

WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Forty-first Report



World Health
Organization

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Geneva, 16–20 October 2006

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1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 16 to 20 October 2006. Dr Howard Zucker, Assistant Director-General, opened the meeting and on behalf of the Acting Director-General of the World Health Organization, welcomed all the participants to the Forty-first session of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. He expressed his appreciation for the willingness of the participants to contribute their knowledge and expertise to the work of WHO in the area of quality assurance of medicines. Those present included members and representatives of the International Atomic Energy Agency (IAEA), the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the United Nations Children's Fund (UNICEF); the Secretariats of the Pharmacopoeias of Brazil, Europe, Republic of Korea, Russian Federation and the United States of America; the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA); the International Generic Pharmaceutical Alliance (IGPA) and World Self-Medication Industry (WSMI); the Pharmaceutical Inspection Co-operation Scheme (PIC/S), as well as representatives from WHO Collaborating Centres in the People's Republic of China, Germany, Singapore, South Africa, Sweden and Thailand. He also welcomed the Special Adviser (Medicines) to the Regional Director of the WHO Regional Office for the Eastern Mediterranean.

Dr Zucker said that the world was changing. Increasing trade, the trend towards new technologies and different lifestyles all have immediate implications for public health. New supply routes for medicines required new approaches to quality assurance in production and distribution worldwide. He said that it was of the utmost importance for WHO to maintain its normative role if it were to meet the needs and expectations of its 193 Member States, including provision of support in assuring quality of medicines and vaccines. Reports of counterfeit and substandard medicines were constantly increasing both in developing and in developed countries. As this was a complex global problem, global solutions involving all stakeholders were needed. Counterfeit drugs lead to a loss of confidence in the entire health system, they adversely affect manufacturers, pharmacists, doctors and private and government institutions alike. This was why every sector affected must be actively involved in the solution.

Dr Zucker stressed that a number of pharmaceutical companies producing medicines exclusively for export were not controlled by the national authorities in the country from which they were exported, or they used

legal loopholes to export to some countries with weak regulatory controls. This raised broader concerns about the current international system of regulation of pharmaceutical producers and how best to reform it.

Concerns included the use of inappropriate ingredients; inconsistent quality or variable concentrations; drug formulations that may not be stable; generic drugs that have not been tested for “bioequivalence”; and inadequate dosing and safety information. He said that recognition of the problem was increasing and that both the US Food and Drug Administration and the European Medicines Agency (EMA) have been paying increased attention to certifying the safety and efficacy of medicines made for the developing world.

Dr Zucker emphasized that donor countries should not only provide good-quality medicines but also contribute to local capacity-building. In addition, the advice and recommendations provided by this Expert Committee could help national and regional authorities (in particular drug regulatory authorities) and procurement agencies, as well as major international bodies and institutions, such as the Global Fund, and international organizations such as the United Nations Children’s Fund (UNICEF) – to combat problems of counterfeit and substandard drug regulatory authorities. The international guidelines, specifications and nomenclature developed under the aegis of the Expert Committee serve all Member States, international organizations, United Nations agencies and regional and interregional harmonization efforts, and underpin important initiatives, including the prequalification of medicines, the Roll Back Malaria Programme and Stop TB.

He expressed appreciation for the work done on the prequalification programme. Prequalification of medicines and laboratories could not function without the guidelines, standards and specifications adopted by this Committee after passage through the usual, rigorous consultative process. Another valuable aspect of the prequalification programme was that it enabled participating members of drug regulatory authorities to obtain “hands-on” experience in joint inspections and joint regulatory assessment activities with the participation of both developed and developing countries. This practical side is later taught in training workshops.

Members were invited to define and harmonize clear, independent and practical standards and guidelines for medicines, particularly in view of the increasingly international dimensions of trade and cross-border health issues. Standards in the area of quality assurance for medicines, developed by the Committee through an international consensus building process,

would not only serve WHO, including all its specific disease programmes, but also other international, regional and national agencies and initiatives dealing with medicines.

Dr Hans V. Hogerzeil, Director, Policy of Medicines and Standards, welcomed the Committee members and other participants including participants from all six WHO Regions, several international organizations, nongovernmental organizations, institutions and WHO collaborating centres from different regions. He thanked those who had made major contributions of technical expertise as well as practical laboratory studies.

He emphasized the importance of normative work carried out by this Expert Committee with its very technical and scientific remit. He thanked the members of the Committee, other organizations, clusters, institutions, bodies and authorities for their contributions and expressed appreciation for the work done in the Prequalification programme.

He also expressed concern that the quality of pharmaceuticals was still a worldwide problem. The export to poor countries with weak regulatory controls of medicines not meeting the safety standards of rich countries can do more harm than good to poor countries in the midst of an epidemic. He was, however, optimistic as there was an increase in the recognition of the problem. He stressed that quality could not be tested into a product and confirmed the need for a comprehensive set of legal texts and standards in the area of quality assurance, both to help prevent the occurrence of, and to detect counterfeit and substandard medicines.

He highlighted some of the major achievements of the Committee which included notification of the Fortieth report of the *WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 937)* by the Executive Board, the publication of the fourth edition of *The International Pharmacopoeia* (both in print and in electronic format), the second update of *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials, Volume 2, Updated edition. Good manufacturing practices and inspection*, and *Training modules for good manufacturing practice (GMP) inspections*.

He strongly encouraged the members of the Committee to guide WHO on future activities in quality assurance, including the use of risk analysis and new technologies, pharmacopoeia monographs, guidelines, prequalification and the International Nonproprietary Names (INN) Programme.

Dr Lembit Rägo, Coordinator, Quality Assurance and Safety: Medicines (QSM) welcomed everyone to the meeting. He was pleased that the work

of the Committee was being expedited as the meetings were now held annually. He noted that important points for discussion in the meeting included guidelines on variations. The concern was that many products entering new markets underwent variations over time, but that the variations were not always suitably managed.

He informed the Committee that WHO was approached frequently with requests to provide training. The updating of the WHO GMP training modules to reflect the current guidelines was, therefore, important.

Dr Sabine Kopp explained the administrative process of appointment of experts and the proceedings of the Expert Committee meeting.

2. General policy

2.1 Cross-cutting pharmaceuticals – quality assurance issues

2.1.1 Quality assurance

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

2.1.2 Herbal medicines

The Committee was informed that the Secretariat was in the process of preparing several technical guidelines related to:

- the quality control of herbal medicines including the development of WHO guidelines for selection of substances for quality control of herbal medicines;
- the development of WHO good processing practice for medicinal plant materials;
- the development of WHO guidelines for quality control of homeopathic medicines; and
- the development of WHO guidelines for evidence-based traditional medicine.

The Committee was pleased to note that new work was in progress in the area of International Regulatory Cooperation for Herbal Medicines (IRCH). This is a network set up to protect and promote public health and safety through improved regulation for herbal medicines. Its main tasks include sharing information on technical matters related to regulatory information

on herbal medicines. Electronic communication is the main tool, through an information focal point nominated by each Member Country of IRCH. Annual meetings of IRCH are also convened.

2.1.3 Malaria

The Committee was informed of the continued collaboration between the Quality Assurance and Safety: Medicines team and the Global Malaria programme to facilitate access to antimalarial products. Concern was expressed about the rapid increase in resistance to conventional treatment of malaria with monocomponent medicines.

The Committee was pleased to note that there was significant progress being made with screening tests as well as monographs for lumefantrine, fixed-dose combinations of antimalarials and doxycycline.

2.1.4 Biologicals/vaccines

The Committee was informed of the activities in the area of quality assurance of biological products including vaccines and other related products such as in vitro diagnostic devices. It was noted that the Expert Committee on Biological Standardization was due to meet in October 2006. Issues for discussion would include the revision and update of the WHO GMP for biological products and the preparation of biological reference preparations. Other guidance documents included regulatory expectations for stability of vaccines; regulatory expectations for authorization of vaccines prequalified by WHO; postmarketing surveillance; and the overall provision of regulatory support by WHO in the area of biological medicines (such as regulation of biological medicines and establishment of a network of vaccine regulators in Africa).

The Committee noted that with the ability to fully characterize certain biological products by physicochemical means, there was a need to consider the potential for a change from using the current biological reference preparations to the use of chemical reference preparations where appropriate. The Committee supported development by the Secretariat, through the WHO collaborating centres, of a draft policy to guide this transition. Due to the complexity and range of biological products, a list of those products concerned, the associated possible problems and their use and administration (e.g. insulin), should be considered. The Committee suggested close interaction between the two

Expert Committees (i.e. Specifications for Pharmaceutical Preparations and Biological Standardization).

2.1.5 International collaboration

International Atomic Energy Agency

The Committee noted with thanks the report from the International Atomic Energy Agency (IAEA) and was pleased to note the considerable progress made in the comprehensive review of monographs. The Committee recommended that the Secretariat continue discussion and close collaboration with the IAEA in the area of monographs and standards; preparation of possible additional chapters on reagents, starting materials and sources of radionuclides; and that the process of review of the jointly published WHO/IAEA GMP text for radiopharmaceuticals be initiated.

United Nations Children's Fund

The Committee was informed of some of the activities of the United Nations Children's Fund (UNICEF) related to pharmaceuticals. UNICEF has been a purchaser of essential medicines for a long time and is the world's largest purchaser of vaccines.

UNICEF relies on WHO prequalification for those products included in its programmes (pharmaceutical products and vaccines). It was explained that for other products, the UNICEF prequalification procedure included approval of suppliers through a technical questionnaire, licensing status review and GMP inspections. From 2003 to 2005, 102 inspections were performed. Prequalification of products was done through a review of product questionnaires and supporting documentation. UNICEF verified by means of inspections that prequalified products were supplied.

Products received were visually inspected. Other checks carried out included verification of the certificate of analysis and the site of manufacture. Random testing of products was done in accordance with an annual quality control testing plan. For direct shipments, pre-delivery inspections were carried out by a third party, and random quality control testing was also done.

The Global Fund

An update on the Global Fund Quality Assurance Policy Implementation was presented to the Committee. It was noted that the Global Fund

spent about 49% of its grant funds on procurement of medicines and health products. Access to and continued availability of quality-assured medicines and health products were essential to fight AIDS, malaria and TB. It was acknowledged that collaboration with the Quality Assurance and Safety: Medicines team of the WHO Department of Medicines Policy and Standards was crucial to achieve responsible quality assurance policies and to fulfil the mission of the Global Fund.

The Global Fund thanked WHO for its technical input when the Global Fund selected quality control laboratories. It was planned to share test results with the Quality Assurance and Safety: Medicines team through a database of these results and immediate alerts for substandard products.

The Global Fund expressed appreciation, trust and support for the collaboration and expertise in the areas of the WHO Prequalification programme, publication of monographs on medicines (e.g. antiretroviral medicines, artemisinin combination therapy and medicines used in the treatment of TB) and other technical expertise.

The Committee was informed that the Global Fund encouraged companies to be WHO-prequalified. The Fund also supports the development of monographs on finished products.

2.2 Pharmacopoeial Discussion Group

The Committee was informed that the Pharmacopoeial Discussion Group (PDG) was actively working towards the harmonization of monographs (focusing on excipients). A number of monographs and general chapters were already harmonized. General chapters, the PDG working procedures and a projected timetable for the PDG harmonization of the ICH Q6A guideline (*Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*) were presented. The Committee was informed that WHO was an observer of the work of the PDG.

2.3 International Conference on Harmonisation

The Committee was provided with an overview of activities related to International Conference on Harmonisation (ICH) quality guidelines including ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), ICH Q10 (Pharmaceutical Quality Systems) and ICH Q4B (Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria (RAAPAC)). The documents were available on the ICH web site (www.ich.org).

The Secretariat confirmed that WHO should continue to be an observer of the ICH process, Steering Committee and Global Cooperation group.

The Committee recommended that the Secretariat should continue to monitor the developments in ICH quality topics in order to assist the Committee to formulate a future strategy.

2.4 International Conference of Drug Regulatory Authorities

The Committee received a summary of the proceedings of the 12th meeting of the International Conference of Drug Regulatory Authorities (ICDRA) held in April 2006 in Seoul, Republic of Korea. The Committee was pleased to note that the report was available, containing all the recommendations from the meeting. It was noted that various workshops were held on herbal medicines' safety through quality, "good review practices" and bioequivalence. The subjects of other workshops included regulation of blood and blood-derived products; the role of regulators; access to treatment for severe pain; pharmacoeconomics and regulation and global challenges for harmonization (stability). During the session on counterfeit medicines, the outcomes of the Rome meeting held in February 2006 were discussed and the Rome Declaration was endorsed (<http://mednet3.who.int/cft/Romedecclaration.pdf>).

