of the original container. The approval of the supplier is necessary for the packaging material used for the repackaging.

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7.7 The re-use of containers should be discouraged unless they have been cleaned using a validated procedure. Recycled containers should not be used unless there is evidence that the quality of the material packed will not be adversely affected.

7.8 Materials should be repackaged only if efficient environmental control exists to ensure that there is no possibility of contamination, cross-contamination, degradation, physicochemical changes and/or mix-ups. The quality of air supplied to the area should be suitable for the activities performed, e.g. efficient filtration.

7.9 Suitable procedures should be followed to ensure proper label control.

7.10 Containers of repackaged material and relabelled containers should bear both the name of the original manufacturing site and the name of the distributor/repacker.

7.11 Procedures should be in place to ensure maintenance of the identity and quality of the material by appropriate means, both before and after repackaging operations.

7.12 Batch release procedures should be in place in accordance with GMP.

7.13 Only official pharmacopoeial methods or validated analytical test methods should be used for the analysis.

7.14 Samples of APIs and excipients of appropriate quantities should be kept for at least 1 year after the expiry or retest date, or for 1 year after distribution is complete.

7.15 The repacker and relabeller should ensure that the stability of the material is not adversely affected by the repackaging or relabelling. Stability studies to justify the expiry or retest dates assigned should be conducted if the pharmaceutical starting material is repackaged in a container different from that used by the original manufacturer. It is recognized that some excipients may not need additional stability studies.

8. Complaints

8.1 All complaints and other information concerning potentially defective materials must be carefully reviewed according to written procedures that describe the action to be taken, and including the criteria on which a decision to recall a product should be based.

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8.2 Any complaint concerning a material defect should be recorded and thoroughly investigated to identify the origin or reason for the complaint (e.g. the repackaging procedure, the original manufacturing process, etc.).

8.3 If a defect in a pharmaceutical starting material is discovered or suspected, consideration should be given as to whether other batches should be checked.

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

8.5 The manufacturer and customers should be informed if action is needed following possible faulty manufacturing, packaging, deterioration, or any other serious quality problems with a pharmaceutical starting material.

9. Recalls

9.1 There should be a system for recalling promptly and effectively from the market, materials known or suspected to be defective.

9.2 The original manufacturer should be informed in the event of a recall.

9.3 There should be established written procedures for the organization of any recall activity; these should be regularly checked and updated.

9.4 All recalled materials should be stored in a secure, segregated area while their fate is decided.

9.5 In the event of serious or potentially life-threatening situations all customers and competent authorities in all countries to which a given material may have been distributed should be promptly informed of any intention to recall the material.

9.6 All records should be readily available to the designated person(s) responsible for recalls. These records should contain sufficient information on materials supplied to customers (including exported materials).

9.7 The effectiveness of the arrangements for recalls should be evaluated at regular intervals.

10. Returned goods

10.1 Goods returned to the supplier should be appropriately identified and handled in accordance with a procedure addressing at least the keeping of the material in quarantine in a dedicated area, and its assessment and disposition by a designated person. Where any doubt arises over the quality of the materials, they should not be considered suitable for reissue or reuse.

11. Handling of non-conforming materials

11.1 Non-conforming materials should be handled in accordance with a procedure that will prevent their introduction or reintroduction into the market. Records covering all activities, including destruction, disposal, return and reclassification, should be maintained.

11.2 An investigation should be performed to establish whether any other batches are also affected. Corrective measures should be taken where necessary.

11.3 The disposition of the material, including downgrading to other suitable purposes should be documented.

11.4 Non-conforming materials should never be blended with materials that do comply with specifications.

12. Dispatch and transport

12.1 Materials should be transported in a manner that will ensure the maintenance of controlled conditions where applicable (e.g. temperature, protection from the environment). The transport process should not adversely affect the materials.

12.2 Requirements for special transport and/or storage conditions should be stated on the label. If the pharmaceutical starting material is intended to be transferred outside the control of the manufacturer's materials management system, the name and address of the manufacturer, quality of contents, special transport conditions and any special legal requirements should also be included on the label.

12.3 The supplier of the materials should ensure that the contract acceptor for transportation of the materials is aware of and provides the appropriate storage and transport conditions.

12.4 Procedures should be in place to ensure proper cleaning and prevention of cross-contamination when liquids (tanks) and bulk or packed materials are transported.

12.5 The bulk transport of pharmaceutical starting materials requires numerous precautions to avoid contamination and cross-contamination. The best practice is to use dedicated equipment, tanks or containers.

12.6 Packaging materials and transportation containers should be suitable to prevent damage to the pharmaceutical starting materials during transport.

12.7 For bulk transport, validated cleaning procedures should be used between loadings, and a list of restricted previous cargoes must be supplied to the transport companies.

12.8 Steps should be taken to prevent unauthorized access to the materials being transported.

12.9 General international requirements regarding safety aspects (e.g. prevention of explosion and of contamination of the environment, etc.) should be observed.

13. Contract activities

13.1 Any activity performed, as referenced in the GMP and GTDP guidelines, delegated to another party, should be agreed upon in a written contract.

13.2 The contract giver should evaluate the proposed contract acceptor's compliance with GTDP before entering into an agreement.

13.3 All contract acceptors should comply with the requirements in these guidelines. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

13.4 There should be a written and approved contract or formal agreement between the contract giver and contract acceptor that addresses and defines in detail the responsibilities, GTDP and which party is responsible for which quality measures.

13.5 Subcontracting may be permissible under certain conditions, subject to approval by the contract giver, especially for activities such as sampling, analysis, repacking and relabelling.

References

1. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth Report.* Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902).
2. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh Report*. World Health Organization, Geneva, 2003 (Technical Report Series, No. 908).

WHO Technical Report Series, No. 917, 2003

Annex 3
WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation

Preamble

The quality of pharmaceuticals has been a concern of WHO since its inception. Owing to the nature of these products, this concern includes the quality of the starting materials, i.e. active pharmaceutical ingredients (APIs) and excipients, used for the production of pharmaceuticals.

This guidance text, in combination with other recommendations and guidelines issued by WHO, will be an important step towards ensuring the quality and traceability of pharmaceutical starting materials and in assigning the responsibility for specifications within the processes of manufacture, storage and distribution of pharmaceutical starting materials.

Member States are urged to establish and maintain a legal framework and regulatory approach to ensure that good practices for the trade and distribution of pharmaceutical starting materials are followed. Member States can establish appropriate regulatory control by implementing one or both of the following approaches:

— licensing of suppliers, including traders, brokers and distributors; and/or
— a registration or notification system of suppliers, including traders, brokers and distributors.

A variety of WHO guidelines ready for use and inclusion into national legislation are available. Their implementation will be crucial throughout the process towards ensuring the availability and use of quality pharmaceutical starting materials in the manufacture of medicines.

Where a licensing system already exists, inspections should be performed by persons from the competent national or regional statutory authority to assess compliance with good trade and distribution practices (GTDP). Where a notification or registration system is to be implemented, voluntary inspections may be performed before certification for compliance with GTDP.

The use of the new certification scheme is based on the existence of a quality assurance system for the production of starting materials.

All parties involved in the trade and distribution of pharmaceutical starting materials are strongly encouraged to comply with the GTDP. Manufacturers of pharmaceutical products should encourage and assist their suppliers to use good storage practice (GSP), GTDP and the relevant parts of good manufacturing practice (GMP).

Trade associations are also encouraged to incorporate these principles into their own codes of practice to be followed by their members.

Another recommendation is the development of a global database listing information on suppliers (e.g. names and addresses) to enable customers to verify supplier information. A global database could later be established to assist in the attempt to address the problem of counterfeiting of pharmaceutical materials.

Training workshops and conferences on GTDP should be planned to promote these principles.

The establishment of model certificates for GSP and GTDP should be envisaged.

National legislation should ensure that penalties can be enforced when persons or suppliers are found to be in violation of legislation.

An alert system should be established by the competent authority to prevent trade in non-conforming materials that could put patients at risk. WHO should be informed of such instances so that this information can be made available to other national or regional authorities for action as necessary.

Ultimate goal

Close collaboration of all partners throughout the distribution and trade chain should be established and maintained to protect patients' health.

Introduction

Further to the discussion during the Thirty-sixth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1999, which was triggered by the reported incidents of contamination with diethylene glycol, several activities to control and ensure safe trade of starting materials for pharmaceutical products have been

identified. The Expert Committee was informed of the recommendations of a consultation on "Starting materials for pharmaceutical products: control and safe trade", held in Geneva in May 1998, as well as of the report from this consultation which is available in Arabic, Chinese, English, French, Spanish and Russian. The report is also available on the Internet at http://www.who.int/medicines/docs/startmats.html.

The Committee also noted that the World Health Assembly had adopted the proposed resolution on the Revised Drug Strategy (WHA52.19) in May 1999, and was informed of a press release dated 22 May 1999 regarding the above-mentioned World Health Assembly resolution. The resolution requested WHO to prepare a new scheme for the certification of starting materials moving in international commerce. It was agreed at the thirty-eighth meeting of the Expert Committee that an increased awareness of existing guidelines should be promoted. The Committee noted that several recommendations had been made in the report of the consultation of May 1998 for action by governments, manufacturers, traders and brokers as well as by WHO. The Organization would need to collaborate with all the parties involved. It was suggested that the above-mentioned recommendations should be consolidated and priorities assigned, and the resulting document distributed widely to relevant associations and representative bodies.

On the basis of the above considerations, a new WHO Scheme for the Certification of Pharmaceutical Starting Materials Moving in International Commerce is being proposed. The document outlining the new scheme was drafted at an informal consultation before being circulated for comments and rediscussed during a consultation held in August 2001. Further rounds of consultation took place in 2002, including a meeting held in July of that year. The text was revised in accordance with the comments received.

There is currently insufficient legislative control over the manufacture and distribution of pharmaceutical starting materials in many WHO Member States. It is, however, recognized that in some Member States, efforts have been made to ensure implementation and monitoring of good manufacturing practices for starting materials. Alternative quality systems (e.g. International Standards Organization (ISO)) have been adopted by some manufacturers. These developments have formed the basis of the newly suggested certification scheme for pharmaceutical starting materials.

The proposed scheme is based on the "WHO certification scheme on the quality of pharmaceutical products moving in international

commerce". It should be noted, however, that the concept of this proposed scheme and its application differ in certain aspects from the scheme for pharmaceutical products, namely, in the provision made for alternative quality assurance systems and self-assessment by the manufacturers of pharmaceutical starting materials. The latter may also be linked to an inspection by a national authority other than the one in the country of manufacture.

It is further suggested to consider the use of the "Model certificate of analysis for active pharmaceutical ingredients, excipients and medicinal products (COA)" that would serve in the trade of starting materials and for manufacturers of pharmaceutical substances, excipients and medicinal products, as recommended by resolution WHA52.19 (Annex 2 of reference (*1*)) together with the "Considerations for requesting analysis of drug samples" (Annex 3 of reference (*1*)) to complement this scheme.

The newly proposed scheme consists of:

1. A Model Certificate for Manufacture of Pharmaceutical Starting Materials issued by the competent national authority,

or, alternatively:

2. A Model Certificate for Manufacture of Pharmaceutical Starting Materials issued by the manufacturer.

Scope

The scheme described in this document is intended for pharmaceutical starting materials, obtained through chemical synthesis. Blood and blood derivatives are beyond the scope of this scheme.

It is envisaged to evaluate this scheme describing a new global mechanism for its applicability and use after a certain length of time.

Contents

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1. Provisions and objectives

1.1 A comprehensive system of quality assurance should normally be founded on a reliable system of licensing and analysis of starting materials, as well as upon assurance, obtained through independent inspection, that all manufacturing operations are carried out in conformity with accepted norms referred to as good manufacturing practices (GMP). Production and quality control should be independent of one another.

1.2 The World Health Assembly endorsed the requirements for good practices in the manufacture and quality control of drugs (*2*) (referred to henceforth as "GMP as recommended by WHO"). The GMP text includes good manufacturing practices for pharmaceutical starting materials (active pharmaceutical ingredients and pharmaceutical excipients).

1.3 The Scheme is an administrative instrument that can be used by:

1.3.1 A Member State to attest that:

— a specific starting material is used in a pharmaceutical product authorized to be placed on the market within its jurisdiction or within another national jurisdiction; and
— the manufacturing site in which a specific starting material is produced is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP as recommended by WHO.

1.3.2 The Scheme can also be used by the manufacturer to attest compliance with a quality assurance system (subject to conditions for issuing a certificate as described in section 5 below).

1.4 The Scheme makes provision for a statement to indicate that the manufacturing site(s) in which the pharmaceutical starting material is produced has (have) implemented a suitable quality system.

2. Participating Member States

2.1 Any Member State intending to participate in the Scheme may do so by notifying the Director-General of WHO in writing, of:

— its willingness to participate in the scheme;
— any significant reservations it intends to observe relating to this participation (i.e. whether it intends to participate actively in the Scheme or to use it as a tool); and
— the name and address of its national regulatory authority or other competent authority.

Documentation on the national system should be provided, depending on the type of participation.

2.2 A Member State may opt to participate solely to control the importation of pharmaceutical starting materials. This intention should be stated explicitly in its notification to the World Health Organization.

2.3 A Member State intending to participate in the Scheme through issuing certificates should first satisfy itself that it can meet the following criteria.

- An effective national system is in place to identify the responsible manufacturers and distributors.
- It can perform inspections according to GMP requirements, consonant with those recommended by WHO, to which all manufacturers of pharmaceutical starting materials are required to conform.
- It is capable of establishing effective controls to monitor the quality of pharmaceutical starting materials manufactured within its country, and has access to an independent quality control laboratory.
- It has a national pharmaceuticals inspectorate, operating as an arm of the national drug regulatory authority, and having the technical competence, experience and resources to assess whether GMP and other controls are being effectively implemented, and has the legal power to conduct appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples.
- It has the necessary administrative capacity to issue the required certificates, to institute enquiries in case of complaint, and to notify expeditiously both WHO and the competent authority in any Member State known to have imported a specific starting material that is subsequently associated with a potentially serious quality defect or other hazard.

2.4 Each Member State assumes the responsibility to determine, through a process of self-evaluation, whether it satisfies these prerequisites. The Scheme contains no provision for external inspection or assessment, either of a competent national authority or of a manu-

facturing facility. However, should a Member State so wish, it may approach WHO, or another drug regulatory authority, to occasionally delegate consultants to act as advisers in the course of national inspections and training activities for inspectors.

3. Requesting a certificate

3.1 A Certificate for Pharmaceutical Starting Materials can be requested within the scope of the Scheme by the exporter, importer or the competent authority of the importing country.

4. Certificates issued by competent regulatory authorities

4.1 The proposed formats for these documents are provided in Appendices 1 and 2 of these guidelines. For ease of use, these documents are presented in forms suitable for generation by a computer. All participating countries are henceforth urged to adopt these formats to facilitate the interpretation of certified information. The explanatory notes that accompany the two documents referred to above are very important. Although they are not part of the document to be certified, they should always be attached to the certificate.

4.2 The certificate should be issued by the competent authority in the format proposed in Appendix 1.

The following information should be listed as a minimum: for details see explanatory notes (Appendix 1).

4.2.1 Number of certificate given by the issuing authority.

4.2.2 Exporting (certifying) country.

4.2.3 Importing (requesting) country/countries.

4.2.4 Name of pharmaceutical starting material (International Nonproprietary Names (INNs) should be used whenever possible; alternatively, national nonproprietary names and/or grades, trademarks and other identifiers, such as official codes, CAS numbers etc. may be used).

4.2.5 Complete reference to, and compliance with, pharmacopoeial monograph(s), where applicable and/or attached specifications.

4.2.6 Information on whether the pharmaceutical starting material subject to this certificate is used in pharmaceutical products registered for marketing in the exporting country.

4.2.7 Indicate category of product, if applicable.

4.2.8. Marketing authorization, licence, Drug Master File or other reference(s), such as a certificate of suitability of pharmacopoeial monographs with which the starting material complies, as applicable.

4.2.9 Name and address of applicant for certificate.

4.2.10 Activities of the applicant (e.g. manufacturing, repacking or relabelling) and, if the applicant is not the original manufacturer, provide the name and address of the original manufacturer.

4.2.11 Compliance of facilities and operations with WHO GMP, if applicable.

4.2.12 Date of last inspection, if applicable.

4.2.13 Information regarding the certifying authority.

4.2.14 Stamp and date.

4.3 The certificate is a confidential document. As such, it can be issued by the competent authority in the exporting country ("the certifying authority") only with the permission of the applicant.

4.4 Once prepared, the certificate is transmitted to the requesting authority through the applicant and, when applicable, the agent in the importing country.

4.5 When any doubt arises about the status or validity of a certificate, the competent authority in the importing country should request a copy directly from the certifying authority, as provided for in section 4.2.13 of these guidelines.

4.6 In the absence of any specific agreement to the contrary, each certificate will be prepared exclusively in the working language(s) of the certifying authority. The applicant will be responsible for providing any notarized translation that may be required by the requesting authority.

4.7 Since the preparation of certificates imposes a significant administrative load on the certifying authorities, the service may need to be financed by charges levied upon applicants.

4.8 The certificate remains valid until the specified date.

4.9 The certificate becomes invalid if the manufacturing process certified is changed or if the manufacturer is no longer considered to be in compliance with GMP.

4.10 The certifying authority is responsible for assuring the authenticity of the certified data. Certificates should not bear the WHO emblem, but a statement should always be included to indicate

whether or not the document has been issued in the format recommended by WHO.

4.11 When the applicant is the manufacturer of the pharmaceutical starting material, the certifying authority should satisfy itself, before attesting compliance with GMP, that the applicant:

(a) applies identical GMP standards to the pharmaceutical starting materials of all batches manufactured within the facility, including those destined exclusively for export; and
(b) consents, in the event of identification of a quality defect consonant with the criteria set out, to relevant inspection reports being released, in confidence, to the competent authority in the country of import, should the latter so require.

4.12 When the applicant is not the manufacturer of the pharmaceutical starting material, the certifying authority should similarly satisfy itself in so far as it has the authority to inspect the records and relevant activities of the applicant, that it has the applicant's consent to release relevant reports on the same basis as described in section 4.11 (b) above.

4.13 Whenever a starting material is purchased through a broker or another intermediary, or when more than one set of premises has been used for the manufacture and packaging of a starting material, the certifying authority should consider whether it has received sufficient information to satisfy itself that those aspects of the manufacture of the starting material for which the applicant is not directly responsible have been undertaken in compliance with GMP and good trading and distribution practices (GTDP)[a] as recommended by WHO.

4.14 Each certificate should identify the importing country and be stamped on every page with the official seal of the certifying authority to avert potential abuse of the Scheme, to frustrate attempts at falsification, to render routine authentication of certificates by an independent authority superfluous and to enable the certifying authority to maintain comprehensive records of countries to which specific starting materials have been exported. If requested, an identical copy, clearly marked as "duplicate", should be forwarded on demand by the certifying authority directly to the requesting authority in the importing country.

[a] WHO Good Trading and Distribution Practices (GTDP), see guidance text in WHO Technical Report No. 917, Annex 2.

5. Certificates issued by manufacturers

5.1 A manufacturer may issue a certificate, for instance when there is no national authority in the exporting country that could issue a certificate and/or no legal framework, and provided that there is an independent certifying body or competent authority to assess the compliance with the quality assurance system.

5.2 The certificate of the manufacturer should be accompanied by a copy of the certificate or document issued by the independent certifying body or competent authority.

5.3 The format of the certificate should be as in Appendix 2.

The following information should be listed.

5.3.1 Number of certificate given by the manufacturer.

5.3.2 Exporting country.

5.3.3 Importing (requesting) country/countries.

5.3.4 Name of pharmaceutical starting material (use International Nonproprietary Names (INNs) whenever possible; alternatively national nonproprietary names and/or grades, trademarks and other identifiers, such as official codes, CAS numbers, etc. may be used).

5.3.5 Complete reference to, and compliance with, pharmacopoeial monograph(s), where applicable and/or attached specifications.

5.3.6 Whether the pharmaceutical starting material is used for pharmaceutical purposes in the exporting country.

5.3.7. Whether the pharmaceutical starting material subject to this certificate is used in pharmaceutical products registered for marketing in the exporting country.

5.3.8 Type of product, if applicable.

5.3.9 Name and address of manufacturer (issuer of certificate), including e-mail address, telephone number and fax number.

5.3.10 (a) Activities of issuer of certificate, e.g. manufacturing or repacking, etc., and, if the issuer of the certificate is not the manufacturer, provide
(b) the name and address of the original manufacturer/manufacturing site(s).

5.3.11 Indication of the main categories of materials produced at the manufacturing site.

5.3.12 Additional regulatory information, such as reference to licence, Drug Master File or other reference as applicable.

5.3.13 The certificate is based on the information obtained from:

5.3.13.1 Inspection by competent authority:

— name of competent authority, including e-mail address, telephone number, fax number and name and function of contact person;
— date of inspection;
— quality assurance system inspected;
— standard used for inspection;
— result of inspection; and
— certificate and supplementary documents to be attached, if available.

5.3.13.2 Audit by an independent certifying body:

— name of independent certifying body, including e-mail, telephone number, fax number and name and function of contact person;
— date of audit;
— quality assurance system audited;
— standard used for audit;
— result of audit; and
— certificate and supplementary documents to be attached, if available.

5.3.14 Name and function of responsible person issuing the statement on behalf of the manufacturer.

5.3.15 Date of issue.

5.3.16 Stamp and signature.

The period of validity of the certificate is suggested to be 2 years.

6. Notifying and investigating a quality defect

6.1 Recognizing that the notification of a defect is an important aspect of the quality assurance of starting materials, the manufacturer should have a system in place to notify its customers and the regulatory authorities of defects that have a potential impact on the quality and safety of the starting material and to ensure that a thorough investigation is conducted. Specifically the manufacturer should notify the recipient(s) of the certificate, as well as the competent authority, of any serious quality defect related to the starting material that was exported in accordance with the provisions of the Scheme, by communicating the relevant facts, through the competent authorities in the importing countries.