The Committee was informed that the 13th ICDRA was planned to take place in Berne, Switzerland from 14 to 19 September 2008. It was anticipated that the pre-ICDRA meeting would focus on paediatric medicines.

3. Quality control – specifications and tests

3.1 *The International Pharmacopoeia* (4th ed.)

The Committee was pleased to note that the fourth edition of *The International Pharmacopoeia* was in press and that texts were in preparation for the first supplement. A prototype CD-ROM of the fourth edition was made available enabling the Secretariat to demonstrate the improved layout and functions. Fifteen monographs adopted by the Expert Committee in October 2005 were ready for inclusion in the first Supplement (five antiretroviral substances, three antiretroviral dosage forms, six antituberculosis dosage forms and one general monograph for oral powders). The final texts for these monographs, with the exception of

the one for oral powders, were available on the WHO Medicines web site (<http://www.who.int/medicines/publications/pharmacopoeia/overview>).

Fourteen new monographs (12 antiretroviral dosage forms, one antimalarial substance and one antimalarial dosage form) and two revised monographs (one antimalarial substance and one antimalarial dosage form) were presented to the Committee.

The Committee approved the general editorial style to be used in future publications and recommended that certain monographs be reviewed and revised where appropriate.

With regard to impurities, where the relevant information was available, this should be included for information at the end of a monograph. In dosage form monographs the impurities should be listed, where possible, by cross-reference to those listed in the monograph for the corresponding substance. The Committee agreed that guidance notes concerning *The International Pharmacopoeia* approach to impurity control in dosage form monographs should be made available (Annex 1).

3.2 New monographs for inclusion in *The International Pharmacopoeia*

The Committee noted that a consultation on specifications for medicines and quality control laboratory issues was held from 25 to 27 July 2006 in Geneva. Input from specific disease programmes, the 14th Model List of Essential Medicines, medicines listed in the various Expressions of Interest within the WHO/UNICEF/United Nations Prequalification programme and the List of Medicines collated by the Global Fund were considered. The Committee confirmed that priority should be given to dosage forms for which monographs already existed for active pharmaceutical ingredients (APIs), paediatric formulations and those medicines included in the List of Essential Medicines.

3.3 Dissolution test requirements

The Committee was pleased to note the progress on developing dissolution tests for addition to the monographs of *The International Pharmacopoeia* and agreed on the general format for text for inclusion in relevant monographs for products containing highly soluble APIs. The proposed dissolution methods for metronidazole tablets, doxycycline tablets, isoniazid tablets, chloroquine phosphate tablets, primaquine diphosphate tablets, ethambutol hydrochloride tablets, pyrazinamide tablets, and rifampicin tablets and capsules would be circulated for comment. The Committee

recommended that these revisions be published in the first supplement following consideration of any comments received.

3.4 Pharmacopoeial monographs on antiretrovirals

Monographs on the following were adopted subject to some minor modifications and inclusion of comments:

- abacavir oral solution
- abacavir sulfate tablets
- didanosine tablets
- didanosine oral solution (adult formulation)
- lamivudine oral solution
- lamivudine tablets
- stavudine capsules
- zidovudine capsules
- zidovudine iv injection
- zidovudine oral solution
- zidovudine and lamivudine tablets
- zidovudine, lamivudine and abacavir tablets.

The Committee recommended that a separate monograph should be considered, if appropriate, for a paediatric formulation of didanosine oral solution.

Monographs on antiretrovirals adopted in 2005: proposed amendment to tests for related substances

The Committee approved the proposed changes to monographs for APIs which were necessary with regard to the availability of reference materials. The final texts on the Medicines web site would be amended before inclusion in the first Supplement to the fourth edition.

3.5 Specifications for antimalarials

The Secretariat reported the progress made on the preparation of monographs for medicines used in the treatment of malaria.

Monographs on the following were adopted subject to some minor modifications and inclusion of comments:

- doxycycline hyclate capsules (new monograph)
- doxycycline hyclate tablets (revision)
- doxycycline hyclate (revision).

A first draft of the monograph for lumefantrine would be circulated for comment.

The Committee was informed that the malaria section in the WHO Model List of Essential Medicines would be updated in the near future.

3.6 Quality specifications for antituberculosis drugs

The Committee noted that the WHO Model List of Essential Medicines would be revised in March 2007. Proposals for medicines for children were also expected.

Antituberculosis monographs adopted in 2005: proposed amendment to tests

The Committee approved the proposed changes to the monographs for dosage forms which were necessary in response to the changes in availability of reference materials. The final texts on the Medicines web site would be amended before inclusion in the first Supplement to the fourth edition.

3.7 Specifications for other medicines

The Committee noted that monographs for the following were in preparation:

- oral liquids (general monograph)
- oseltamivir phosphate
- oxytocin
- zinc preparations (paediatric use).

The Committee suggested several changes to the text of a new draft monograph for oseltamivir phosphate, which then follows the normal consultation process.

Medicines for children

The Committee noted the joint WHO/UNICEF press releases on an improved formula for oral rehydration salts to save children's lives, and on the problem of lack of essential medicines for children (23 March and 14 August 2006, respectively).

4. Quality control – International Reference Materials

4.1 International Chemical Reference Substances

The Committee expressed its appreciation of the work done by the WHO Collaborating Centre for Chemical Reference Substances, as presented in the report for 2005, and by the collaborating laboratories. It was noted that the total number of International Chemical Reference Substances (ICRS) distributed from the Centre in 2005 was 1360. The five most frequently requested substances were, in order of demand: tetracycline hydrochloride, artesunate, caffeine melting point reference substance (MP), phenacetin MP and vanillin MP.

Four ICRS were established in 2005. These were didanosine, didanosine for system suitability, efavirenz and nevirapine. A list of available ICRS is included as Annex 2.

The Committee noted that there was considerable variation between regions in the use of reference substances. Members emphasized the importance of the use of reference substances and urged the Secretariat to encourage the regions to make better use of these resources.

The Committee adopted the report and the new ICRS and expressed support for the continuation of the activities of the Collaborating Centre.

4.2 Guidelines for chemical reference substances

The revised draft guidelines, including the expanded section on secondary reference substances, and incorporating the additional comments received were reviewed, discussed and amended. The Committee adopted the guidelines as Annex 3.

5. Quality control – national laboratories

5.1 External Quality Assurance Assessment Scheme

The Committee noted the reports on Phase 3 of this Scheme. Six different regions participated in the five studies in Phase 3 of the WHO External Quality Assurance Assessment Scheme (EQAAS) organized by WHO and performed through the European Directorate for the Quality of Medicines (EDQM).

The five studies carried out during the period from July 2004 to June 2006 were the following:

- EQAAS 3.1: assay by ultraviolet (UV)-Vis spectrophotometry (pyrazinamide tablets);
- EQAAS 3.2: assay by high-performance liquid chromatography (HPLC) (zidovudine);
- EQAAS 3.3: assay by titration (primaquine tablets);
- EQAAS 3.4: water content by Karl-Fischer (mefloquine HCl);
- EQAAS 3.5: assay by HPLC and UV-Vis spectrophotometry (artemether tablets).

In noting the results of the procedures, the Committee recommended that:

- The laboratories should be requested to give additional feedback in cases where results were found to be doubtful or unsatisfactory.
- The laboratories should be encouraged to continue to participate in the Scheme.
- There should be greater involvement of the WHO regional offices in capacity building for those laboratories from which doubtful or unsatisfactory results have been reported.
- The Scheme should be continued.

6. Quality assurance – Good Manufacturing Practices

6.1 Biologicals

The Committee was informed of the process for revision of the WHO GMP for biologicals and supported collaboration between the two Expert Committees (Specifications for Pharmaceutical Preparations, and Biological Standardization) in this area.

Blood products

The Secretariat presented a report on the progress being made in the preparation of GMP guidelines for blood products, blood establishments and related activities which were in line with the recommendations of ICDRA.

6.2 Sterile pharmaceutical products

A discrepancy between the limits for microbial contamination in clean areas in the GMP guidelines of WHO and others was noted. The Committee

supported the proposal to investigate the need for a review of the table for limits for microbial contamination and endorsed the amendment if needed.

6.3 New guidelines

The Committee requested the Secretariat to initiate a process of preparing supplementary guidelines in the areas of good practices for microbiological laboratories and transfer of technology, and to review the guidelines on the Application of Hazard Analysis and Critical Control Point (HACCP) method to pharmaceuticals. If an informal consultation were arranged, then topics such as quality risk management, quality systems and the responsibilities of an authorized person could be discussed. A gap analysis should be done to identify which additional or supplementary guidelines to the main text of the GMP might be needed.

7. Quality assurance – inspection

7.1 Training modules for inspectors

The Committee was informed that all the basic training modules as well as the supplementary training modules, which included topics such as GMP for heating, ventilation and air-conditioning (HVAC) systems for non-sterile pharmaceutical dosage forms, water for pharmaceutical use, and validation and inspecting quality control laboratories, had been reviewed and amended to reflect the latest guidelines. The training modules included PowerPoint presentations referring to WHO texts, photographs and trainer's notes. These would be made available on CD-ROM as well as on the WHO Medicines web page (<http://mednet3.who.int/prequal/> and http://www.who.int/medicines/areas/quality_safety/quality_assurance/production).

The Committee requested that the tests for participants, which follow completion of each training module, be revised.

8. Quality assurance – distribution and trade related

8.1 Good distribution practices for pharmaceutical products

The Committee was provided with information on regulatory pathways, to address the need in countries. The WHO Prequalification programme,

tentative approval by the US Food and Drug Administration under the President's Emergency Plan for AIDS Relief (PEPFAR) scheme, European Medicines Agency (EMA) approval under Article 58 and the Canadian Access Scheme were explained. The products covered in the WHO Prequalification programme include HIV/AIDS medication, TB medicines and antimalarial products. Reproductive health products were recently included in an Expression of Interest. The PEPFAR and the Canadian programmes focus mainly on antiretrovirals whereas the EMA Article 58 is relatively open to various groups of medicines.

The Committee supported the activities and cooperation between the organizations.

WHO guidelines on good trade and distribution practices for starting materials (GTDP)

The Secretariat informed the Committee that an International Pharmaceutical Excipients Council (IPEC) guide was published in 2006 using the WHO guidelines with explanatory notes for implementation by suppliers of excipients.

9. Quality assurance – risk analysis

9.1 New approach to inspections and manufacture

The Committee was informed that the Secretariat was still in collaboration with various agencies in the approach to inspections. Joint inspections were also done in some cases where possible, e.g. WHO prequalification and EDQM. It was mentioned that some manufacturers were concerned with the burden imposed by the increasing trend of multiple inspections performed within a year by different national regulatory authorities.

The Committee requested that:

- the data on the number of inspections conducted be made available by the European Federation of Pharmaceutical Industries and Associations (EFPIA);
- a risk-based approach in selection of inspections be attempted based on the sharing of information;
- better cooperation on a regional basis be considered; and
- information on databases be made available where possible.

10. Quality assurance – Stability

Concern was expressed by some manufacturers about the numerous different storage conditions in the various stability guidelines. In addition, there was a lack of information on stability requirements from some regions and countries.

The Committee noted the continuing work and efforts of the Secretariat on the WHO stability guidelines and the recommendations resulting from the discussions at the 12th ICDRA meeting on various aspects of stability including the conditions for Zones IVa and IVb. The key recommendations were:

1. Member States should identify their stability testing conditions in order to facilitate import to and export from their country. Ideally these should be based on conditions currently being applied, thus avoiding the creation of barriers to access to medicines.
2. Member States should make information available to WHO regarding stability conditions to be applied within their markets.
3. WHO should make available country information to facilitate its accessibility to manufacturers and any interested party on an international basis.

The Committee further noted the guidelines on *Stability testing of active substances and pharmaceutical products* from the WHO Eastern Mediterranean Region. It was suggested that this document could be used as a basis for a revision of the global WHO guidelines on stability testing (Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms, Annex 5, WHO Technical Report Series, No. 863, 1996) with the intention of including a comprehensive listing of WHO Member States and their stability testing conditions. Various comments received in this respect were discussed and it was agreed that the document should be made consistent with WHO terminology before being circulated for wider comment.