6.2 The competent authority should follow up on the investigation undertaken by the manufacturer and take action as necessary.

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6.3 It is the responsibility of the Member State adhering to the Scheme to ensure that provisions for carrying out the tasks described in 6.1 and 6.2 above are in place.

6.4 In the case of obvious doubt, a participating national authority may request WHO to assist in providing a list of quality control laboratories to carry out tests for the purposes of quality control.

6.5 Each certifying authority undertakes to inform WHO and, as far as possible, all competent national authorities, of any serious hazard newly associated with a starting material exported under the provisions of the Scheme, or of any criminal abuse of the Scheme, in particular, the export of falsely labelled, spurious, counterfeited or substandard pharmaceutical starting materials. On receipt of such notification, WHO will immediately inform the competent national authority in each Member State.

6.6 WHO stands prepared to offer advice should any difficulty arise in implementing any aspect of the Scheme or in resolving a complaint, but it cannot be a party to any resulting litigation or arbitration.

References

1. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902).
2. Quality control of drugs. In: *Twenty-second World Health Assembly, Boston, Massachusetts, 8–25 July 1969. Part 1. Resolutions and decisions, annexes*. Geneva, World Health Organization, 1969 (Official Records of the World Health Organization, No. 176): 99–105.

Further reading

Certification scheme on the quality of pharmaceutical starting materials moving in international commerce. *In: Twenty-eighth World Health Assembly, Geneva, 13–30 May 1975. Part 1. Resolutions and decisions, annexes*. Geneva, World Health Organization, 1975 (Official Records of the World Health Organization, No. 226): 94–95.

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WHO certification scheme on the quality of pharmaceutical starting materials moving in international commerce. In: *Forty-first World Health Assembly, Geneva, 2–13 May 1988. Resolutions and decisions, annexes*. Geneva, World Health Organization, 1988 (Document WHA41/1988/REC/1): 53–55.

Revised drug strategy. In: *Fifty-second World Health Assembly, Geneva, 17–25 May 1999*. Geneva, World Health Organization, 1999 (Resolution WHA52.19).

Appendix 1

Model Certificate for Pharmaceutical Starting Materials issued by the competent national authority

(Letterhead of issuing authority)

Certificate of a Pharmaceutical Starting Material[1]

This certificate conforms to the format recommended by the World Health Organization (general instructions and explanatory notes attached).

1. Certificate number:

_____

2. Exporting (certifying) country:

_____

3. Importing (requesting) countries:

_____

4. Name of Pharmaceutical Starting Material:[2]

_____

5. Indicate complete reference and compliance with pharmacopoeial monograph(s), where applicable and/or attached specifications:

_____

6. Is the Pharmaceutical Starting Material subject to this certificate used in pharmaceutical products registered for marketing in the exporting country? yes / no / unknown *(key in as appropriate)*

7. If yes, which types of product?[3]

_____

8. Indicate marketing authorization, licence, Drug Master File or other reference as applicable:

_____

9. Applicant for certificate (name and address):

_____

10. Activities and site(s):

10.1 Activities of applicant: specify whether the manufacturer responsible for placing the Pharmaceutical Starting Material on the market:

(a) manufactures the Pharmaceutical Starting Material;
(b) repackages and/or relabels the Pharmaceutical Starting Material manufactured by an independent company, or;
(c) is involved in none of the above (e.g. distributes, trades);
(d) manufactures the Pharmaceutical Starting Material and further manufacturing sites may be involved.[4]

10.2 If answers b, c or d apply, provide name and address of the manufacturing site(s):

_____

11. Does the manufacturer comply with WHO GMP?[5]
yes / no / not applicable[6] *(for* "no" *and* "not applicable"*: please explain and specify)*:

_____

12. Date of last inspection, if applicable: _____

I herewith confirm that the data above are valid. Any changes that could affect the validity of this certificate shall be notified by the applicant. Under normal circumstances the certificate is valid for 2 years.

13. ***Information regarding the regulatory certifying authority***

Name and address of certifying competent authority: _____ _____ E-mail: _____ Telephone no.: _____ Fax no.: _____ Name and function of responsible person: _____ Signature of responsible person: _____

14. Stamp and date:

_____

Attachments:[7]

List of documents attached:

_____

_____

General instructions

Please refer to the guidelines for full instructions on how to complete this form and for information on the implementation of the Scheme. Only originals or certified copies will be accepted.

The forms are suitable for generation by computer. They should always be submitted as hard copy, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Certifying authorities shall indicate the total number of pages included in the certificate and shall number them, e.g. page *x* of *y*, and initial every page.

Explanatory notes

(1) This certificate, which is in the format recommended by WHO, establishes the status of the Pharmaceutical Starting Material and of the applicant for the certificate in the exporting country. It is for a single Pharmaceutical Starting Material only.

(2) Whenever available, use International Nonproprietary Names (INNs); alternatively, national nonproprietary names and/or grades, trademarks and other identifiers, such as official codes, CAS numbers etc. may be used.

(3) List the dosage forms and categories. Example given below.

Pharmaceutical Product(s)[a]	Category(ies)
Dosage form(s):	
Tablets	Cytotoxic
	Hormone
	Penicillin
Injectables	Cefalosporin

(4) Specify whether the manufacturer responsible for placing the Pharmaceutical Starting Material on the market:

(a) manufactures the Pharmaceutical Starting Material;
(b) repackages and/or relabels the Pharmaceutical Starting Material manufactured by an independent company, or;

[a] Pharmaceutical products: Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage for or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

(c) is involved in none of the above (e.g. distributes, trades);
(d) manufactures the pharmaceutical starting material and further manufacturing sites may be involved.

If the manufacturer is not the original manufacturer, the site should be given.

(5) The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Good manufacturing practices and inspection, Volume 2, Updated edition.* Geneva, World Health Organization, 2004.
(6) "Not applicable" means that no legal requirements may be in place or implemented for GMP inspection of the Pharmaceutical Starting Materials for which the certificate is issued.
(7) Including specifications referred to under point 5.

Appendix 2

Model Certificate for Manufacture of Pharmaceutical Starting Materials issued by the manufacturer[1]

(*Letterhead of the manufacturer*)

Certificate of a Pharmaceutical Starting Material[1]

This certificate conforms to the format recommended by the World Health Organization (general instructions and explanatory notes attached).

1. Certificate number:

_____

2. Exporting country:

_____

3. Importing country:

_____

4. Name of Pharmaceutical Starting Material:[2]

_____

5. Indicate complete reference and compliance with pharmacopoeial monograph(s) where applicable and/or attached specifications:

_____

6. Is this Pharmaceutical Starting Material used for pharmaceutical purposes in the exporting country? yes / no / unknown *(key in as appropriate)*

_____

7. Is the Pharmaceutical Starting Material subject to this certificate used in pharmaceutical products registered for marketing in the exporting country? yes / no / unknown *(key in as appropriate)*

8. If yes, which types of product:[3]

9. Name and address of manufacturer (issuer of certificate):

_____

E-mail: _____ Telephone no.: _____ Fax no.: _____

10. Activities and site(s):

10.1 Activities of issuer of the certificate[4]:

State whether the issuer:

(a) manufactures the Pharmaceutical Starting Material;
(b) repackages and/or relabels the Pharmaceutical Starting Material manufactured by an independent company, or;
(c) is involved in none of the above (e.g. distributes, trades);
(d) manufactures the Pharmaceutical Starting Material and further manufacturing sites may be involved.

10.2 If answers a, b, c or d apply, provide name and address of the manufacturing site(s):

_____

11. Main categories of materials produced on site:[5]

— Pharmaceutical starting materials: _____

— Active pharmaceutical ingredients: _____

— Excipients: _____

— Cosmetics: _____

— Foodstuffs: _____

— Agrochemicals: _____

— Others (please specify): _____

12. Indicate additional regulatory information, such as reference to licence, Drug Master File, or other reference as applicable:

_____

13. Information based on:

_____

13.1 Inspection by competent authority:
Country: _____

Name of competent authority: _____

E-mail: _____ Telephone no.: _____ Fax no.: _____

Name and function of contact person: _____

— date of inspection: _____

— quality assurance system inspected: _____

— standard used for inspection:[6] _____

— result of inspection: _____

— attach certificate or supporting document, if available.

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13.2 Audit by an independent certifying body:

_____

Name of independent certifying body: _____

E-mail: _____ Telephone no.: _____ Fax no.: _____

Name and function of contact person: _____

— date of audit: _____

— quality assurance system audited: _____

— standard used for audit: _____

— result of audit: _____

— attach certificate or supporting document, if available.

14. Name and function of responsible person:

_____

I herewith confirm that the data above are valid. Any changes that could affect the quality of the pharmaceutical starting material and that will change the data on the certificate will be communicated. Under normal circumstances the certificate is valid for 2 years.

15. Date: _____

16. Stamp and signature: _____

Attachments:[7]

List of documents attached:

_____

_____

General instructions

Please refer to the guidelines for full instructions on how to complete this form and for information on the implementation of the Scheme. Only originals or certified copies of this document will be accepted.

The forms are suitable for generation by computer. They should always be submitted as hard copy, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Certifying authorities shall indicate the total number of pages included in the certificate and shall number them, e.g. page *x* of *y*, and initial every page.

Explanatory notes

(1) This certificate, which is in the format recommended by WHO, establishes the status of the Pharmaceutical Starting Material and of the applicant for the certificate in the exporting country. It is for a single Pharmaceutical Starting Material only.

(2) Whenever available, use International Nonproprietary Names (INNs); alternatively, national nonproprietary names and/or grades, trademarks and other identifiers, such as official codes, CAS numbers etc. may be used.

(3) List the dosage forms and categories. Example given below.

Pharmaceutical Product(s)[a]	Category(ies)
Dosage form(s):	
Tablets	Cytotoxic
	Hormone
	Penicillin
Injectables	Cefalosporin

(4) Specify whether the manufacturer responsible for placing the Pharmaceutical Starting Material on the market:
  (a) manufactures the Pharmaceutical Starting Material;
  (b) repackages and/or relabels the Pharmaceutical Starting Material manufactured by an independent company, or;
  (c) is involved in none of the above (e.g. distributes, trades);
  (d) manufactures the pharmaceutical starting material and further manufacturing sites may be involved.

If the manufacturer is not the original manufacturer, the site should be given.

(5) The categories of materials produced on site will give information about the profile of the manufacturing site.

(6) The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in *Quality assurance of pharmaceuticals: a compendium*

[a] Pharmaceutical products: Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage for or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

of guidelines and related materials. Good manufacturing practices and inspection, Volume 2, Updated edition. Geneva, World Health Organization, 2004.

(7) Including specifications referred to under point 5.

Appendix 3
Glossary and key words

This glossary explains terms used in these Guidelines and/or refers to relevant sections. It is intended as supplementary information and not as a formal part of the Scheme. Note that the definitions given below apply to the terms as used in these Guidelines. They may have different meanings in other contexts.

Applicant
The party applying for a certificate for a pharmaceutical starting material.