11. Prequalification

11.1 Prequalification of priority medicines

The Committee was provided with a report on the progress of the Prequalification programme. It was pleased to note that a report had been

published on the activities in 2005 and that an annual report would be published in the future.

The Committee was also pleased to note that the programme was expanding and that the number of staff would be increased. Government support from a number of countries including France and the People's Republic of China where staff were seconded to WHO was appreciated. A future plan including a rotational post for assessors and greater involvement of inspectors in countries was being developed to help increase availability of further technical expertise to the programme.

Lack of capacity and technical expertise in some countries was identified through the programme. It was planned that a separate pool of experts (not assessors and inspectors) would be used to assist manufacturers and countries.

As explained in the procedures, all efforts would be made to maintain confidentiality and prevent conflict of interests.

The Committee was pleased to note that funds to support the programme had been received from the Bill and Melinda Gates Foundation, and also would possibly be received from the air tax programme initiated by the Government of France.

The prequalification of quality control laboratories in the WHO Region for Africa was continuing. One of the objectives of this part of the programme was to build capacity in countries. Three laboratories in the region were prequalified: two in South Africa and one in Algeria. Work was in progress in Ethiopia and the United Republic of Tanzania to build capacity further.

The Committee noted that several changes to the procedure for prequalification, as discussed at its last meeting, had been finalized. Amendments included the assessment of contract research organizations (CROs) and manufacturers of APIs.

The Committee adopted the amended procedure "Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies" (Annex 4).

11.2 Ongoing quality monitoring of prequalified medicines

The Committee was pleased to note that an article on the ongoing quality monitoring of HIV/AIDS medicines had been published in the *Journal of Generic Medicines* in January 2006. The Secretariat informed the

Committee that other studies (testing of samples including a large study on antiretrovirals) were continuing and that the results were to be published.

11.3 Prequalification of quality control laboratories

In response to the proposals that had been made at the Committee meeting in October 2005, the Committee revised the current draft, and after further discussion, adopted the procedure subject to the clearance from the WHO Legal Counsel “Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies” (Annex 5).

11.4 Procedure for prequalification – manufacturers of active pharmaceutical ingredients

The Committee was informed that there had been suggestions from various parties that it would be beneficial to move towards the prequalification of APIs and manufacturers of APIs. The Committee recommended that:

- the applicable prequalification policies, procedures and related documents be revised as appropriate; and
- the WHO GMP guidelines for APIs be reviewed for possible amendment if required.

11.5 Guidance on variations to a prequalified dossier

The Committee was given a presentation on the amended guidance document. Any changes to prequalified products (variations) may involve administrative and/or more substantial changes and are subject to approval. Procedures for the implementation of the different types of variations were set out to facilitate the tasks of both suppliers and WHO and to guarantee that variations to the medicinal product do not give rise to public health concerns. The guidance describes “minor” and “major” variations. The comments received were discussed. The Committee adopted the amended guidance document “Guidance on variations to a prequalified product dossier” (Annex 6).

12. Regulatory guidance

12.1 Medicines for children

Concern was expressed about the number of children living with HIV/AIDS. It was estimated that only about 40 000 of the 660 000 HIV-

positive children needing treatment for HIV/AIDS were being treated. It was noted that several initiatives were in progress to facilitate access to treatment. The need for paediatric formulations was not limited to HIV/AIDS, but also extended to other disease groups such as malaria and TB.

The Committee encouraged the Secretariat to investigate the possibility of establishing:

- guidance on general principles for paediatric formulations – including pharmaceutical development, formulation and stability – in collaboration with other departments in WHO and other organizations as needed (e.g. on safety or efficacy);
- training modules; and
- pharmacopoeia monographs for paediatric formulations as required. (It was noted that in general the monographs in *The International Pharmacopoeia* were designed to cover various strengths.)

12.2 Revision/update of the guidance on the selection of comparator pharmaceutical products for equivalence assessment

The Secretariat informed the Committee of the progress that had been made with the revision of the published list of comparator products (published in WHO Technical Report Series, No. 902, Annex 11). More cooperation from industry was urgently needed to ensure the preparation of the list (see: www.who.int/medicines).

12.3 Proposal to waive in vivo bioequivalence requirements for immediate release, solid oral dosage forms

The Committee was informed that several “biowaiver monographs” had been prepared and published by the International Pharmaceutical Federation (FIP). Others were in the process of preparation. The Committee noted its appreciation of the work that had been done so far (see www.fip.org).

It was noted that the Pan American Network for Drug Regulatory Harmonization had included biowaivers as part of a risk-based approach for priority setting in establishing bioequivalence in countries of the region (see <http://www.paho.org/english/ad/thse/ev/RedParf-home.htm>).

12.4 WHO Certification scheme

The Committee recommended that the WHO Certification scheme be discussed during its next meeting as was requested in the previous meetings.

13. Nomenclature and computerized systems

13.1 International Nonproprietary Names (INN) for pharmaceutical substances

The Committee was informed of a review and consultation on International Nonproprietary Names (INN) for biological and biotechnological substances including the issue of “biosimilars”. A report was being prepared following the consultation with regulators in September 2006. An open meeting with the Pharmaceuticals Manufacturers’ Associations on Nomenclature for Biological and Biotechnological Substances, including biosimilars, was planned for November 2006. The Committee noted with thanks the report and update by the Secretariat.

13.2 WHO terminology used in quality assurance

The newly updated database was presented to the Committee. The information was now available on the World Wide Web. The Committee expressed appreciation for the work done as the database could be consulted when guidelines were being prepared. This would ensure consistency of the terms used.

14. Miscellaneous

14.1 Index of pharmacopoeias

The Committee noted with appreciation the update of the Index of Pharmacopoeias. Links to pharmacopoeia web sites together with information on the frequency of publication were provided where available. The list will replace the current version on the WHO Medicines web site and will be updated as information is made available.

14.2 Article on the Expert Committee

The Committee was pleased to note that an article on its activities had been published in the *Regulatory Affairs Journal* (Charlish P. WHO Committee

considers drug specifications. *Regulatory Affairs Journal Pharma*, 2006, 17:591–593).

14.3 Promotional materials on quality

The Secretariat informed the Committee of plans to publish some promotional materials on quality of medicines. The Committee was requested to submit comments on these materials which were intended to raise awareness of the importance of ensuring the highest possible quality of pharmaceutical preparations and to convince governments and manufacturers of the need for better regulation of the quality of medicines.

15. Summary and recommendations

The advice and recommendations provided by this Expert Committee are intended to help national and regional authorities (in particular drug regulatory authorities) and procurement agencies, as well as major international bodies and institutions, such as the Global Fund, and international organizations such as UNICEF, to combat problems of counterfeit and substandard medicines. The international guidelines, specifications and nomenclature developed under the aegis of the Expert Committee serve all Member States, international organizations, United Nations agencies, regional and interregional harmonization efforts, and underpin important initiatives, including the prequalification of medicines, the Roll Back Malaria Programme, and Stop TB. Making resources available for these activities is, therefore, very cost-effective.

The Programme on Prequalification of medicines and laboratories could not function without the guidelines, standards and specifications adopted by this Committee after passage through the usual, rigorous consultative process. Moreover, as a result of using the guidelines and specifications and other materials in the field, practical suggestions for potential revisions or the need for additional guidance can be transmitted directly to the Expert Committee. Another valuable aspect of the link between the normative side and the Prequalification programme is that participating members of drug regulatory authorities obtain “hands-on” experience in joint inspections and joint regulatory assessment activities with the participation of both developed and developing countries. This practical side is later taught in training workshops, thus allowing even more colleagues to benefit from

the programme. Manufacturers and quality control laboratories benefit from special advice given in the inspection reports. National authorities benefit from the availability of those inspection reports and the regulatory information they provide.

The Expert Committee members work towards developing clear, independent and practical standards and guidelines for medicines, particularly in view of the increasing international dimensions of trade and cross-border health issues. Standards in the area of quality assurance for medicines were developed by the Committee through an international consensus-building process. This Committee expressed satisfaction that its meeting had been held annually for the second time in order to respond more swiftly to the needs in this area worldwide. The Committee strongly recommended that the meetings should continue to be held annually.

In conclusion, the Expert Committee oversees activities in the area of quality assurance that it considers should continue efficiently and swiftly in order to enable Member States, international organizations, United Nations agencies, regional and interregional harmonization efforts to benefit therefrom. Sustainability of the activities discussed is considered essential if WHO is seriously committed to providing these services laid down in its Constitution.

15.1 New standards and guidelines adopted and recommended for use

1. *The International Pharmacopoeia*. Related substances tests: dosage form monographs (Annex 1).
2. List of available International Chemical Reference Substances (Annex 2).
3. General guidelines for the establishment, maintenance and distribution of chemical reference substances (Annex 3).
4. Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies (Annex 4).
5. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies (Annex 5).
6. Guidance on variations to a prequalified product dossier (Annex 6).
7. Monographs for inclusion in *The International Pharmacopoeia*.

The following 12 monographs were adopted for antiretrovirals subject to some minor modifications:

- abacavir oral solution
- abacavir sulfate tablets
- didanosine tablets
- didanosine oral solution (adult formulation)
- lamivudine oral solution
- lamivudine tablets
- stavudine capsules
- zidovudine capsules
- zidovudine iv injection
- zidovudine oral solution
- zidovudine and lamivudine tablets
- zidovudine, lamivudine and abacavir tablets;

and the following four monographs were adopted for antimalarial medicines:

- doxycycline hyclate capsules (new monograph)
- doxycycline hyclate tablets (revision)
- doxycycline hyclate (revision)
- lumefantrine (new monograph) – subject to further studies.

The Committee adopted the following new ICRS:

- didanosine
- didanosine for system suitability
- efavirenz
- nevirapine.

The Committee also adopted dissolution tests for the following monographs for inclusion in the first supplement of *The International Pharmacopoeia*, fourth edition, subject to circulation, provided no comments that would lead to major revision are received:

- metronidazole tablets
- doxycycline tablets
- isoniazid tablets
- chloroquine phosphate tablets
- primaquine diphosphate tablets
- ethambutol hydrochloride tablets
- pyrazinamide tablets
- rifampicin capsules
- rifampicin tablets.

On the basis of studies performed by WHO Collaborating Centres, as well as the recommendations of experts, the Expert Committee members endorsed

several amendments to recently adopted monographs; these were necessary due to the non-availability of the respective reference standards.

In addition to the above, the Committee recommended that:

- the existing WHO guide on stability testing be revised using the newly revised WHO Eastern Mediterranean Region guidelines as a basis, and be completed by a list identifying the national requirements for the stability testing conditions in each Member State, as notified to WHO;
- the revision of the previously adopted list of comparator products be continued;
- the consolidated database on nomenclature used in WHO quality assurance documentation be maintained and made available on the Medicines web site to facilitate consistency in future guidance in this area.

15.2 Activities that should be pursued and progress reported at the next meeting of the Expert Committee

The following activities should be pursued and progress reported at the next meeting of the Expert Committee. Development of specifications and guidelines will be carried out using the established international consultative process.

The International Pharmacopoeia

The activities to be carried out in relation to *The International Pharmacopoeia* are as follows:

- continuation of the development of specifications for medicines included in the *WHO Model List of Essential Medicines* with a focus on priority diseases and medicines for children; and
- continuation of collaboration with the IAEA with a view to replacing monographs for radiopharmaceuticals.

International Reference Standards

In collaboration with the WHO Expert Committee on Biological Standardization, a draft policy should be elaborated for cases in which a transition from biological to chemical reference preparations may be appropriate in the future.

International Chemical Reference Substances

The Committee recommended promotion of the use of ICRS through various activities, including a promotional offer to national authorities.

Regulatory guidance

The work on regulatory guidance will include:

- continuation of the development of guidance on variations;
- collaboration with the EMEA and other national inspectorates in an exchange of information aimed to allow a better risk analysis when planning for foreign inspections;
- investigating the possibility of establishing guidance on general principles for paediatric formulations in collaboration with other parties within and outside WHO;
- providing details with a view to revising the WHO Certification scheme for products moving in international commerce.

Quality assurance system

The work on the quality assurance system will be to study the need for further guidance in this area, including discussion on the need for guidelines or revision of guidance, and gap analysis.