Competent authority
The national regulatory authority in the Member State. The competent authority can issue or receive certificates.

Good manufacturing practices (GMP)
That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. (In: *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Good manufacturing practices and inspection. Volume 2, Updated edition*. Geneva, World Health Organization, 2004).

GTDP
Good Trade and Distribution Practices (Annex 2, WHO Technical Report Series, No. 917).

Manufacture
All operations of purchase of materials and starting materials, production, quality control, release, storage, shipment of finished starting materials, and the related controls.

Pharmaceutical starting material
Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials. This includes active pharmaceutical ingredients (APIs) and pharmaceutical excipients.

Starting material (see pharmaceutical starting material)

Certificate of a pharmaceutical starting material
A document containing the information (as set out in Appendix 1 of these Guidelines) that is validated and issued for a specific starting

material by the competent authority of the exporting country and intended for use by the competent authority in the importing country or in the absence of such an authority by, for example, the manufacturer of the finished product when exporting.

WHO responsibility (see item 6.6 of guidelines above)

WHO Technical Report Series, No. 917, 2003

Annex 4

Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies

1. Introduction

The World Health Organization (WHO) could provide United Nations agencies with advice on the acceptability, in principle, of quality control laboratories that are found to meet WHO recommended quality standards, for use by such agencies. This will be done through a standardized quality assessment procedure. The purpose of the quality assessment procedure is to evaluate whether quality control laboratories meet the requirements recommended by WHO for such

laboratories to be used for the analysis of pharmaceutical products purchased as part of the pre-qualification procedure for products including, but not limited to, those for the treatment of HIV/AIDS, tuberculosis (TB) and malaria. Participation in the pre-qualification procedure is voluntary and any laboratory (private or governmental) could participate. Certification such as ISO (in terms of ISO/IEC17025) is encouraged and will also be considered in the pre-qualification procedure. It is recommended that laboratories should work towards obtaining certification.

The quality assessment procedure established by WHO is based on the following principles:

— reliance on the information supplied by the national drug regulatory authority;
— a general understanding of the quality control activities of the laboratory;
— evaluation of information submitted by the laboratory; and
— assessment of consistency in quality control through compliance with good manufacturing practice(s) and WHO guidelines.

WHO should collaborate with national drug regulatory authorities in the quality assessment. WHO recommends that laboratories expressing their interest in testing drugs on behalf of United Nations agencies inform the regulatory authorities and other networks (e.g. OMCL) of their intention to be pre-qualified and request the regulatory authorities to collaborate with WHO in the quality assessment process.

This procedure provides advice and recommended standards on a process to be followed for pre-qualification of quality control laboratories by and/or for the United Nations. Many of the recommendations are also relevant to non-United Nations organizations.

2. Steps of the procedure

WHO requires information related to the activities and quality control of products in laboratories. Interested quality control laboratories should submit the required information as requested by WHO about their activities (see point 2.2). In addition to the evaluation of the information submitted, a site inspection(s) may be performed. WHO reserves the right to terminate the quality assessment procedure of a laboratory when the laboratory is not able, or fails to provide the required information within a specified time period, or when inadequate information is supplied to complete the quality assessment effectively.

2.1 Publication of Invitation for Expression of Interest

WHO will publish an invitation widely in the international press and on WHO's web pages, and when necessary repeat it at regular intervals, to request laboratories to submit an Expression of Interest (EOI) in testing pharmaceutical products on behalf of United Nations agencies. The invitation should be open and transparent, inviting all laboratories to submit the EOI for the tests listed in the invitation.

Laboratories should submit their EOI with the relevant information requested, before the date specified by WHO.

When WHO receives the EOI, it will record the receipt of the EOI from each laboratory in a register.

2.2 Submission of laboratory information file

Each interested laboratory should provide the specified focal point indicated in the EOI with a laboratory information file (LIF) containing the required information, before a date specified by WHO.

The information should be submitted as described in the document "Guidelines for preparing a laboratory information file (LIF)" (WHO Technical Report Series, No. 917, Annex 5) and contain information on the areas listed below:

— general information
— documentation
— personnel
— handling of samples
— materials
— premises
— equipment
— quality control
— contract operations and activities
— out-of-specification investigation
— self-inspection
— stability testing
— microbiological testing
— instrumental tests
— water system.

2.3 Screening of submitted laboratory information file

The LIF submitted by the laboratory will be screened for completeness prior to its assessment. Incomplete information will not be considered for evaluation. The laboratory will be informed that an incomplete LIF has been received, and be requested to complete the

LIF within a specified time period. In the event that this request is not complied with, the LIF will in principle be rejected on grounds of incompleteness and returned to the laboratory.

LIFs that comply with the format recommended by WHO will be (1) retained for evaluation purposes and (2) the laboratory will be considered for a possible site inspection (if this is warranted based on the outcome of the evaluation of the LIF).

2.4 Assessment of the laboratory information file

The LIF will be evaluated by WHO in accordance with a standard operating procedure established by WHO for assessing LIFs to ensure uniformity in evaluation.

2.5 Site inspection

Dependent on the outcome of the evaluation of the LIF, WHO will plan and coordinate inspections at the laboratory to assess compliance with "Good practices for control laboratories" as recommended by WHO.[1] The inspection will be performed by an inspector or a team of inspectors consisting of experts appointed by WHO, preferably from regulatory authority inspectorates. A WHO staff member will coordinate the team and the team members will act as temporary expert advisers to WHO. The inspector or team will perform the inspections and report on the findings in accordance with a standard operating procedure describing the planning and performance of site inspections to ensure a standard harmonized approach.

A representative or representatives of the drug regulatory authority of the country where the laboratory is located would normally be expected to accompany the team to the laboratory to assess compliance with good practices standards.

Evaluators and inspectors must have the relevant qualifications and experience.

2.6 Report and outcome of evaluation

The inspector or inspection team will finalize a report according to the established WHO format describing the findings. These will be communicated to the laboratory.

[1] Good practices for national pharmaceutical control laboratories. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902).

If any additional information is required, or if corrective action has to be taken by the laboratory, WHO will postpone its final recommendations until the additional information has been evaluated, or the corrective action has been taken and found satisfactory in light of the specified standards.

In the event of any disagreement between a laboratory and WHO, a standard operating procedure for the handling of appeals and complaints will be followed to discuss and resolve the issue.

As WHO is responsible for the quality assessment, the ownership of the reports lies with WHO (without prejudice, however, to any confidential and proprietary information of the laboratory contained in this report).

2.7 Results of assessment

Once WHO is satisfied that the quality assessment process for the laboratory is complete, and that the laboratory is acceptable in principle for use by United Nations Agencies (i.e. it has been found to meet the WHO recommended standards), the laboratory at the specified site will be included in a list referred to as "List of quality control laboratories meeting WHO norms and standards".

Laboratories on the List will be considered to be able to test products in compliance with WHO recommended good practices standards.

Each laboratory will receive a letter from WHO informing it of the outcome of the quality assessment process for that particular laboratory. A copy of this letter will be sent to the national drug regulatory authority of the country where the laboratory is located.

The List will be compiled in accordance with a standard operating procedure and the List will be subjected to review at least once a year. The List will be published and will also be included on the WHO web page.

There should be an agreement between the organization (contract giver) and the pre-qualified laboratory (contract acceptor) indicating the responsibilities of both parties.

Laboratories should ensure that the testing of products would not be in breach of their national legislation including patent restrictions.

Laboratories should declare any possible conflict of interest in testing product samples prior to agreeing to perform work on behalf of the contract giver.

2.8 Re-qualification

Routine re-qualification

- Re-inspections of laboratories should be made at regular intervals at least once every 3 years.
- Re-evaluation of LIFs should be done every 3 years, or sooner should any change be implemented by the laboratory.

Non-routine re-qualification

Non-routine re-qualification may be done in the following situations:

— in case of any omission of information in the initial assessment, or if false or misleading information is suspected during the follow-up assessment;
— if changes are implemented that may have an impact on the pre-qualification of the laboratory, such as changes to key personnel, equipment or testing apparatus, testing method, facility or other aspects;
— if a complaint considered to be serious in nature has been received by WHO or one or more of the United Nations agencies or organizations;
— WHO may suspend or withdraw a pre-qualified quality control laboratory from the List when there is evidence of non-compliance with the predetermined general notes and conditions or with the good practices for national pharmaceutical control laboratories.

2.9 Proficiency testing

The laboratory should provide evidence of participation in appropriate proficiency testing schemes.

2.10 Monitoring of complaint(s)

Complaint(s) concerning the results of analysis of pharmaceutical product(s) or batches of product(s) supplied by the laboratory or concerning a service provided by the laboratory, that are communicated to WHO, will be investigated in accordance with a standard operating procedure.

After conducting its investigation, WHO will provide a written report of the problem and include recommendations for action where relevant in accordance with a standard operating procedure.

A copy of the report should be sent to the manufacturer of the product and to the drug regulatory authority of the country where the

manufacturing site is located. The drug regulatory authority could also be invited to participate in the investigation of the complaint.

WHO will make a copy of the report available to the laboratory under assessment.

2.11 Cost recovery

WHO reserves the right to charge for the quality assessment procedure on a cost recovery basis.

2.12 Confidentiality undertaking

The inspectors will treat all information to which they gain access during the inspections, or otherwise in connection with the discharge of their responsibilities in regard to the above-mentioned project, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below and those contained in the attached Provisions for inspectors (team members participating in site visits) within the scope of the quality assessment procedure of laboratories (see Appendix).

Inspectors will take all reasonable measures to ensure:

— that confidential information is not used for any purpose other than the inspection activities described in this document; and
— that confidential information is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

— was known to them prior to any disclosure by or on behalf of WHO (including by laboratories); or
— was in the public domain at the time of disclosure by or on behalf of WHO (including by laboratories); or
— has become part of the public domain through no fault of theirs; or
— has become available to them from a third party not in breach of any legal obligations of confidentiality.

2.13 Conflict of interest

Before undertaking the work, each inspector will (in addition to the above-mentioned confidentiality undertaking) be required to sign a Declaration of Interest in accordance with the terms set forth below and those contained in the attached Provisions for inspectors (see Appendix). If based on this Declaration of Interest, it is felt that there

is no risk of a real or perceived conflict of interest and it is thus deemed appropriate for the inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each inspector is required to confirm that the information disclosed by him/her in the Declaration of Interest is correct and that no situation of real, potential or apparent conflict of interest is known to him/her, including that he/she has no financial or other interest in, and/or relationship with a party, which:

— may have vested commercial interest in obtaining access to any confidential information disclosed to him/her in the course of the inspection activities described in this document; and/or
— may have a vested interest in the outcome of the inspection.

Each inspector will undertake to promptly advise WHO of any change in the above circumstances, including if an issue arises during the course of his/her work for WHO.

All inspectors furthermore agree, that at the laboratory's request, WHO will advise the laboratory in advance of the identity of each inspector and the composition of the team performing the site inspection, and provide curricula vitae of the inspectors. The laboratory then has the opportunity to express possible concerns regarding any of the inspectors to WHO prior to the visit. If such concerns cannot be resolved in consultation with WHO, the laboratory may object to a team member's participation in the site visit. Such an objection must be made known to WHO by the laboratory within ten days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel its agreement with the inspector, and the activities to be undertaken by that inspector, in whole or in part.