Good manufacturing practices

Work on GMP will include:

- follow-up on the revision process for GMP for biological products currently taking place under the aegis of the Expert Committee on Biological Standardization;
- follow-up on developments in the area of blood products and related biologicals.

Prequalification project

The Committee strongly recommended that sufficient resources should be made available to enable the programme to continue, with regard to prequalification of products, quality control laboratories, update of the procedure and requalification as necessary.

15.3 New areas of work suggested

The following new working areas were suggested to be undertaken and progress to be reported to the next Expert Committee.

- Continue the preparatory work of the supplement to *The International Pharmacopoeia*, fourth edition, both in printed and in electronic form (CD-ROM).

- Revise general chapters included in *The International Pharmacopoeia*, as identified by the group of experts and endorsed by the Expert Committee.
- Promote and widely distribute the newly updated GMP training modules.
- Continue and strengthen the External Quality Control Laboratory Assessment Scheme through greater involvement of the WHO regional offices with regard to capacity building for those laboratories from which doubtful or unsatisfactory results are reported.

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and Drugs Board, Quality Control Laboratory, Accra, Ghana; Institute for Quality Control of Medicines, Sarajevo, Bosnia and Herzegovina; Instituto Especializado de Análisis, Universidad de Panamá, República de Panamá; Instituto Nacional de Higiene “Rafael Rangel”, Caracas, Venezuela; Instituto Nacional de Medicamentos, Buenos Aires, Argentina; Laboratoire National de la Santé du Mali, Bamako, Mali; Laboratoire National de Contrôle des Médicaments, Rabat Instituts, Rabat, Morocco; Laboratoire National de Contrôle des Médicaments, Dakar Étoile, Senegal; Laboratoire National de Contrôle des Médicaments, Bab Saadoun, Tunisia; Laboratoire National de Contrôle des Produits Pharmaceutiques, Algiers, Algeria; Laboratoire National de Santé Publique et d’Expertise, Niamey, Niger; Laboratorio Control de Productos MSP, Comisión Para El Control de Calidad de Medicamentos, Montevideo, Uruguay; Laboratorio de Análisis y Asesoría Farmacéutica, San Pedro de Montes de Oca, San José, Costa Rica; Laboratorio de Normas y Calidad de Medicamentos, Caja Costarricense de Seguro Social, Universidad de Costa Rica, San Jose, Costa Rica; LTD Centre for Medicine Quality Control, Tbilisi, Georgia; Medicines Control Authority, Control Laboratory of Zimbabwe, Harare, Zimbabwe; Mission for Essential Drugs and Supplies (MEDS) Nairobi, Kenya; National Drug Quality Assurance Laboratory, Colombo, Sri Lanka; National Drug Quality Control Laboratory, National Drug Authority, Kampala, Uganda; National Institute for the Control of Pharmaceutical and Biological Products, Beijing, People’s Republic of China; National Institute of Drug Quality Control, Hanoi, Viet Nam; National Laboratory for Drug Quality Control, Phnom Penh, Cambodia; Provincial Quality Control Laboratory of Drug and Food, Yogyakarta, Indonesia; Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa; Royal Drug Research Laboratory, Department of Drug Administration, Kathmandu, Nepal; Tanzania Food and Drugs Authority, Dar-es-Salaam, United Republic of Tanzania; WHO Collaborating Centre for Chemical Reference Substances, Apoteket AB, Central Laboratory, Kungens Kurva, Sweden; WHO Collaborating Centre for Chemical Reference Substances, National Corporation of Swedish Pharmacies, Central Laboratory, Kungens Kurva, Sweden; WHO Collaborating Centre for Drug Quality Control, Therapeutic Goods Administration Laboratories, Woden, Australian Capital Territory, Australia; WHO Collaborating Centre for Drug Quality Assurance, National Institute for the Control of Pharmaceutical and Biological Products, Temple of Heaven, Beijing, People’s Republic of China; WHO Collaborating Centre for Biopharmaceutical Aspects of Drug Quality Control, Biopharmaceutical Laboratory, University of Clermont-Ferrand, Clermont-Ferrand, France; WHO

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Annex 1

***The International Pharmacopoeia* – related substances tests: dosage form monographs guidance notes**

Objective

For dosage form monographs, the main purpose of a test for related substances is to control degradation impurities. Wherever possible, however, a further objective is to limit impurities arising during synthesis of the active pharmaceutical ingredient (API). This approach provides the means for an independent control laboratory (e.g. a small regulatory laboratory) without access to manufacturer's data to establish whether or not an API of pharmacopoeial quality has been used to manufacture the dosage form under examination. Such an approach is consistent with the aims and purpose of *The International Pharmacopoeia*.

General considerations

It is recognized that the limits for degradation impurities given in dosage form monographs may sometimes need to be higher than the limits for the same impurities that appear in the monograph for the corresponding API.

The limits set for degradation impurities may also need to be different for different types of dosage form. For example, higher limits may need to be set for an oral solution than for tablets.

Total limits need to be interpreted with caution since the numerical limits given in parentheses for individual impurities are only approximate values given for information only. In addition, the limits given in any one monograph may be a mixture of “real” limits (where a solution of the impurity – either as a reference substance (RS) or a reagent – is used to set the limit) and nominal limits (where a dilution of the test solution is used).

In the absence of evidence that the limit for any particular impurity needs to be set on the basis of its toxicity, limits will normally be chosen on the basis of batch data for products manufactured in accordance with good manufacturing practices (GMP) and will take account of factors such as the number of impurities normally present, the type of dosage form, route of administration and dose regimen. Limits given in monographs for formulated preparations will also take account of the limits set in the monograph for the API.

Application

The extent to which the above objective can be met will depend on a variety of factors including the nature and availability of impurities (as RS, reagents or made in situ), the number of active ingredients and the complexity of the formulation. In applying this overall approach to individual dosage form monographs, the following cascade will, therefore, be followed to adapt the test to the particular circumstances:

- If a test mix RS can be established for use in the monograph for the API, the same approach as for the substance monograph will be adopted. Limits may need to be different.
- If a test mix RS cannot be obtained, the responsible laboratory will examine whether the monograph could include instructions on generating certain impurities by in situ degradation.
- In cases where in situ degradation alone or together with the use of reagents permits satisfactory identification of peaks, specific limits for certain impurities will be included.
- In cases where none of the above means is available to identify specific impurity peaks unequivocally, a general test with an “open” design will be used (that is, nominal limits for any secondary peaks will be set using a dilution of the test solution). Where it is known that several impurities are likely to be present at significant concentrations, a two- or three-level test allowing the area of no more than a certain number of peaks to exceed a particular level will be used and a total limit and a disregard limit will be set.
- In cases in which the main degradation impurity/impurities can be identified, but the chromatogram is complicated by the presence of excipient peaks that cannot be identified and excluded, a limit will be specified for the main degradation impurity/impurities only. This may be the case for some oral liquids. Similar considerations may apply for dosage forms containing two or more APIs.
- *Note:* In some cases when difficulties are encountered, it may be worthwhile considering the use of thin-layer chromatography (TLC) for related substances (using, e.g. the method already specified in the monograph for identification). The use of TLC may facilitate differentiation of API(s) and impurities (spots of different R_f value colours) and certain excipients may be more easily excluded (e.g. because they are left on the line of application).

Annex 2

List of available International Chemical Reference Substances and International Infrared Reference Spectra

1. International Chemical Reference Substances

International Chemical Reference Substances 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 medicines 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 required analytical data for the use described in the relevant specifications of *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 this use.

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 lists may also be obtained on request.

Ordering information

Orders for International Chemical Reference Substances should be sent to:

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

The current price for the International Chemical Reference Substances is US\$ 70 per package. An administration charge of US\$ 10 is added to each order to cover costs for handling and dispatch by air mail or air parcel post. If dispatch by air freight is requested, the freight costs will amount to about US\$ 200 and these costs have to be paid by the purchaser. Payment should be made according to the invoice. Kindly direct all payments (cheques, bills of exchange, banker's drafts or banker's transfers) to:

Nordea Bank Sweden, SE-105 71 Stockholm
(Apoteket AB/APL/ACL/WHO)
Swift: NDEASESS
Account no. (PG): 2 98 40-6
IBAN: SE 65 9500 0099 6026 0029 8406

The invoice number must be quoted when payment is made.

If, however, payment in advance is requested but not allowed according to the regulations of certain countries, **documentary remittance (cash against documents)** may be used. This means that the invoice is paid at the buyer's bank and against that receipt the parcel is collected at the customs office or, when so agreed, at the bank.

The WHO Centre cannot accept payment by letter of credit.

Nor can the WHO Centre issue a **Certificate of Origin**, as the bulk material for the International Chemical Reference Substances originates from different parts of the world. Also the Centre cannot assist in any legalization of such or other documents sometimes asked for, which has to be respected by the purchaser.

On dispatch by air freight, the freight cost is paid directly to the carrier by the purchaser.

In all cases the payment should be net of charge for the WHO Collaborating Centre.

The administration charge of US\$ 10 covers cost for **handling and dispatch by airmail** (small parcel or air parcel post). If **registered air mail** or **express air mail** is required, an extra charge is payable. If safe delivery is possible by means of airmail, this is the preferred option as it is much less expensive for all parties.

International Chemical Reference Substances are only supplied in standard packages as indicated in the following list.

Available International Chemical Reference Substances

Catalogue number	Reference substances	Package size	Control number
9930375	<i>p</i> -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
9931408	artemether	100 mg	103225
9931406	artemisinin	100 mg	103222
9931407	artemotil	100 mg	103226
9931410	artenimol	100 mg	103223
9931409	artesunate	100 mg	103224
9930215	atropine sulfate	100 mg	183111
9930216	azathioprine	100 mg	172060
9930218	bacitracin zinc	200 mg	192174
9930219	beclometasone dipropionate	200 mg	192175
9930225	benzylpenicillin potassium	200 mg	180099
9930226	benzylpenicillin sodium	200 mg	280047
9930227	bephenium hydroxynaphthoate	100 mg	183112
9930228	betamethasone	100 mg	183113

Catalogue number	Reference substances	Package size	Control number
9930229	betamethasone sodium phosphate	100 mg	196203
9930230	betamethasone valerate	100 mg	190145
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
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
9930261	clomifene citrate Z-isomer see zuclomifene	200 mg	274005
	cloxacillin sodium		
9930262	colecalfiferol (vitamin D3)	500 mg	190146
9930263	cortisone acetate	100 mg	167006
9930265	dapsone	100 mg	183115
9930266	desoxycortone acetate	100 mg	167007

Catalogue number	Reference substances	Package size	Control number
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
9930282	diazoxide	100 mg	181103
9930283	dicloxacillin sodium	200 mg	174071
9930285	dicoumarol	100 mg	178077
9931413	didanosine	100 mg	104228
9931414	didanosine for system suitability	10 mg	104230
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
9931411	efavirenz	100 mg	104229
9930197	4-epianhydrotetracycline hydrochloride	25 mg	288097
9930295	ergocalciferol (vitamin D2)	500 mg	190147
9930296	ergometrine hydrogen maleate	50 mg	277012
9930297	ergotamine tartrate	50 mg	385013
9930298	erythromycin	250 mg	191154
9930299	erythromycin B	100 mg	205186
9930300	erythromycin C	25 mg	194187
9930301	estradiol benzoate	100 mg	167014
9930302	estrone	100 mg	279015
9930304	ethambutol hydrochloride	100 mg	179081
9930305	ethinylestradiol	100 mg	301016
9930306	ethisterone	100 mg	167017
9930307	ethosuximide	100 mg	179088
9930309	flucloxacillin sodium	200 mg	195194
9930310	flucytosine	100 mg	184121
9930311	fludrocortisone acetate	200 mg	195199
9930312	fluorouracil	100 mg	184122
9930313	fluphenazine decanoate dihydrochloride	100 mg	182107

Catalogue number	Reference substances	Package size	Control number
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	205183
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- <i>o</i> -methylcarbidopa)	25 mg	193180
9930189	(-)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine (3- <i>o</i> -methylmethyldopa)	25 mg	179085
9930328	ibuprofen	100 mg	183117
9930329	imipramine hydrochloride	100 mg	172064
9931415	indinavir	100 mg	105231
9930330	indometacin	100 mg	178078
9930331	isoniazid	100 mg	185124
9930332	kanamycin monosulfate	12 mg	19721
9931416	lamivudine	100 mg	105232
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

Catalogue number	Reference substances	Package size	Control number
Melting point reference substances			
9930217	azobenzene (69 °C)	1 g	192168
9930438	vanillin (83 °C)	1 g	299169
9930222	benzil (96 °C)	1 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
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
9930345	methotrexate 3- <i>o</i> -methylcarbidopa see (-)-3-(4-hydroxy-3-methoxyphenyl)-2-hydrazino-2-methylalanine 3- <i>o</i> -methylmethyldopa see (-)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine	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
9931417	nelfinavir mesilate neomycin B sulfate see framycetin sulfate	100 mg	105233
9930356	neostigmine metilsulfate	100 mg	187135
9931412	nevirapine anhydrous	100 mg	104227
9930357	nicotinamide	100 mg	200090
9930358	nicotinic acid	100 mg	179091
9930359	nifurtimox	100 mg	194189
9930360	niridazole	200 mg	186129

Catalogue number	Reference substances	Package size	Control number
9930361	niridazole-chlorethylcarboxamide	25 mg	186130
9930366	norethisterone	100 mg	186132
9930367	norethisterone acetate	100 mg	185123
9930369	nystatin	200 mg	405152
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
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
9930398	procaine hydrochloride	100 mg	183119
9930399	procarbazine hydrochloride	100 mg	184120
9930400	progesterone	100 mg	167033
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
9930408	riboflavin	250 mg	382035

Catalogue number	Reference substances	Package size	Control number
9930409	rifampicin	300 mg	191151
9930410	rifampicin quinone	200 mg	202148
9931421	ritonavir	100 mg	105237
9931418	saquinavir mesilate	100 mg	105234
9930412	sodium amidotrizoate	100 mg	198221
9930413	sodium cromoglicate	100 mg	188140
9930415	spectinomycin hydrochloride	200 mg	193176
9931419	stavudine	100 mg	105235
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 <i>E</i> -isomer	10 mg	205209
9930427	testosterone enantate	200 mg	194192
9930428	testosterone propionate	100 mg	167036
9930429	tetracycline hydrochloride	200 mg	205095
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
9930440	vincristine sulfate	9.7 mg/ vial	193181
9930439	warfarin	100 mg	168041
9931420	zidovudine	100 mg	105236
9930260	zuclomifene	50 mg	187137

2. List of available International Infrared Reference Spectra

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

The current price is US\$ 5 for a single spectrum and US\$ 200 for a set of 50 spectra, including a hardcover binder. The binder can be ordered separately for US\$ 10.

An administrative charge of US\$ 10 is added to each order to cover costs for handling and dispatch by air mail or air parcel post.

Orders should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteket AB
Produktion & Laboratorier
Farmaci/Centrallaboratoriet (ACL)
Prismavägen 2
SE-141 75 Kungens Kurva
Sweden
Fax: + 46 8 740 60 40
or e-mail: who.apl@apoteket.se
web site: <http://www.apl.apoteket.se/who>

Payment should be made according to the invoice. Kindly direct all payments to:

Nordea Bank Sweden, SE-105 71 Stockholm
(Apoteket AB/APL/ACL/WHO)
Swift: NDEASESS
Account no (PG): 2 98 40-6
IBAN: SE 65 9500 0099 6026 0029 8406

The invoice number must be quoted when payment is made.

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

aceclidine salicylate	lidocaine
acetazolamide	lidocaine hydrochloride
allopurinol	lindane
amiloride hydrochloride	
amitriptyline hydrochloride	metronidazole
ampicillin trihydrate	miconazole nitrate
beclometasone dipropionate	niclosamide

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
dicolinium iodide
dicoumarol
diethylcarbamazine dihydrogen citrate
diphenoxylate hydrochloride

erythromycin ethylsuccinate
erythromycin stearate
etacrynic acid
ethionamide
ethosuximide

furosemide

gallamine triethiodide
glibenclamide

haloperidol
hydrochlorothiazide

ibuprofen
imipramine hydrochloride
indometacin
isoniazid

nicotinamide
noscapine

oxamniquine

papaverine hydrochloride
phenobarbital
phenoxymethylpenicillin calcium
phenytoin
primaquine phosphate
propylthiouracil
protionamide
pyrimethamine

salbutamol
salbutamol sulfate
sulfadimidine
sulfadoxine
sulfamethoxazole
sulfamethoxypyridazine

tiabendazole
trihexyphenidyl hydrochloride
trimethoprim

valproic acid
verapamil hydrochloride

Annex 3

General guidelines for the establishment, maintenance and distribution of chemical reference substances

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References

Introduction

In 1975 the WHO Expert Committee on Specifications for Pharmaceutical Preparations recommended the “General guidelines for the establishment, maintenance and distribution of chemical reference substances” (1). At that time these general guidelines were aimed at fostering greater collaboration and harmonization among various national and regional authorities responsible for collections of chemical reference substances. This aim is still relevant. The guidelines were initially drawn up specifically for use by the WHO Collaborating Centre for Chemical Reference Substances in Sweden, which supplies International Chemical Reference Substances (ICRS). These substances are primarily intended for use with pharmacopoeial monographs included in *The International Pharmacopoeia* (2).

It became evident that to ensure ready availability and cost-effectiveness, and in order to meet particular national or regional pharmacopoeial requirements, it was necessary to establish chemical reference substances external to the WHO Collaborating Centre for Chemical Reference Substances. Since the meticulous work of the WHO Collaborating Centre establishing the international collection would have to be duplicated in local or regional laboratories, guidelines were necessary to ensure the integrity of national or regional collections. The 1975 guidelines were reviewed and modified in 1982 (3) and subsequently revised in 1999 (4).

In 2004, the WHO Expert Committee on Specifications for Pharmaceutical Preparations recommended the development of more detailed guidelines on the establishment of secondary chemical reference substances. This additional guidance forms part B of the present revision and is intended to apply to secondary reference substances supplied as “official”, e.g. regional/national standards, and not to the working standards of manufacturers or other laboratories. However, in principle, secondary reference standards prepared by manufacturers can be prepared as “working standards” using the same procedures.

The purpose of establishing chemical reference substances is to achieve accuracy and reproducibility of the analytical results required by pharmacopoeial testing and pharmaceutical control in general. These substances are normally prepared and issued by the regional or national pharmacopoeia commission or the regional or national quality control laboratory on behalf of the drug regulatory authority. In the context of these guidelines, the general use of a chemical reference substance should be considered an integral part of a compliance-oriented monograph or

test procedure used to demonstrate the identity, purity and content of pharmaceutical substances and preparations.

The purpose of establishing secondary reference substances is for use in routine analysis to determine the identity, purity and, in particular, the content of pharmaceutical substances in pharmaceutical preparations. The extent of characterization and testing of a secondary reference substance is less than that for a primary reference substance. It is essential that a secondary reference substance is traceable to a primary reference substance, such as a pharmacopoeial or other officially recognized reference substance. In the cases of doubtful results or dispute when using secondary chemical reference substances, the test should be repeated using the primary standard.

The establishment of a chemical reference substance is based on the evaluation of the results of analytical testing. The report should subsequently be approved and adopted by a certifying body, normally the relevant pharmacopoeial committee or drug regulatory authority. The establishment of the reference substance can be on an international, national or regional basis. Each substance is generally established for a specific analytical purpose, defined by the issuing body. Its use for any other purpose becomes the responsibility of the user and a suitable caution is included in the accompanying information sheet. The present guidelines are concerned with both primary and secondary chemical reference substances as defined below.

The preparation of a chemical reference substance should comply with the requirements for quality assurance systems, including applicable principles of good manufacturing practices (GMP) and good control laboratory practices (5–10).

Adequate training programmes are also required. Both the WHO Collaborating Centre and other laboratories concerned with the evaluation and establishment of chemical reference substances give assistance in training, subject to the availability of resources.

Glossary

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

chemical reference substance

The term *chemical reference substance*, as used in this text, refers to an authenticated, uniform material that is intended for use in specified

chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use.

primary chemical reference substance

A designated primary chemical reference substance is one that is widely acknowledged to have the appropriate qualities within a specified context, and whose assigned content when used as an assay standard is accepted without requiring comparison with another chemical substance.

secondary chemical reference substance

A secondary chemical reference substance is a substance whose characteristics are assigned and/or calibrated by comparison with a primary chemical reference substance. The extent of characterization and testing of a secondary chemical reference substance may be less than for a primary chemical reference substance. Although this definition may apply *inter alia* to some substances termed “working standards”, part B of these guidelines is intended to apply to secondary reference substances supplied as “official”, e.g. regional/national standards, and not to manufacturers’ or other laboratories’ working standards.

International Chemical Reference Substance

International Chemical Reference Substances (ICRS) are primary chemical reference substances established on 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 ICRS may be used to calibrate secondary standards.

pharmacopoeial reference standards

The specificity of pharmacopoeial reference substances has been addressed in the introduction of *ISO Guide: General requirements for the competence of reference material producers*. “Pharmacopoeial standards and substances are established and distributed by pharmacopoeial authorities following the general principles of this Guide. It should be noted, however, that a different approach is used by the pharmacopoeial authorities to give the user the information provided by certificate of analysis and expiration dates” (9).

Part A.

Primary chemical reference substances

A.1 Assessment of need for the establishment of chemical reference substances

The production, validation, maintenance and distribution of chemical reference substances is a costly and time-consuming undertaking. It is, therefore, crucial to determine for certain whether a need for a given substance exists. Requests for new chemical reference substances usually arise when a particular approach to developing a specification for a new substance or product has been adopted. Methods may have been proposed in a specification that require the establishment of a chemical reference substance for use as a comparative standard. Therefore, the first matter that should be assessed is whether an alternative, equally satisfactory, procedure could be adopted that does not require a comparative standard.

Analytical procedures currently used in specifications for pharmaceutical substances and products that may require a chemical reference substance are:

- infrared (IR) spectrophotometry, whether for identification or quantitative purposes;
- quantitative methods based on ultraviolet (UV) absorption spectrophotometry;
- quantitative methods based on the development of a colour and the measurement of its intensity, whether by instrumental or visual comparison;
- methods based on chromatographic separation for identification or quantitative purposes;
- quantitative methods (including automated methods) based on other separation techniques that depend on partition of the substance to be determined between solvent phases, where the precise efficiency of the extraction procedure might depend upon ambient conditions that occasionally vary and from laboratory to laboratory;
- quantitative methods, often titrimetric but sometimes gravimetric, that are based on non-stoichiometric relationships;
- assay methods based on measurement of optical rotation; and
- methods that might require a chemical reference substance consisting of a fixed ratio of known components (for example, *cis/trans* isomers, spiked samples).

A.2 Obtaining source material

Source material of satisfactory quality can be selected from a batch (lot) of the substance originating from the normal production process, if the purity is acceptable. Further purification techniques may be needed to render the material acceptable for use as a chemical reference substance.

The purity requirements for a chemical reference substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification, since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test.

On the other hand, chemical reference substances that are to be used in assays should possess a high degree of purity. As a guiding principle, a purity of 99.5% or higher is desirable, calculated on the basis of the material in its anhydrous form or free of volatile substances. However, where the selectivity of the analytical procedure for which the chemical reference substance is required is low, such a degree of purity may not be necessary. In making a decision about the suitability of a chemical reference substance, the most important consideration is the influence of the impurity on the attribute measured in the assay when used in a non-specific assay procedure. Impurities with physicochemical characteristics similar to those of the main component will not diminish the usefulness of a chemical reference substance, whereas even traces of impurities with significantly different properties may render a substance unsuitable for use as a chemical reference substance.

When source material to be used as a chemical reference substance is obtained from a supplier, the following should be supplied with the material:

- certificate of analysis with complete information on test methods employed, values found and number of replicates used, where applicable, and relevant spectra and/or chromatograms;
- results of any accelerated stability studies;
- information on optimal storage conditions required to ensure stability (temperature and humidity considerations);
- results of any hygroscopicity study and/or statement of the hygroscopicity of the source material;
- identification of impurities detected and/or specific information on the relative response factor as determined in compendial methods concerning the principal component, and/or the percentage mass of the impurity;

- updated material safety data sheet outlining any health hazards associated with the material.