Appendix

Provisions for inspectors (team members participating in site visits) within the scope of the quality assessment procedure of quality control laboratories

In the course of discharging your functions as an expert adviser to WHO under the attached Agreement for the Performance of Work (APW), you will gain access to certain information, which is proprietary to WHO or entities collaborating with WHO, including the laboratories which need to be assessed as part of the quality assessment procedure by WHO. You undertake to treat such information (hereinafter referred to as "the Information") as confidential and proprietary to WHO or the aforesaid parties collaborating with WHO. In this connection, you agree:

— *not to use the Information for any other purpose than discharging your obligations under the above-mentioned APW; and*
— *not to disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.*

However, you will not be bound by any obligations of confidentiality and non-use to the extent that you are clearly able to demonstrate that any part of the Information:

(i) was known to you prior to any disclosure by or on behalf of WHO (including by the laboratory(s)); or
(ii) was in the public domain at the time of disclosure by or on behalf of WHO (including the laboratory(s)); or
(iii) becomes part of the public domain through no fault of your own; or
(iv) becomes available to you from a third party not in breach of any legal obligations of confidentiality.

You also undertake not to communicate your deliberations and findings and/or those of the team(s) of experts in which you will participate, as well as any resulting recommendations to, and/or decisions of, WHO to any third party, except as explicitly agreed by WHO.

You will discharge your responsibilities under the above-mentioned APW exclusively in your capacity as an expert adviser to WHO. In this connection, you confirm that the information disclosed by you in the Declaration of Interest is correct and that no situation of real, potential or apparent conflict of interest is known to you, including that you have

no financial or other interest in, and/or other relationship with, a party, which:

(i) may have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or
(ii) may have a vested interest in the outcome of the evaluation of the laboratory.

You undertake to promptly advise WHO of any change in the above circumstances, including if an issue arises during the course of your work for WHO.

I hereby accept and agree with the conditions and provisions contained in this document.

Signed _____

Name (typewritten) _____

Institute _____

Place _____ Date _____

WHO Technical Report Series, No. 917, 2003

Annex 5
Guidelines for preparing a laboratory information file

A laboratory information file (LIF) is a document prepared by the laboratory. It contains specific and factual information about the operations carried out at the named site and any closely integrated operations of the laboratory. If only some of the operations are carried out on the site, the LIF need describe only those operations, e.g. sampling, chemical analysis or stability testing. The LIF does not include information specific to environmental management, occupational health and safety management, financial management or risk management.

A LIF should be succinct and, if possible, should not exceed 25 A4 pages.

The laboratory should give a short description of its activities under each of the following headings. Where appropriate, supportive documentation should be appended.

1. General information

1.1 Brief information on the laboratory (including name, address and contact details).

1.2 Summary of laboratory activities (including those listed below).

Activity	Performed by laboratory itself (mark X)	Contracted to: (give name and address)
Conventional chemical analysis		
Instrumental analysis		
Microbiological analysis		
Biological testing		
Stability testing		

1.3 Any other activities carried out on site. In addition, state the relation (if any) to a manufacturing site.

1.4 Short description of the quality management system of the laboratory (including reference to the existence or not of a quality manual). (Include reference here regarding certification e.g. ISO 17025.)

2. Documentation and quality assurance systems

2.1 Brief description of the procedures for the preparation, revision and distribution of necessary documentation for specifications, standard test procedures, analyst workbooks or worksheets.

2.2 Brief description of any other documentation related to product testing, including reports, records, arrangements for the handling of results (including laboratory information management systems (LIMS) where used).

2.3 Procedures for release of certificates and analytical reports, standard operating procedures, etc.

2.4 Brief description of general policy for validation of analytical methods.

3. Personnel

3.1 Number of employees engaged in the following activities:

Activity	Number
Supervisors	
Analysts	
Technicians	
Microbiologists	
Other	
Total:	

3.2 Organization chart showing the arrangements, responsibilities and reporting lines in the laboratory.

3.3 Qualifications, experience and responsibilities of key personnel.

3.4 Outline of arrangements for basic and in-service training and how records are maintained.

4. Handling of samples

4.1 Brief description of general policy for sampling and handling of samples.

4.2 Brief description of the procedures followed. Where possible, flow sheets and charts describing important steps, pooling of samples, storage, work allocation in the laboratory and related aspects should be supplied.

5. Materials

5.1 Brief description of general policy for purchasing and handling of materials including chemicals and reagents, and handling of waste.

5.2 Brief description of the arrangements for the storage of materials including retention samples, toxic substances and poisons.

5.3 Brief description of the system for purchasing, preparation, handling and testing of reference materials.

6. Premises

6.1 Simple plan or description of the layout of the laboratory areas with an indication of scale (architectural or engineering drawings not required, but photographs may be submitted if available).

6.2 Nature of construction and finishes.

6.3 Brief description of ventilation systems including those for microbiological testing areas, storage areas, etc. (Include reference to air circulation and to control of temperature and relative humidity.)

6.4 Brief description of special areas for the handling of highly toxic, hazardous, and sensitizing materials.

6.5 Description of planned programmes for preventive maintenance of the premises and the system for recording maintenance activities.

Sanitation

6.6 Brief description of the procedures for cleaning of areas and equipment.

Storage

6.7 Types of products stored on the site, and information about any specifically toxic or hazardous substances handled.

6.8 Short description of the site (size, location, and immediate environment and other activities conducted on the site).

7. Equipment

7.1 Brief description of main equipment used in the laboratory. Attach a list of equipment in use, in table form, indicating the equipment and its make and model.

7.2 Brief description of planned programme for the preventive maintenance of equipment and the system for recording the maintenance activities.

7.3 Brief description of qualification (e.g. installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)) as well as calibration, including the recording system.

7.4 Brief description of computer system, access to data, data integrity management and validation of the computer system.

8. Contract operations and activities

8.1 List of activities contracted out to other laboratories, including names, addresses and contact details. Description of the way in which the compliance with standards for activities contracted out is assessed.

9. Out-of-specification investigation

9.1 Brief description of the procedure for recording and investigation of out-of-specification results.

10. Self-inspection

10.1 Brief description of the self-inspection procedure.

11. Stability testing (where applicable)

11.1 Brief description of the stability-testing procedure.

11.2 Brief description of the conditions under which samples are kept, the arrangements for monitoring and the equipment used.

12. Microbiological testing (where applicable)

12.1 Brief description of the activities for microbiological testing.

12.2 Brief description of preparation of media and types of media used.

12.3 Brief description of the procedure in place for positive and negative controls.

12.4 Brief description of validation policy.

12.5 Brief description of arrangements for waste disposal.

13. Water system

13.1 Brief description of the water system in the laboratory.

13.2 Brief description of arrangements for the sampling and testing of water used in the laboratory.

WHO Technical Report Series, No. 917, 2003

Annex 6
Procedure for assessing the acceptability, in principle, of procurement agencies for use by United Nations agencies

1. Introduction

The World Health Organization (WHO) could provide United Nations agencies with advice on the acceptability, in principle, of procurement agencies which are found to meet WHO recommended quality standards, for use by United Nations agencies. This will be done through a standardized quality assessment procedure.

The purpose of the quality assessment procedure is to evaluate whether the procurement agencies meet the requirements recom-

mended by WHO and operate in compliance with relevant principles for good pharmaceutical procurement.

The quality assessment procedure established by WHO is based on the following principles:

— reliance on the information supplied by the procurement agency;
— general understanding of the activities performed by the procurement agency;
— evaluation of information submitted by the procurement agency in a procurement agency information file (PAIF);
— assessment of consistency in pre-qualification, purchasing, storage and distribution through compliance with interim guidelines for the assessment of a procurement agency or a Model Quality Assurance System (MQAS)[1] as recommended by WHO.

WHO should collaborate with national authorities in the quality assessment. WHO will advise United Nations agencies of the procurement agencies that have been found acceptable in principle for use through a procedure of quality assessment based on WHO recommended guidelines and standards.

2. Steps of the procedure

WHO requires information related to the activities of the procurement agency to enable it to perform the assessment. Interested procurement agencies provide this information by submitting a procurement agency information file (PAIF) with the information requested about the procurement agency to WHO. In addition to the evaluation of the information submitted, a site inspection(s) may be performed. WHO reserves the right to terminate the quality assessment procedure of a procurement agency when the procurement agency is not able or fails to provide the required information within a specified time period, or when inadequate information is supplied to complete the quality assessment effectively.

In the context of this document, procurement is defined as the entire process of planning, design, determination of standards, writing of specifications, assessment (of products, manufacturers and suppliers), purchasing mechanism and selection of offers, financing, contract administration, storage, distribution, disposals and other related functions.

[1] *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report.* Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 917, Annex 8).

2.1 Publication of Invitation for Expression of Interest

WHO will publish an invitation widely in the international press and on its web pages at regular intervals, when necessary, to request procurement agencies to submit an Expression of Interest (EOI) to perform procurement activities on behalf of United Nations agencies. The invitation should be open and transparent, inviting any procurement agency to submit the EOI for the performance of the activities to be listed in the invitation.

Procurement agencies should submit their EOI with the relevant information requested before the date specified by WHO.

WHO will receive the EOI and record the receipt of the EOI from each procurement agency. Guidelines developed for the submission of the PAIF shall then be sent to the interested procurement agencies.

2.2 Submission of a procurement agency information file

Each interested procurement agency should provide the focal point indicated in the EOI with a PAIF containing the required information before a specified date set by WHO.

The information should be submitted as described in the document "Guidelines for preparing a Procurement Agency Information File (PAIF)"[2] and provide the information listed below:

— general information
— documentation
— personnel
— pre-qualification
— purchasing
— storage
— quality control
— contract operations and activities
— distribution
— complaints and recalls
— self inspection.

2.3 Screening of submitted procurement agency information file

Each PAIF submitted by the procurement agency will be screened for completeness prior to its evaluation.

[2] *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report.* Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 917).

PAIFs that are incomplete will not be considered for evaluation. The procurement agency will be informed that an incomplete file has been received, and be requested to complete the file within a specified time period. In the event that this is not complied with, the file will, in principle, be rejected on grounds of incompleteness and returned to the procurement agency.

PAIFs that comply with the requirements of WHO will be (1) retained for evaluation purposes and (2) the site will be considered for a possible inspection (if this is warranted based on the outcome of the evaluation of the PAIF).

2.4 Assessment of the procurement agency information file

The PAIF will be evaluated by WHO in accordance with a standard operating procedure for assessing PAIFs based on the WHO guidelines to ensure uniformity in evaluation.

2.5 Site inspection

Dependent on the outcome of the evaluation of the PAIF, WHO will plan and coordinate the performance of inspections at the sites to assess compliance with the "Interim guidelines for the assessment of a procurement agency" or a "Model quality assurance system" (MQAS)[3] as recommended by WHO. The inspection will be performed by an inspector or a team of inspectors consisting of experts appointed by WHO. A WHO staff member will coordinate the team and the team members will act as temporary expert advisers to WHO. The inspector or inspection team(s) will perform the inspections and report on the findings in accordance with standard operating procedures for planning and performing site inspections to ensure a standard harmonized approach.