For new drug substances, manufacturers should be aware that elaboration of pharmacopoeial monographs will be necessary, and a batch of the new substance should be set aside to be used if necessary as the chemical reference substance. It is desirable for bodies that issue chemical reference substances to share the same batch of material, even if the substance will be employed for different test methods. This will require exchange of information concerning the establishment process, supplier(s), availability and conditions of supply.

A.3 Evaluation of chemical reference substances

The suitability of a substance proposed for use as a chemical reference requires careful evaluation by the issuing body. It is necessary to consider all data obtained from testing the material by a wide variety of analytical methods. When taken as a whole, this will ensure that the substance is suitable for its intended use. The extent of the analyses required depends on the purpose(s) for which the chemical reference substance is to be employed, and may involve a number of independent laboratories.

A.3.1 Use in identification tests

For use in identification tests (IR spectrophotometry and/or chromatographic methods), a batch of good quality material selected from the normal production process is satisfactory if it is of acceptable purity. Additional purification by the supplier may be necessary. The most important check is the application of the test(s) for which the substance is intended. It is usual for at least one laboratory to apply all the chemical and physical tests described in the relevant monograph; some tests, such as those for sterility or for bacterial endotoxins, may not be necessary for materials intended as reference standards.

A.3.2 Use in purity tests

The characterization of a chemical reference substance for use in the determination of a specific impurity is more extensive, especially when used in a limit test. If the technique employed is thin-layer chromatography (TLC), an acceptable minimum purity is recommended (normally at least 90%), but purer material (at least 95%) may be required for liquid

chromatography (LC) or gas chromatography (GC). It is usually enough to involve only one laboratory when the reference substance is used in purity tests. If the proposed reference substance is being prepared or isolated for the first time, appropriate chemical and physicochemical tests, such as nuclear magnetic resonance (NMR), mass spectrometry (MS) and elemental analysis, must be applied to characterize it.

A.3.3 Use in assays

If the chemical reference substance is to be used in an assay (colorimetry, LC, GC or UV spectrophotometry), the extent of testing is much greater. Several (a minimum of three) laboratories should collaborate in testing the proposed substance, using a variety of established and validated techniques, including the method used in the pharmacopoeial specification. The relative reactivity or relative absorbance of the impurities present must be checked when a nonspecific assay method is employed, e.g. by colorimetry or UV spectrophotometry. When a selective assay method is employed, it is particularly important to determine the quantity of impurities. In such a case, it is best to examine the proposed reference substance by as many methods as practicable including, where possible, absolute methods. For substances that are acidic or basic a titration with alkali or acid is simple, but other reactions which are known to be stoichiometric may be used. Phase solubility analysis and differential scanning calorimetry may also be employed in certain cases.

The total of the determinations of water content, organic solvents, mineral impurities and organic components should amount to 100%. For most chemical reference substances intended for assays, the content may be expressed “as is”. When establishing the chemical reference substance it is, therefore, essential to determine the content of water and residual solvents for a non-specific assay, and also to determine the content of impurities for a selective assay.

A.3.4 Use in the calibration of an instrument

Where the chemical reference substance is to be employed as calibration material, the extent of testing is similar to that for a chemical reference substance used in assays. Several laboratories should collaborate in testing the proposed substance using a variety of techniques to check that its purity is adequate. An appropriate number of collaborating laboratories should also participate, after the reference substance has been deemed suitable, to establish a value for the essential property of the substance using an appropriate instrument.

A.4 Chemical and physical methods used in evaluating chemical reference substances

It is important to establish by individual testing that a substance proposed for use as a chemical reference is suitable for that purpose.

The methods used to establish the suitability of such a substance fall into two broad groups: those intended primarily to identify the substance and those used to establish its purity. With most methods, the percentage purity of a chemical reference substance cannot be expressed as an absolute value if the impurities have not been identified. The quoted purity is then an estimate based upon the data obtained by the various analytical methods.

A.4.1 Methods used to verify the identity of chemical reference substances

Where a proposed reference substance is a substance whose structure has been satisfactorily defined, its identity may be confirmed by matching the IR spectrum of the substance to that of an authentic specimen. Particular care should be taken when polymorphism exists (8). Other highly specific techniques, such as NMR spectroscopy, MS, or X-ray diffraction crystallography, may also be used for such comparisons. The identity of a substance that is intended to replace an established chemical reference substance of the same molecular constitution must be verified, to determine that the characteristic properties of the two specimens are identical. For this purpose it is often sufficient to compare their IR absorption spectra.

However, where no authentic specimen of the proposed substance is available for comparison, and definitive data about its properties are lacking, it may be necessary to verify its identity by applying several of the analytical techniques currently used to characterize new compounds. Such analytical methods may include elemental analyses, crystallographic studies, MS, NMR spectroscopy, functional group analyses, and IR or UV spectrophotometry, as well as other supplementary tests, as required, to establish that the proposed substance is fully characterized.

A.4.2 Methods used to determine the purity of chemical reference substances

The analytical methods to be employed in examining a substance should be considered in relation to its intended use. These analytical methods may be divided into three broad categories:

- those that require comparison with an external chemical reference substance (e.g. chromatographic or spectrophotometric methods);
- those that depend solely on an intrinsic dynamic property (e.g. phase solubility analysis and differential scanning calorimetry); and
- other methods.

A.4.2.1 Separation techniques

The methods used for the determination of purity should be established and validated with system suitability requirements as appropriate.

Chromatographic methods. Methods of analysis based on chromatographic separation are especially useful for detecting and determining impurities in chemical reference substances. High-performance liquid chromatography (HPLC) is the most widely used chromatographic method, but TLC and GC are also used. The individual components separated by chromatographic methods may sometimes be recovered for characterization.

The selectivity of HPLC and of GC usually exceeds that of TLC. Both of the first two methods also have the advantage of being readily applicable on a quantitative basis, but they require more complex equipment. HPLC, employing a spectrophotometric method of detection, is of particular value in the examination of chemical reference substances intended for use in UV spectrophotometric assays. The UV wavelength of detection employed for determining the impurity content of the chemical reference substance should be chosen so that the detection responses of the substance and its impurities are similar. When the response factors are significantly different at the optimal wavelength of detection, appropriate corrections must be made to estimate the content of impurities. LC with diode-array detection is very useful for recording the UV spectra of both the main peak and the impurities. LC with MS detection is used for identification of separated impurities as well as for the main component, and is particularly important for use with chemical reference substances for which no other reference standards or IR reference spectra are available.

In a GC method used for an assay, as with LC, the detection responses of the impurities are determined. Generally, monograph methods using GC are of particular value in detecting and determining volatile impurities, including solvent residues, in chemical reference substances.

TLC uses apparatus that is simple and inexpensive; the technique is easy to carry out and is readily applicable even in the microgram range. It can separate closely related compounds, such as geometric isomers and

the members of a homologous series. All the constituents of a substance subjected to chromatography appear somewhere on the chromatogram. However, some constituents may remain on the starting line, some may move with the solvent front, some may migrate at the same rate as the main component and some may remain undetected. For this reason, the usefulness of the method may be greatly enhanced by performing two-dimensional chromatography and by using a number of different solvent systems and a variety of detection methods. In some cases the method may be used quantitatively with acceptable accuracy by using a densitometer.

Capillary electrophoresis. Capillary electrophoresis (CE) is an increasingly common method. It may be considered as complementary to LC for detecting impurities.

A.4.2.2 Methods based on intrinsic thermodynamic properties

Methods in this group measure total impurity levels in absolute terms.

Differential scanning calorimetry. This technique is used to check for the presence of different polymorphic forms and to determine the total amount of solid impurities. Purity estimation is based on determination of the heat of fusion of the sample and of the change in its melting point caused by the presence of impurities. This analytical method can be performed rapidly and with high precision. However, it is not applicable if the substance decomposes on melting. This limits its value as a general procedure for estimating the purity of chemical reference substances. It is also inapplicable if solid solutions are formed.

Phase solubility analysis. The method has occasionally been used but its value is limited and the procedure is time consuming. It may be employed to detect contaminating substances, including isomeric species, and to estimate their concentration. Some factors that may make the method inapplicable are degradation of the substance during the course of analysis, formation of a solid solution and polymorphism in the main component.

A.4.2.3 Other methods

Spectrophotometric methods. UV spectrophotometry is occasionally used to determine purity. Since it depends upon the presence of a characteristic chromophore, it can detect impurities that contribute excessively to the absorbance value and may indicate the presence of impurities that have a negligible or distinctive absorbance.

However, the utility of the method is limited by the small number of absorption maxima in the UV range, the large numbers of compounds containing similar characteristic chromophores, and the need for an external chemical reference substance.

IR spectrophotometry may be used to identify and determine the proportions of geometric isomers. NMR spectroscopy, a powerful spectroscopic identification tool, is also occasionally useful in the determination of purity.

Titrimetric methods. Titrimetric methods provide a valuable means of confirming the identity and purity of a proposed chemical reference substance and are useful in confirming purity values obtained by other methods.

Optical rotation methods. Many chemical reference substances are optically active and the relative proportion of optical isomers can sometimes be determined by an optical rotation method, but generally such methods lack specificity and sensitivity. However, the quantitative use of these techniques is well established and can yield results of high precision, depending on the solvent and the wavelength chosen for measurement, provided that pure substances of individual isomers are available. Chiral chromatography, NMR and CE are becoming increasingly important.

Determination of water and organic volatiles. It is essential that an accurate assessment of the moisture content and the content of volatile substances be made. These total values may often be obtained by drying under defined conditions that are appropriate to the proposed substance. Sometimes this may not be possible or may yield misleading results. In such cases, thermogravimetric analysis may be used to determine the content of water and organic volatiles. Alternatively, the water content may be determined by Karl Fischer titration and the content of volatile solvents by GC. Without an accurate assessment of these values at the time that other determinations are being made, judgements of the acceptability of the proposed chemical reference substance will be invalid.

A.5 Assignment of content

If a content is to be assigned to a chemical reference substance, it should be borne in mind that the value is based on the results of a collaborative interlaboratory programme using different analytical methods. This experimentally obtained value represents the best estimate of the true value. In general, the value must be further corrected for the fraction of impurity. Sometimes the chemical reference substances must be dried before use, in which case the content is expressed on the basis of the dried material.

A.6 Handling and distribution of chemical reference substances

The handling, distribution and use of established chemical reference substances must ensure that their integrity is safeguarded and maintained throughout their period of use.

A.6.1 Packaging operations

Appropriate GMP requirements (6) should be observed. The various stages in packaging chemical reference substances should be clearly defined and controlled, to avoid contamination of the sample, mislabelling of containers, or any other event which might result in mishandling or mismanagement.

Containers for chemical reference substances should protect their contents from moisture, light and oxygen and must be tested for permeability to moisture. Additional measures may be necessary to ensure long-term integrity and stability. Most chemical reference substances, however, are conveniently supplied in moisture-proof containers which should be uniform in type and size to facilitate distribution. The lack of permeability to moisture and the compatibility of the material of which the closure is made with the chemical reference substance are important factors in determining the suitability of container closure systems. The best containers for chemical reference substances from the point of view of stability are sealed glass ampoules, but these have certain disadvantages. There is a risk of contaminating the substance with glass particles when the ampoules are opened.

It is preferable to restrict the quantity of reference substance held in each container to that required to perform the test(s). The use of multidose containers is not excluded, but is not recommended.

Before undertaking any packaging operations, the health hazards of the item to be packaged should be assessed using suitable information sources, e.g. the material safety data sheet. Appropriate precautions should be taken to protect the person(s) handling the chemical reference substance.

The packaging of a batch of a chemical reference substance into containers is a small-scale operation for which suitable equipment is not always available to the manufacturer of the material. Therefore, the packaging of chemical reference substances is usually undertaken by the responsible issuing body. Screw-type feeders have been constructed, but generally the packaging of chemical reference substances is carried out manually. Substances which are expensive or available only in very small quantities

may have to be divided between containers in solution and then lyophilized, or evaporated to dryness.

Some chemical reference substances must be packaged under an inert gas or in conditions of controlled humidity. Therefore, the use of a glove-box or an air-tight cabinet is necessary. Single-use vials can be used for hygroscopic materials.

A.6.2 Storage

Information about suitable storage conditions can often be obtained from the manufacturer of the source material and should be requested routinely when a new chemical reference substance is established. Theoretically, the stability of the substances should be enhanced by keeping them at low temperatures but, for substances that contain water, storage below 0 °C may impair the stability. It should also be remembered that the relative humidity in normal refrigerators or cold rooms may be high and, unless ampoules or other tightly closed containers are used, the improvement in stability may be more than offset by degradation due to the absorption of moisture. Storage at about 5 °C, with precautions to prevent such absorption, has proved satisfactory for most chemical reference substances. Vials should, however, not be opened until they have attained room temperature to prevent ingress of moisture by condensation.

A.6.3 Stability

A chemical reference substance is an integral part of the drug specification. Thus, if the reference substance deteriorates, this will change the specification of the drug. It is, therefore, of the utmost importance that the stability of chemical reference substances is monitored by regular re-examination and that they should be replaced as soon as a significant change in a property is noted.

The definition of a “significant change” differs according to the intended use of the chemical reference substance. Several per cent of degradation products found in a substance may not impair the usefulness of the material in identification tests. For chemical reference substances that are used in chromatographic assays, however, even small amounts of impurities may be unacceptable. When establishing a chemical reference substance, consideration must be given to its intended use and to the performance characteristics of the analytical methods in which it will be used. The tolerable degree of degradation will differ from case to case but should be predefined.

Laboratories in charge of collections of chemical reference substances should have a system for regular re-examination of the materials in stock. The frequency of re-testing may be modified according to need. It must be borne in mind that the stability of a specially prepared chemical reference substance may not always be the same as that of commercial samples of the same material.

The selection of suitable analytical methods for monitoring the stability of chemical reference substances depends on the nature and intended use of the substance. A substance used solely for identification purposes will normally only require demonstration that it is still suitable for this use, e.g. that the IR spectrum is identical to that obtained during establishment. If substances are employed for other purposes, the testing must be more extensive, but should use methods which are rapid and sensitive so as not to consume too much of the existing stock. In many cases it is important to check that there has been no significant uptake of moisture, which could result in degradation by hydrolysis and/or a decrease in the assigned content of the substance. Chromatography is employed extensively, as are absolute methods such as differential scanning calorimetry where applicable. Changes in the impurity profile or purity determination usually mean that the batch must be replaced. Changes which compromise the integrity of the batch indicate that it should immediately be withdrawn from use. Sometimes a batch of a chemical reference substance will discolour or otherwise change in appearance. Steps should be taken to replace this substance whether or not the results of subsequent analyses indicate significant degradation. Such changes in physical appearance reduce the confidence of the user in the suitability of the chemical reference substance. Appropriate testing of active bulk substance should be carried out before further dispensing into vials or ampoules.

A.6.4 Information to be supplied with chemical reference substances

The labels on chemical reference substances should give the following information:

- the appropriate name of the substance: the international nonproprietary name (INN) should be used wherever possible;
- the name of the issuing body;
- the approximate quantity of material in the container; and
- the batch or control number.

Where associated documents are provided they should incorporate relevant items from the list above. The following information should be given, as necessary, on the labels and/or in associated documents:

- the name and address of the issuing body;
- the recommended storage conditions (if special conditions apply);
- the intended use of the chemical reference substance;
- directions for use (e.g. storage and handling);
- information about the assigned analytical value of the chemical reference substance (needed for calculation of the results of tests in which the substance will be used);
- a disclaimer of responsibility in cases where chemical reference substances are misused, or stored under inappropriate conditions, or used for purposes other than those intended by the issuing body; and
- health hazard information or warnings in conformity with national and regional regulations or international agreements.

If analytical data are to be supplied with the chemical reference substances, it is recommended that the data provided be limited to what is necessary for the proper use of the substances in the tests and assays.

A.6.5 Distribution and supply

Distribution of chemical reference substances within the same country usually does not present problems. However, when samples are to be sent to other countries, both the sender and the receiver of the goods may encounter difficulties because of the vagaries of postal and customs regulations, e.g. the application of special procedural requirements applicable to substances under international control. Distributors of chemical reference substances waste considerable resources in seeking information on different international import regulations, and in completing the required forms. A way of reducing such difficulties and barriers to effective distribution of chemical reference substances should be sought. There should be a minimum of delay in providing the chemical reference substances to the users, and the most speedy means of transport should be chosen.

A.6.6 Period of use

Chemical reference substances do not carry an “expiry date” in the conventional sense. To avoid the unnecessary discarding of satisfactory substances, a mechanism for general control of the batch of a chemical reference substance may be used by the issuing body. If the issuing body applies stability considerations and a monitoring procedure to its collection based on its experience, this should be a guarantee to the user of the acceptability of the chemical reference substance for its intended use.

Whenever a batch of primary reference standards needs to be replaced, the issuing body should, wherever practical, allow for a transition period.

If, exceptionally, it is considered necessary to specify an expiry or re-test date, this should be stated on the label and/or in a document accompanying the chemical reference substances. Adequate shipping records should be kept to enable contact to be made with the purchaser of a batch for recall or other notification.

The storage and maintenance of unopened containers of the chemical reference substance in accordance with the information provided are integral to its suitability for use. To avoid potential doubts concerning the integrity of opened containers, it is suggested that potential users obtain only the quantities of substances necessary to meet their short-term needs and to obtain fresh stocks (held under controlled and known conditions) when required. Long-term storage of substances in opened containers should be avoided. Similarly, efforts should be made to avoid possible degradation, contamination and/or introduction of moisture during the repeated use of portions of a substance from the same container.

Part B.

Secondary chemical reference substances

This new Part B is intended to apply to secondary reference substances supplied as “official”, e.g. regional or national standards. In principle, secondary reference standards prepared by manufacturers can be prepared as “working standards” using the same procedures.

B.1 Assessment of need

The establishment of a secondary chemical reference substance, calibrated against a primary reference standard substance, may be desirable for various practical reasons, e.g. the primary standard may not be available in adequate quantities to supply all local needs. Moreover, the availability of such secondary chemical reference substances (for example, on a regional basis) would reduce the cost and the delay in receiving the reference material.

The body that establishes a secondary chemical reference substance for national or regional use should be clearly defined by the appropriate regional or national drug regulatory authority. The traceability between the secondary and the primary chemical reference substance must be documented.

B.2 Obtaining source material

B.2.1 Selection of candidate substance

When it is intended to establish a secondary reference substance for use as an assay standard for the determination of the content of the drug substance itself or in a drug formulation, a source(s) of pharmaceutical grade substance(s) is (are) identified. Availability of the required quantity is assured. The guidelines given in Section 2 of Part A also apply in this case. If a substance is intended to be used as an impurity standard, the candidate material may be obtained from commercial suppliers, provided that the percentage purity is more than 95% (or 90% if for use in TLC).

B.2.2 Documentation to be supplied with the candidate reference substance

The supplier of the candidate reference substance is requested to supply the same documentation as required for a candidate primary reference substance (see Section 2, Part A).

B.2.3 Initial testing for compliance with the requirements of the monograph

The coordinating laboratory is responsible for verifying that the candidate reference substance complies with the requirements of the monograph, where applicable. In such a case compliance is a prerequisite to proceeding to the interlaboratory study to assign the content of the secondary standard.

B.3 Packaging

See Section 6.1 in Part A of these guidelines.

B.4 Interlaboratory testing to establish the assigned content

Having demonstrated the suitability of the substance, the content value is assigned on the basis of the results generated by an interlaboratory trial. At least three laboratories participate in testing the proposed substance (10).

B.4.1 Competence of the participating laboratories

Participating laboratories will have demonstrated their adherence to the concepts of an appropriate quality management system (9–12).

B.4.2 Dispatch of the candidate materials

The proposed secondary reference substance is packaged in appropriate unit quantities. The quantity of each unit is dependent on the intended use. The proposed substance and the primary reference substance are dispatched to the participating laboratories in sufficient amounts for replicate analysis as required by the test protocol. The participating laboratories are instructed to record any abnormalities observed with the proposed substance. The packaging facilities are adequate and environmental conditions are controlled to ensure the integrity of the material throughout the packaging process.

The following documents should be supplied with the material:

- test protocol;
- test result report form;
- health and safety information; and
- information on the primary chemical reference substance.

B.4.3 Test protocol

While the testing of primary chemical reference substances employs different analytical methods in a collaborative study, an alternative approach is normally applied to the testing of a secondary chemical reference substance. Since most secondary reference substances are established to determine the content of the drug substance itself (for which a pharmacopoeial monograph exists) and/or the amount of the drug substance contained in a pharmaceutical preparation, it is essential to use the method specified in the relevant pharmacopoeia to obtain the assigned value.

The coordinating laboratory prepares the testing protocol, including predefined acceptance criteria of the results. The protocol clearly describes each step of the procedure and includes data reporting sheets. The experimental design of the interlaboratory study is such that the results are statistically evaluated to assign a content with an acceptable confidence interval in relation to the permitted limits of content as set in the definition. Both the number of independent replicate determinations to be performed and acceptance criteria to be applied are predefined.

B.4.4 Evaluation of test results

Test results submitted by the participating laboratories are evaluated in accordance with the criteria set out in the protocol. The data submitted by each laboratory are tested statistically for “outliers” and for conformity with the system suitability criteria. Apparent “outliers” are investigated by the laboratory concerned, remedial action taken, and the analysis repeated. If a valid reason is discovered for the “outliers” then these are excluded from the statistical evaluation.

The mean and confidence interval are then calculated. The reference value is assigned using the mean of the laboratory means.

B.4.5 Traceability

The term for “traceability”, for the purposes of this document, is defined as the property of a result of measurement which can be related to the appropriate standards, generally international or national standards, through an unbroken chain of comparison. In other words, when the result of a measurement is described as traceable, it is essential to specify to what (value of) “appropriate standards” traceability has been established.

The assigned value of a secondary chemical reference substance is traceable to the relevant primary reference substance. In the context of WHO quality

specifications the relevant primary chemical reference substance is usually the ICRS established for use with *The International Pharmacopoeia*. In other contexts the relevant primary chemical reference substance will be the reference substance established for use with another internationally recognized pharmacopoeia (e.g. the European Pharmacopoeia chemical reference substances (Ph.Eur CRS), British Pharmacopoeia chemical reference substances (BPCRS), or the United States Pharmacopoeia reference substances (USPRS)).

B.5 Adoption of the secondary reference substance

The report of the collaborative trial to establish the secondary reference standard is submitted to the appropriate national or regional body to approve the secondary standard for the uses described.

B.6 Retesting programme

See also Section 6.3 in Part A of these guidelines.

A system must be in place to ensure the continued fitness for use of the reference substances. Normally, a re-test programme is applied.

Reference substances are regularly tested for stability during their storage. A testing programme is applied which is designed to detect any sign of decomposition at an early stage using appropriate analytical techniques. The methods employed are suitable for small quantities, are both rapid and sensitive, and will have been performed during the establishment phase.

The frequency and extent of re-testing reference substances depends on a number of factors including stability, container and closure system, storage conditions, hygroscopicity, physical form and intended use. The frequency of testing and the testing methods to be employed for each reference substance must be documented.

Reference substances should preferably be subdivided and presented as single-use units. However, if the reference substance is kept in a multiuse container then re-testing will need to be more frequent because there is a greater risk of the uptake of moisture and/or decomposition of the reference substance. The testing methods should include the determination of water content and decomposition products. The maximum permitted variation from the assigned value should be predefined and if exceeded the batch should be re-established or replaced.

If the batch of primary reference substance used to calibrate the secondary reference substance is replaced, the secondary reference substance must be recalibrated against the new batch of the primary reference substance.

B.7 Information to be supplied with secondary chemical reference substances

For details of the information to be supplied see Section 6.4 of Part A of these guidelines: “Information to be supplied with chemical reference substances”.

B.8 Period of use

The expiry date is not indicated for secondary reference substances because the substances comply, where applicable, with the requirement of the pharmacopoeial monograph and are monitored regularly according to the re-testing programme. The issuing body should have effective means of communication to inform users of the validity of reference substances. It is recommended that only an amount sufficient for immediate use be purchased, and that the substances are used as soon as possible. Once the container has been opened efforts should be made to avoid possible degradation, contamination and/or introduction of moisture and/or exposure to air.

B.9 Distribution and supply

The distribution of secondary reference substances is carried out in such a manner as to maintain the integrity of the substance and avoid unnecessary delay in delivery to the users. The following factors are taken into account:

- conformity with safety and transport requirements;
- export and import procedure when the substance is to be delivered outside the country of the issuing body;
- customs regulations, e.g. special requirements applicable to substances under international control; and
- means of transportation.