Inspectors must have the relevant qualifications and experience.

2.6 Report and outcome of evaluation

The inspector or inspection team(s) will finalize a report according to the WHO format describing the findings of the inspection. These will be communicated to the procurement agency concerned.

If any additional information is required, or corrective action has to be taken by the procurement agency, WHO will postpone its final recommendations until such information has been evaluated, or the

[3] *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report.* Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 917).

corrective action has been taken and found satisfactory in light of the specified standards.

In the event of any disagreement between a procurement agency and WHO, a standard operating procedure for the handling of appeals and complaints will be followed to discuss and resolve the issue.

As WHO is responsible for the quality assessment, the ownership of the reports lies with WHO (without prejudice, however, to any confidential and proprietary information of the procurement agency contained in this report).

2.7 Results of assessment

Once WHO is satisfied that the quality assessment process for the procurement agency is complete, and that the agency is acceptable in principle for use to carry out procurement on behalf of a United Nations agency (i.e. it has been found to meet the WHO recommended standards), the agency will be included in the "List of procurement agencies meeting the WHO standards".

Procurement agencies on the list will be considered to be performing procurement activities in compliance with WHO's recommended Interim guidelines for the assessment of a procurement agency or a MQAS.

Each procurement agency will receive a letter from WHO informing it of the outcome of the quality assessment process in regard of the particular activity performed by that procurement agency.

The list will be compiled in accordance with a standard operating procedure for final decision-making for inclusion in the list. The list should be reviewed and updated at least once a year. The list will be published and will be included on the WHO web page.

2.8 Re-qualification

Routine re-qualification

- Re-inspections of procurement agencies will be made at regular intervals at least once every 3 years.
- Re-evaluation of PAIFs will be done every 3 years.

Non-routine re-qualification

Re-qualification may also be done in the following situations:

— in case of changes that may have an impact on the pre-qualification, purchasing, storage and distribution of products, including changes to key personnel or to the procurement agency site;

— in case of any omission of information in the initial assessment, or if false or misleading information is suspected during the follow-up assessment;
— if any batch or batches of supplied product(s) are considered by WHO or one or more of the UN agencies or organizations, not to be in compliance with the agreed specification of the product (as accepted in the dossier as part of the pre-qualification procedure for products and manufacturers); or
— receipt of a complaint considered to be serious in nature by WHO or one or more of the United Nations agencies or organizations.

Withdrawal and suspension

WHO may suspend or withdraw a pre-qualified procurement agency from the list when there is evidence of noncompliance with the pre-determined general notes and conditions or interim guidelines for the assessment of a procurement agency or a MQAS.

2.9 Testing of samples

Random samples of pharmaceutical product(s) supplied by procurement agencies may be taken for independent testing as appropriate.

In the event of failure to meet the established criteria for re-qualification and testing, WHO will investigate the problem and communicate this to the procurement agency.

2.10 Monitoring of complaint(s)

Complaint(s) concerning the service provided by the procurement agency, or a pharmaceutical product(s) or batch of product(s) supplied by the procurement agency, communicated to WHO, will be investigated in accordance with a standard operating procedure.

After investigation, WHO will provide a written report and include recommendations for action where relevant.

WHO will make a copy of the report available to the procurement agency.

2.11 Cost recovery

WHO reserves the right to charge for the quality assessment procedure on a cost recovery basis.

2.12 Confidentiality undertaking

The inspectors will treat all information to which they will gain access during the inspections, or otherwise in connection with the discharge

of their responsibilities in regard to the above-mentioned project, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below and those contained in the attached Provisions for inspectors (team members participating in site visits) within the scope of the quality assessment procedure of procurement agencies (see Appendix).

Inspectors will take all reasonable measures to ensure:

— that confidential information is not used for any purpose other than the inspection activities described in this document; and
— that it is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

— was known to them prior to any disclosure by or on behalf of WHO (including by procurement agencies); or
— was in the public domain at the time of disclosure by or on behalf of WHO (including by procurement agencies); or
— has become part of the public domain through no fault of theirs; or
— has become available to them from a third party not in breach of any legal obligations of confidentiality.

2.13 Conflict of interest

Before undertaking the work, each inspector will (in addition to the above-mentioned confidentiality undertaking) be required to sign a Declaration of Interest in accordance with the terms set forth below and those contained in the attached "Provisions for inspectors" (see Appendix). If based on this Declaration of Interest, it is felt that there is no risk of a real or perceived conflict of interest and it is thus deemed appropriate for the inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each inspector is required to confirm that the information disclosed by him/her in the Declaration of Interest is correct and that no situation of real, potential or apparent conflict of interest is known to him/her, including that he/she has no financial or other interest in, and/or relationship with a party, which:

— may have vested commercial interest in obtaining access to any confidential information disclosed to him/her in the course of the inspection activities described in this document; and/or
— may have a vested interest in the outcome of the inspection.

Each inspector will undertake to promptly advise WHO of any change in the above circumstances, including if an issue arises during the course of his/her work for WHO.

All inspectors furthermore agree, that at the procurement agency's request, WHO will advise the procurement agency in advance of the identity of each inspector and composition of the team performing the site inspection, and provide curricula vitae of the inspectors. The procurement agency then has the opportunity to express possible concerns regarding any of the inspectors to WHO prior to the visit. If such concerns cannot be resolved in consultation with WHO, the procurement agency may object to a team member's participation in the site visit. Such an objection must be made known to WHO by the procurement agency within ten days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel its agreement with the inspector, and the activities to be undertaken by that inspector, in whole or in part.

Appendix

Provisions for inspectors (team members participating in site visits) within the scope of the quality assessment procedure of procurement agencies

In the course of discharging your functions as an expert adviser to WHO under the attached Agreement for the Performance of Work (APW), you will gain access to certain information, which is proprietary to WHO or entities collaborating with WHO, including the procurement agencies which need to be assessed as part of the quality assessment procedure by WHO. You undertake to treat such information (hereinafter referred to as "the Information") as confidential and proprietary to WHO or the aforesaid parties collaborating with WHO. In this connection, you agree:

— *not to use the Information for any other purpose than discharging your obligations under the above-mentioned APW; and*
— *not to disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.*

However, you will not be bound by any obligations of confidentiality and non-use to the extent that you are clearly able to demonstrate that any part of the Information:

(i) was known to you prior to any disclosure by or on behalf of WHO (including by the procurement agency(s)); or
(ii) was in the public domain at the time of disclosure by or on behalf of WHO (including the procurement agency(s)); or
(iii) becomes part of the public domain through no fault of your own; or
(iv) becomes available to you from a third party not in breach of any legal obligations of confidentiality.

You also undertake not to communicate your deliberations and findings and/or those of the team(s) of experts in which you will participate, as well as any resulting recommendations to, and/or decisions of, WHO to any third party, except as explicitly agreed by WHO.

You will discharge your responsibilities under the above-mentioned APW exclusively in your capacity as an expert adviser to WHO. In this connection, you confirm that the information disclosed by you in the Declaration of Interest is correct and that no situation of real, potential or apparent conflict of interest is known to you, including that you have

no financial or other interest in, and/or other relationship with, a party, which:

(i) may have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or

(ii) may have a vested interest in the outcome of the evaluation of the procurement agencies.

You undertake to promptly advise WHO of any change in the above circumstances, including if an issue arises during the course of your work for WHO.

I hereby accept and agree with the conditions and provisions contained in this document.

Signed _____

Name (typewritten) _____

Institute _____

Place _____ Date _____

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Annex 7
Guidelines for the preparation of a procurement agency information file

Introduction

A procurement agency information file (PAIF) is a document prepared by the procurement agency (PA) that contains specific and factual information about the operations carried out at the named site including any closely integrated operations of the PA.

A PAIF should be succinct and, if possible, should not exceed 25 A4 pages.

The PA should give a short description of its activities under each of the following headings. Where appropriate, supportive documentation should be appended.

1. General information

1.1 Brief information on the PA (including name, address and contact details).

1.2 Activities of PA as licensed by the national authority (including those listed below). (Attach a copy of the licence. Where a licence is not available, please state reasons.)

Activity	Performed by agency itself (mark X)	Contracted to: (give name and address of contractor)
Pre-qualification of products and manufacturers		
Purchasing		
Storage		
Distribution		

1.3 Short description of the quality management system of the PA.

2. Documentation

2.1 Brief description of procedures for the preparation, revision and distribution of necessary documentation for pre-qualification, purchasing, quality control, storage and distribution.

2.2 Any other documentation related to product quality that is not mentioned elsewhere in this file.

2.3 Any other activities carried out on the site.

3. Personnel

3.1 Number of employees engaged in the following activities:

Activity	Number of employees
Pre-qualification	
Purchasing	
Quality control	
Storage	
Distribution	

3.2 Organization chart showing the arrangements for all departments (e.g. quality assurance, including pre-qualification, purchasing and quality control).

3.3 Qualifications, experience and responsibilities of key personnel.

3.4 Outline of arrangements for basic and in-service training and how records are maintained.

4. Pre-qualification

4.1 Brief description of general policy for pre-qualification of products manufactured by specific manufacturers.

4.2 Brief description of the pre-qualification procedure followed. Where possible, flow sheets and charts specifying important steps and standards for assessment of dossiers, suppliers and manufacturers, should be provided.

5. Purchasing

5.1 Brief description of general policy for purchasing.

5.2 Brief description of purchasing operations and procedures.

5.3 Description of tender system used.

6. Storage

6.1 Simple plan or description of storage areas, with indication of scale, including receiving, quarantine, returned goods, rejected goods, storage, staging and dispatch (architectural or engineering drawings not required).

6.2 Nature of construction and finishes.

6.3 Brief description of ventilation systems for storage areas with reference to control of temperature and relative humidity.

6.4 Brief description of special areas for the handling of highly toxic, hazardous and sensitizing materials.

6.5 Brief description of planned programmes for preventive maintenance of premises and of the system for recording these activities.

Equipment

6.6 Provide a list of equipment used in activities.

6.7 Brief description of computer systems used in all operations including quality control where relevant.

Sanitation

6.8 Brief description of procedures for cleaning.

6.9 Brief description of procedure for rodent and pest control.

7. Handling of materials

7.1 Types of products stored on the site and information about any specifically toxic or hazardous substances handled.

7.2 Brief description of the site (including access control, size, location, immediate environment and other activities carried out on the site).

7.3 Brief description of procedures for the handling of products (e.g. receiving, quarantine, storage, stock rotation and issue of products).

7.4 Brief description of procedure for release of products for storage after receipt and prior to distribution.

7.5 Brief description of procedure for the handling of rejected products.

7.6 Brief description of procedure for the handling of returned products.

8. Distribution

8.1 Brief description of procedure and recording system for distribution of products (including packing for dispatch, handling of hazardous materials, cold chain management etc., where relevant).

8.2 Brief description of procedure for release of products for dispatch.

8.3 Brief description of procedure to verify that the recipient is authorized to receive the product(s).

9. Complaints and product recall

9.1 Brief description of procedures for the handling of complaints and product recalls.

10. Contract operations and activities

10.1 Brief description of the way in which the compliance with standards for activities that are contracted out is assessed.

10.2 Brief description of the quality control system. (This could include, where relevant, the activities of a quality control laboratory, pre-shipment sampling and testing etc.)

11. Self-inspection

11.1 Brief description of the self-inspection system.

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Annex 8
Interim guidelines for the assessment of a procurement agency (based on the draft model quality assurance system for procurement agencies)

1. Introduction and background

WHO has established a procedure describing the process of pre-qualifiying procurement agencies (PAs). PAs interested in being pre-qualified for possible use by other organizations (including the United Nations) will have to submit information about their activities for assessment as part of a pre-qualification procedure. This information should be provided in a procurement agency information file (PAIF).

To further harmonize norms and standards in activities in PAs, WHO in collaboration with other United Nations procurement organizations, nongovernmental organizations and interested organizations, is in the process of preparing norms and standards for PAs. These will be reflected in a model quality assurance system (MQAS).

As the MQAS is not yet available in its final format, an "interim assessment Guideline" has been prepared that can be used until the MQAS document is available. The immediate objective of this interim assessment guideline is to provide an interim assessment tool for the pre-qualification of PAs. It recommends key (interim) requirements for quality assurance for PAs which could, in principle, be used, among others, by the Global Fund to Fight AIDS, TB and Malaria (GFATM) to pre-qualify such organizations. This document further reflects strategic objectives and operational principles for procurement and wholesale distribution that were developed and endorsed by the Interagency Pharmaceutical Coordination Group (IPC), which involved the pharmaceutical advisers of the United Nations Children's Fund (UNICEF), the United Nations Population Fund (UNFPA), WHO and the World Bank.

Two of the objectives of these Guidelines are to ensure that reliable suppliers of high-quality products are pre-selected, and that active quality assurance programmes involving both surveillance and testing, are implemented.

It is recommended that:

- Procurement procedures (including pre-qualification of products and manufacturers as well as purchasing procedures) should be transparent.
- Efficient procedures should be in place to pre-select potential suppliers and manufacturers, to manage procurement and delivery, to ensure good quality of the product and to monitor the performance of suppliers and manufacturers and of the procurement system.
- Written procedures (describing the use of explicit criteria to award contracts) should be used throughout the process.
- Pre-qualified and selected products, manufacturers and suppliers should be monitored through a process which takes into account product quality, service reliability, delivery time and financial viability.

For the purpose of this interim assessment Guideline, the activities associated with the PA may include inter alia:

— pre-qualification (product dossier assessment and manufacturing site inspections);
— purchasing;
— storage; and
— distribution.

A PA could perform all four of the above-mentioned activities, but in some cases, one or more of the four may be contracted out to another organization. In such a case, the PA is still responsible for all the activites associated with the procurement or wholesale distribution of the products.

This interim assesssment Guideline focuses on aspects of the active pharmaceutical ingredients and finished pharmaceutical products used in the treatment of HIV-related diseases, malaria and tuberculosis, as listed in the Invitations for Expression of Interest (EOIs) of the Pilot Procurement Quality and Sourcing Project (more information is available on the Internet at http://www.who.int/medicines/). However these principles are also applicable to other pharmaceutical products.

The checklist that follows can be used for guidance as well as an assessment tool during the interim pre-qualification period of PAs. Once the checklist is completed, it could serve as an assessment report.

An assessment report with the observations recorded should be communicated to the PA concerned.

The organization responsible for the interim assessment should decide whether an organization responsible for some of the activities (e.g. distribution by a distributor licensed by a national authority to perform this activity) should be inspected.

2. Interim assessment tool for pre-qualification of a procurement agency site

This report (based on the checklist) contains confidential information and shall not be divulged to any person other than those mentioned on this page, or without prior consent of the procurement agency. The report is the property of the organization responsible for performing the inspection.

Part 1: General information about the agency

Name of procurement agency:	
Physical address:	
Postal address:	
Telephone number:	
Fax number:	
E-mail address:	
24-hour contact number:	
Web page address:	
Summary of activities of the agency: (e.g. pre-qualification, purchasing, storage, distribution). List the names, addresses and contact details of organizations contracted to perform specific activities where relevant) Indicate type of products:	
Contact person:	
Person responsible for pre-qualification:	

Person responsible for purchasing:	
Person responsible for quality assurance:	
Person responsible for quality control:	
Person in charge of distribution/ shipping:	

Names of inspectors:	
Date of inspection:	
Project:	

Summary and conclusion

Summary:

(Provide a brief summary of the findings)

Conclusion:

(*Select appropriate option*)

Based on the findings of the inspection, and the observations listed in the inspection report, the procurement agency was found to be operating/not operating (*select option*) at an acceptable level of compliance with the WHO recommendations for quality assurance systems for procurement agencies.

Guideline and checklist: procurement agency

Organizational structure

Guidelines	*C*	*PC*	*NC*	*NA*
The agency should have an organizational chart indicating key persons in positions of responsibility.				
Persons in key positions should have written job descriptions.				
There should be a sufficient number of persons with suitable qualifications and experience responsible for pre-qualification.				
There should be a sufficient number of persons with suitable qualifications and experience responsible for purchasing.				

Organizational structure (continued)

Guidelines	*C*	*PC*	*NC*	*NA*
There should be a sufficient number of persons with suitable qualifications and experience responsible for storage.				
There should be a sufficient number of persons with suitable qualifications and experience responsible for distribution.				
The agency should be licensed by the national authority to perform the activities listed above (licence number: _____) (Attach).				
There should be a responsible person who is authorized to perform the activities listed above.				
Clarification of observations made:				

C, compliant; NA, not applicable; NC, noncompliant; PC, partially compliant

Quality assurance

Guidelines	*C*	*PC*	*NC*	*NA*
The agency should have a documented quality policy and quality systems should be defined in writing.				
All activities should be defined in clear, unambiguous written procedures.				
Records should be maintained for defined periods of time that ensure traceable actions.				
Written contracts should exist with other organizations (as applicable), for performing activities on behalf of the agency.				
Provisions should be made for confidentiality undertakings regarding confidential information submitted to the agency by manufacturers and suppliers.				
The agency should have a written procedure for self-inspections (self-audits). These should be performed at regular intervals.				

Guidelines	*C*	*PC*	*NC*	*NA*
The agency should have procedures for and records of the training provided to employees.				
Clarification of observations made:				

C, compliant; NA, not applicable; NC, noncompliant; PC, partially compliant

Pre-qualification

Guidelines	*C*	*PC*	*NC*	*NA*
The procurement agency should follow a written policy, standards and procedures describing the pre-qualification of products, suppliers and manufacturers.				
Product data and information should be requested from manufacturers and be assessed in accordance with the minimum data and information reflected in attachment A.				
Manufacturers should manufacture their products in compliance with WHO good manufacturing practices.				
Pre-qualification of manufacturers should include evaluation of evidence of compliance with WHO good manufacturing practices through assessment of: • valid manufacturing licence issued by the competent authority; and • certificate of a pharmaceutical product (WHO type) issued by the competent authority; and /or • on-site inspection when necessary.				
The pre-qualification of products should be linked to the manufacturing site for that particular product.				
Records of the assessment of products and manufacturers indicating the results and outcome of the assessment should be maintained.				
Clarification of observations made:				

C, compliant; NA, not applicable; NC, noncompliant; PC, partially compliant

Monitoring of product quality

Guidelines	*C*	*PC*	*NC*	*NA*
A person should be responsible for the review of the certificate of analysis and/or related documents supplied by the manufacturer for the batches of products.				
The review should be carried out in accordance with a written procedure.				
Records for this should be maintained.				
The agency should have a written procedure to ensure that random samples of shipments are taken for analysis. The results of the analysis should be reviewed by a responsible person.				
The agency should have access to a laboratory, either their own or one contracted to perform analysis of the samples taken.				
A written procedure should be in place to review "out-of-specification" results, including the investigation of these results and appropriate action to be taken.				
The agency should have written procedures for the detection, identification and handling of counterfeit products.				
There should be a procedure for handling product complaints.				
Clarification of observations made:				

C, compliant; NA, not applicable; NC, noncompliant; PC, partially compliant

Purchasing

Guidelines	*C*	*PC*	*NC*	*NA*
The agency should have written, transparent procedures for purchasing of pre-qualified products from pre-qualified manufacturers and suppliers.				
The person responsible for purchasing should be free from any possible conflict of interest.				
Limited invitations for competitive bidding from pre-qualified suppliers should be the preferred option.				

Guidelines	*C*	*PC*	*NC*	*NA*
Internationally accepted principles for purchasing should be followed. If tenders are used, these should be published with specifications for the products to be purchased.				
The adjudication should be transparent and fair. All decisions should be recorded and records kept.				
Procedures and agreements should be in place to ensure that the product purchased is the same as the product that had been pre-qualified.				
Clarification of observations made:				

C, compliant; NA, not applicable; NC, noncompliant; PC, partially compliant

Storage

(The following key points are a summary of the guidelines on Good Storage Practices referred to in the text under "Introduction and background".)

Guidelines	*C*	*PC*	*NC*	*NA*
Personnel				
There should be an adequate number of suitably qualified personnel to achieve pharmaceutical quality assurance objectives at each storage site. National regulations on qualifications should be followed.				
All personnel should receive proper training in relation to good storage practice, regulations, procedures and safety.				
All members of staff should be trained in, and observe high levels of, personal hygiene and sanitation.				
Personnel employed in storage areas should wear suitable protective or working garments appropriate for the activities they perform.				
Premises and facilities				
Precautions must be taken to prevent unauthorized persons from entering storage areas.				

Storage *(continued)*

Guidelines	*C*	*PC*	*NC*	*NA*
Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are specified on the label (e.g. for temperature and relative humidity), these should be provided, checked, monitored and recorded. Materials and 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.				
Storage areas should be clean and free from accumulated waste and from vermin. A written sanitation programme should be available indicating the frequency of cleaning, and the methods to be used to clean the premises and storage areas. There should also be a written programme for pest control. The pest-control agents should be safe, and there should be no risk of contamination of the materials and pharmaceutical products. There should be appropriate procedures for the cleaning up of any spillage to ensure complete removal of any risk of contamination.				
Physical or other equivalent validated (e.g. electronic) segregation should be provided for the storage of rejected, expired, recalled or returned materials or products. The materials or products, and storage areas concerned should be appropriately identified.				
Materials and pharmaceutical products should be stored in conditions which assure that their quality is maintained, and stock should be appropriately rotated. The "first expired/first out" principle should be followed.				
Narcotic drugs should be stored in compliance with international conventions, and national laws and regulations on narcotics.				

Guidelines	*C*	*PC*	*NC*	*NA*
Storage requirements				
Written instructions and records should be available which document all activities in the storage areas including the handling of expired stock. These should adequately describe the storage procedures and define the route of materials and pharmaceutical products and information through the organization in the event of a product recall being required.				
Comprehensive records should be maintained showing all receipts and issues of materials and pharmaceutical products according to a specified system, e.g. by batch number.				
All containers should be clearly labelled with at least the name of the material, the batch number, the expiry date or retest date, the specified storage conditions and reference to the pharmacopoeia, where applicable. Unauthorized abbreviations, names or codes should not be used.				
Returned goods				
Returned goods, including recalled goods, should be handled in accordance with approved procedures and records should be kept.				
Product recall				
There should be a procedure to recall from the market, promptly and effectively, pharmaceutical products and materials known or suspected to be defective.				
Clarification of observations made:				

C, compliant; NA, not applicable; NC, noncompliant; PC, partially compliant

Distribution

Guidelines	*C*	*PC*	*NC*	*NA*
Dispatch and transport				
Materials and pharmaceutical products should be transported in such a way that their integrity is not impaired and that suitable storage conditions are maintained.				
Records for dispatch should be retained, stating at least: • the date of dispatch • the customer's name and address • the product description, e.g. name, dosage form and strength (if appropriate), batch number and quantity				
The transport should be readily accessible and available on request.				
There should be a procedure to ensure that the products are supplied to authorized recipients only.				
Appropriate documentation should accompany the consignment to the recipient.				
Clarification of observations made:				

C, compliant; NA, not applicable; NC, noncompliant; PC, partially compliant

_____ _____

Inspector's signature: Date:

Name: _____

Appendix

Attachment A: interim assessment guideline for procurement agencies

Pharmaceutical product questionnaire

I. Product identification

Active pharmaceutical ingredient(s) (use INN where possible):

_____

Generic name of the product:

_____

Dosage form: ☐ Tablets ☐ Capsules ☐ Ampoules
☐ Vial ☐ Other

Strength per dosage unit:

_____

Route of administration: ☐ Oral ☐ Intramuscular ☐ Intravenous
☐ Subcutaneous ☐ Other

Pack size: ☐ 50 ☐ 100 ☐ 1000 ☐ 1000 ml ☐ Other

Description of primary packaging materials: _____

Description of secondary packaging materials: _____

II. Manufacturer of the product

Name, address and activities of the manufacturer(s) (or contract manufacturer(s))

Name	Physical address	Telephone number, facsimile number and e-mail contact details	Activity (e.g. packaging)

Are all sites listed above licensed by the relevant authority to perform the activity? ☐ Yes ☐ No

Is the manufacturing site for THIS product pre-qualified by the Procurement Agency? ☐ Yes ☐ No

Has the manufacturing method for each standard batch size been validated? ☐ Yes ☐ No

List the standard batch size: _____

III. **Supplier identification** *(to be filled in if information is not identical to that given in answer to question II)*

Name: _____

Address: _____

_____

Telephone number: _____

Facsimile number: _____

E-mail contact details: _____

Link with the product: ☐ Marketing licence holder ☐ Distributor ☐ Manufacturer ☐ Other: ___

IV. **Regulatory situation (licensing status) in the country of manufacture**

☐ Product registered and currently marketed licence no. _____

☐ Product registered for marketing in the country of manufacture but not currently marketed licence no. _____

☐ Product registered for export only licence no. _____

☐ Product not registered (please clarify) : _____

Please attach a Certificate of Pharmaceutical Product according to the WHO Certification Scheme (WHO Technical Report Series No. 863 (1996): an earlier version is not acceptable).

V. **Regulatory situation (licensing status) in other countries**

List the other countries where the product is registered and is currently marketed:

_____

_____

VI. Finished product specifications

☐ British Pharmacopoeia; edition _____

☐ US Pharmacopeia; edition _____

☐ International Pharmacopoeia; edition _____

☐ Other: _____

Please attach a copy of the finished product specification, if different from the British Pharmacopoeia, US Pharmacopeia or International Pharmacopoeia specification.

Limits expressed as percentages for the assay of active ingredient(s):

☐ 95–105% ☐ 90–110% ☐ Other: _____

Additional specifications to those in the pharmacopoeia (*e.g. dissolution, syringeability*):

_____

Attach a copy of the model certificate of analysis for batch release.

Are you willing to provide necessary information (analytical method) to enable the tests to be replicated by another quality control laboratory?

☐ Yes ☐ No

VII. Stability

Stability testing data available: ☐ Yes ☐ No

If yes, type and conditions of testing:

☐ accelerated testing

☐ 40 °C/ 75% relative humidity for 6 months

☐ other

In the same packaging as specified in point I (p. 1)

☐ Yes ☐ No

☐ real time testing

Temperature: ☐ ambient ☐ 25 °C ☐ 30 °C ☐ other

Relative humidity: ☐ not controlled ☐ 45% ☐ 65% ☐ other

Period of time: ☐ 1 year ☐ 2 years ☐ 3 years ☐ other

In the same packaging as specified in point I (p. 1)

☐ Yes ☐ No

Can a stability report be forwarded within one week of being requested?

☐ Yes ☐ No

Was the stability testing done on a product of the same formula, manufactured on the same site and packed in the same packaging material as that for the product that will be supplied?

☐ Yes ☐ No

VIII. Label and insert information

Shelf-life: ☐ 2 years ☐ 3 years ☐ 4 years ☐ 5 years
other: _____

Storage conditions *(e.g. "Do not store above 30°C — protect from light")*:

_____

_____

Language used on label: ☐ Bilingual English/French

☐ English ☐ French ☐ Other: _____

Package insert: ☐ Yes *(attach a copy)* ☐ No

IV. Samples

Can free non-returnable samples be obtained upon request within one week of being requested?

☐ Yes ☐ No

X. Therapeutic equivalence

☐ demonstrated

☐ by in vivo bioequivalence studies

Reference product: _____

Number of volunteers: _____

Country of study: _____

Year performed: _____

☐ by another method claimed to be suitable by the supplier/manufacturer (please describe briefly):

_____

☐ by in vitro dissolution tests

Reference product: _____

☐ not demonstrated

☐ not relevant

☐ unknown

Can a copy of the report be obtained upon request within one week of being requested?

☐ Yes ☐ No

Is the product used in the trial or test essentially the same as the one that will be supplied (i.e. same materials from the same suppliers, same formula, same manufacturing method)?

☐ Yes ☐ No

XI. Active pharmaceutical ingredient(s) (APIs)

(If more than one active ingredient is used, please supply answers to this question separately for each active ingredient used.)

Specifications and standard test methods exist for each API and excipient:

☐ Yes ☐ No

Each API used (give INN where this exists):

_____

☐ has a Certificate of suitability to the European Pharmacopoeia (CEP)
Certificate no.: _____

☐ The CEP is in our possession (including annex if any).

☐ The CEP is in the possession of the manufacturer of the finished product (including annex if any).

☐ has a Drug Master File (DMF)
registered in (country): _____

☐ The full or open part of the DMF is in our possession.

☐ The full or open part of the DMF is in the possession of the manufacturer of the finished product.

Quality standard:

☐ BP ☐ USP ☐ EP ☐ International Pharmacopoeia

☐ Other (e.g. "in-house"); specify: _____

☐ No pharmacopoeia monograph exists*

*If there is no monograph in a recognized pharmacopoeia, then the following information should be provided and evaluated:

Chemical structure

If relevant,

— state the isomeric nature of the active ingredient, including stereochemical configuration (e.g. acemate, pure (*S*)-isomer, 50/50 mixture of (*Z*)- and (*E*)-isomers);
— the solubility of the active ingredient in water at 25 °C or 35 °C;
— the solubility of the active ingredient in other solvents such as ether, ethanol, acetone and buffers, if different pH (if the active ingredient is acidic or basic);
— other relevant physicochemical characteristics of the active ingredient such as partition coefficient (usually octanol/water) and the existence of polymorphs;
— copies of infrared, nuclear magnetic resonance (proton and C_{13}), ultraviolet and mass spectra; and
— information on the chemical stability of the API, and on physicochemical stability if relevant (e.g. formation of a hydrate, change of polymorphic form).

Manufacturer (name, physical address and country):

_____

GMP certified: ☐ Yes *(attach a copy of the GMP certificate if any*)

Certified by: _____

☐ No

☐ Unknown

XIII. Commitment

I, the undersigned, _____, (*position in the company, e.g. General Manager, Authorized Person, Responsible Pharmacist*), acting as responsible person for the company _____ (*name of the company*), certify that the information provided (above) is correct and true

(if the product is marketed in the country of origin, tick the appropriate box below)

☐ and I certify that the product offered is identical in all aspects of manufacturing and quality to that marketed in _____

G

(*country of origin*), including formulation, method and site of manufacture, sources of active pharmaceutical ingredients and excipients, quality control of the product and starting material, packaging, shelf-life and product information

☐ and I certify that the product offered is identical to that marketed in _____ (*name of country*), except:

_____

_____

(*e.g. formulation, method and site of manufacture, sources of active pharmaceutical ingredients and excipients, quality control of the finished product and starting material, packaging, shelf-life, indications, product information*)

Date: _____ Signature: _____

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The international pharmacopoeia, third edition.
Volume 1: general methods of analysis. 1979 (223 pages)
Volume 2: quality specifications. 1981 (342 pages)
Volume 3: quality specifications. 1988 (407 pages)
Volume 4: tests, methods, and general requirements: quality specifications for pharmaceutical substances, excipients and dosage forms. 1994 (358 pages)
Volume 5: tests and general requirements for dosage forms. Quality specifications for pharmaceutical substances and dosage forms. 2003 (371 pages)

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. 2004 (236 pages)

Quality control methods for medicinal plant materials.
1998 (123 pages)

WHO Expert Committee on Specifications for Pharmaceutical Preparations.
Thirty-sixth report.
WHO Technical Report Series, No. 902, 2002 (215 pages)

International nonproprietary names (INN) for pharmaceutical substances. Cumulative list no. 10.
2002 (available in CD-ROM format only)

The use of essential drugs.
Ninth report of the WHO Expert Committee (including the revised Model List of Essential Drugs).
WHO Technical Report Series, No. 895, 2000 (66 pages)

WHO Expert Committee on Biological Standardization.
Fiftieth report.
WHO Technical Report Series, No. 904, 2002 (113 pages)

Further information on these and other WHO publications can be obtained from Marketing and Dissemination, World Health Organization, 1211 Geneva 27, Switzerland.

This report presents the recommendations of an international group of experts convened by the World Health Organization to consider matters concerning the quality assurance of pharmaceuticals and specifications for drug substances and dosage forms. Of particular relevance to drug regulatory authorities and pharmaceutical manufacturers, this report discusses the latest volume of *The International Pharmacopoeia* and quality specifications for pharmaceutical substances and dosage forms, as well as quality control of reference materials, good manufacturing practices (GMP), inspection, distribution and trade and other aspects of quality assurance of pharmaceuticals, and regulatory issues.

The report is complemented by a number of annexes, including recommendations on good trade and distribution practices for pharmaceutical starting materials, guidelines on the WHO scheme for the certification of pharmaceutical materials moving in international commerce, draft procedures for assessing quality control laboratories and procurement agencies for use by United Nations agencies, and guidelines for preparing a laboratory information file and a procurement agency information file.

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