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Annex 4

Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies¹

1. Introduction
2. Steps of the procedure
 - 2.1 Publication of invitation for Expression of Interest (EOI)
 - 2.2 Submission of dossiers
 - 2.3 Screening of dossiers submitted
 - 2.4 Dossier assessment
 - 2.5 Site inspection
 - 2.6 Report and outcome of evaluation
 - 2.7 Assessment results
 - 2.8 Procurement, sourcing and supply
 - 2.9 Re-evaluation
 - 2.10 Testing of samples
 - 2.11 Monitoring of complaint(s)
 - 2.12 Cost recovery
 - 2.13 Confidentiality undertaking
 - 2.14 Conflict of interest

References

Appendix

Provisions for evaluators of product dossiers and for inspectors (team members participating in site visits) within the scope of the quality assessment procedure of pharmaceutical products

¹ The procedure was first adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 2001, and is included in its thirty-seventh report (WHO Technical Report Series, No. 908), Annex 8, published in 2003.

1. Introduction

The World Health Organization (WHO) could provide United Nations agencies with advice on the acceptability, in principle, of pharmaceutical products which are found to meet WHO recommended quality standards, for purchase by such 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 pharmaceutical products meet the requirements recommended by WHO for multisource (generic) pharmaceutical products as appropriate (1) and are manufactured in compliance with good manufacturing practices (GMP) (2).

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

- reliance on the information supplied by the national drug regulatory authority (DRA);
- general understanding of the production and quality control activities of the manufacturer;
- assessment of product data and information on safety, efficacy and quality submitted by the manufacturer including product formulation, manufacture and test data and results;
- assessment of the manufacturing site(s) for consistency in production and quality control of starting materials (with specific emphasis on active pharmaceutical ingredient(s) (API(s)) and finished product through compliance with GMP;
- assessment of clinical testing units or organizations (i.e. units within the legal structure of the manufacturer and/or its affiliates performing clinical trials on the product, or third parties contracted by the manufacturer to perform one or more clinical trials on the product) for compliance with good clinical practices (GCP), good laboratory practices (GLP) and good practices for national pharmaceutical control laboratories, as appropriate;
- random sampling and testing of medicines supplied;
- distribution of the product;
- handling of complaints and recalls;
- monitoring of complaints from agencies and countries.

WHO could also collaborate with DRAs in the quality assessment. WHO recommends that manufacturers expressing interest in supplying drugs through the United Nations agencies inform the DRAs of their intention and request them to collaborate with WHO in the quality assessment process. It is recommended that the manufacturers provide the DRA with the necessary authorization to discuss the relevant product files with WHO

representatives during inspections where relevant or required (subject to appropriate confidentiality provisions, if necessary).

WHO will advise United Nations agencies of the manufacturers whose products have been found acceptable in principle for procurement through a procedure of quality assessment based on WHO recommended guidelines and standards.

2. Steps of the procedure

WHO requires information related to the manufacturing and control of the starting materials and finished product, and the manufacturing site and clinical testing units or organizations. Interested manufacturers provide this information by submitting a product file with the required information, and information as requested about the manufacturing site and clinical testing units or organizations. In addition to the evaluation of the product information submitted, inspection(s) of the manufacturing site and clinical testing units or organizations may be performed. WHO reserves the right to terminate the procedure of quality assessment of a manufacturer when the manufacturer is not able or fails to provide the required information in a specified time period, or when the information supplied is inadequate to complete the quality assessment effectively.

2.1 Publication of invitation for Expression of Interest (EOI)

At regular intervals, WHO will publish an invitation to manufacturers of specific products as identified in the invitation to submit a product dossier for evaluation in accordance with this procedure. Such an invitation will be published widely, i.e. on the WHO web site and possibly also through other media, such as the international press. The invitation should be open and transparent, inviting all manufacturers to submit the EOI for the drugs listed.

Manufacturers should submit their product dossiers with the relevant information requested, before the date specified by WHO. Guidelines developed for the submission of the dossiers will be available on the WHO web site and be sent to interested manufacturers upon request.

2.2 Submission of dossiers

Each interested manufacturer should provide the focal point indicated in the EOI with a dossier containing the required information before a specified date determined by WHO.

The information should be submitted in a format reflecting the information summarized below. Alternatively, a standard dossier, as prepared for or submitted to the DRA can be submitted, provided that it contains the information required. In such cases, a covering letter cross-referencing the information should be provided by the manufacturer.

The following aspects must be covered:

For innovator products (from manufacturers whose products are manufactured and registered in a country with a stringent DRA, including *inter alia* USA, European Union (EU)/European Economic Area (EEA) and Japan):

- a WHO-type certificate of a Pharmaceutical Product² issued by one of the regulatory authorities of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) regions together with the summary of product characteristics;
- assessment report(s) issued by the respective DRA;
- WHO-type batch certificate from the manufacturer;
- in the case that the packaging of the product is different from the one approved by the DRAs of the ICH regions, then stability testing data should be submitted;
- in the case that the formulation, strength, specifications, etc. are different from those of the product for which the WHO-type Product Certificate(s) was issued, arguments and/or data to support the applicability of the certificate(s) despite the differences should be submitted.

For multisource (generic products), the data and information to be submitted should be as described in *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products. A manual for a drug regulatory authority (1)*. and its revisions, as well as revisions of individual WHO documents that form part of this manual, including (as summarized below):

- details of the product;

² The WHO-type certificate of a Pharmaceutical Product refers to the certificate issued by the international drug regulatory authority in accordance with the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. Further information, and the full text of the WHO document "Guidelines on the implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce" can be found in the web site <http://www.who.int/medicines/>

- regulatory situation in other countries;
- API(s);
 - properties of the API(s),
 - sites of manufacture,
 - route(s) of synthesis,
 - specifications,
 - API described in a pharmacopoeia
 - API not described in a pharmacopoeia
 - stability testing;
- finished product;
 - formulation,
 - sites of manufacture,
 - manufacturing procedure,
 - specifications for excipients,
 - specifications for the finished product,
 - container/closure system(s) and other packaging,
 - stability testing,
 - container labelling,
 - product information,
 - patient information and package inserts,
 - justification for any differences from the product in the country or countries issuing the submitted WHO-type certificate(s),
 - interchangeability,
 - summary of pharmacology, toxicology and efficacy of the product.

2.3 Screening of dossiers submitted

Each dossier submitted by the manufacturer will be screened for completeness prior to being evaluated.

Dossiers that are incomplete will not be considered for evaluation. The manufacturer will be informed that an incomplete dossier has been received, and be requested to complete the dossier within a specified time period. In the event of noncompliance, the dossier will in principle be rejected on grounds of incompleteness and returned to the manufacturer.

Dossiers that are in compliance with the requirements of WHO will be retained for evaluation purposes. If warranted, based on the outcome of the evaluation of the dossier, a site inspection will be considered for:

- the manufacturing site(s) of the API(s);
- the manufacturing site(s) of the finished product; and

- the clinical testing units or organizations where one or more clinical studies on the product (e.g. bioequivalence studies) were performed.

2.4 Dossier assessment

The dossiers will be evaluated by a team of experts appointed by WHO in the field of pharmaceutical development, pharmaceuticals, bioequivalence and other appropriate related fields. Evaluators will be appointed in accordance with a standard operating procedure (SOP) established by WHO for appointment of evaluators of product information, and will be mainly from DRAs. The evaluation will be done in accordance with an (SOP) established by WHO for assessing product files based on the WHO guidelines to ensure uniformity in evaluation.

WHO will give technical support for the evaluation of product information supplied, if required.

2.5 Site inspection

Dependent on the outcome of the evaluation of the product dossier, WHO will plan and coordinate performance of inspections at the manufacturing site(s) to assess compliance with GMPs as recommended by WHO (2,3). WHO will also plan and coordinate performance of inspections at the clinical testing units or organizations where one or more clinical trials on the product have been performed to assess compliance with GCP, GLP and good practices for national pharmaceutical control laboratories (hereafter referred to as GCP/GLP), where appropriate, as recommended by WHO (4–6). The inspections will be performed by a team of inspectors consisting of experts appointed by WHO, preferably from DRA inspectorates. The experts will be competent in areas such as production and quality control, and have appropriate experience in GMP and GCP/GLP.

A WHO staff member will coordinate the team and the team members will act as temporary expert advisers to WHO. The team(s) will perform the inspections and report on the findings in accordance with SOPs established by WHO for planning and performing site inspections to ensure a standard harmonized approach.

A representative(s) of the DRA of the country of manufacture would normally be expected to accompany the team to the manufacturing and testing facility to assess the compliance with GMP and GCP/GLP.

Evaluators and inspectors must have the relevant qualifications and experience.

2.6 Report and outcome of evaluation

The evaluators and inspection team(s) will finalize a report according to the established WHO format describing the findings and including recommendations to the manufacturers. This will be communicated to the manufacturers.

If any additional information is required, or corrective action has to be taken by the manufacturer(s) or clinical testing units or organizations, WHO will postpone its final recommendations until such 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 manufacturer and WHO, an SOP established by WHO 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 manufacturer contained in this report).

2.7 Assessment results

Once WHO is satisfied that the quality assessment process is complete for the manufacturer of the relevant starting materials and/or product, and the clinical testing units or organizations, and that the product is acceptable in principle for procurement by United Nations agencies (i.e. it has been found to meet the WHO recommended standards), the product, as produced at the specified manufacturing site, will be included in the list.

Manufacturers on the list will be considered to be manufacturing the relevant listed pharmaceutical products, of acceptable quality, and in compliance with WHO recommended GMP guidelines and other recommended standards, such as described in *“Marketing authorization of pharmaceutical products with special reference to multisource (generic) products. A manual for a drug regulatory authority (1) and its revisions, as well as revisions of individual WHO documents that form part of this manual. The quality assessment is valid only for those product(s) submitted by the manufacturer in the EOI, evaluated by WHO, and appearing on the list.*

Each manufacturer receives a letter from WHO informing them of the outcome of the quality assessment process in regard of the particular products(s) of that particular manufacturer. A copy of this letter will be sent to the DRA of the country of manufacture.

This list will be compiled in accordance with an SOP established by WHO for final decision-making on inclusion in the list and will be subjected to review at least once a year. The list will be published and be included on the WHO web page.

In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, WHO will publish WHO Public Assessment Reports (WHOPAR(s)) on the products, and WHO Public Inspection Reports (WHOPIR(s)) on the manufacturers and clinical testing units or organizations that were considered to be in compliance with WHO recommended guidelines and standards. These reports will be published on the WHO web site.

2.8 Procurement, sourcing and supply

The WHO quality assessment procedure should be independent from procurement. The United Nations agencies may use the list to guide them in the sourcing of pharmaceutical products.

2.9 Re-evaluation

Requalification should be done at regular intervals. Manufacturers and suppliers will be required to communicate details to WHO of any changes that may have an impact on the safety, efficacy or quality of the product.

- Re-inspections of manufacturing sites will be done at regular intervals, as required, normally every 1–3 years, but at least once every 5 years.
- Re-inspections of clinical testing units or organizations will be done when required, as defined in the relevant WHO SOP.
- Re-evaluation of dossiers will be done as required, should any change regarding the formula, manufacturing method, manufacturing site or any other variation be implemented by the manufacturer, as defined in the relevant WHO SOP. In the absence of any changes, the dossier should be re-evaluated every 5 years.

Re-evaluation may also be done as necessary, including in the following situations:

- If any fraud or omissions by the manufacturer or clinical testing units or organizations in the initial assessment procedure or during the follow-up activities is evident in relation to the requirements, including compliance with GMP and GCP/GLP, as recommended by WHO.
- If any batch or batches of supplied product(s) are considered by WHO or one or more of the United Nations agencies or organizations not to be in compliance with the agreed specification of the product.

- 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.
- If suspension of supply is equal to or greater than one year.
- If, in the opinion of WHO, changes made in the sourcing of the API(s), formulation, manufacturing method, facility or other production or clinical testing aspects require that a re-assessment be made.

2.10 Testing of samples

Random samples of pharmaceutical product(s) supplied by listed manufacturers or suppliers, will be taken for independent testing of final product characteristics. Certificates of Analysis of final products released by the manufacturer and specifications for test methods should be provided by the manufacturer to WHO for review, on request.

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

2.11 Monitoring of complaint(s)

Complaint(s) concerning a pharmaceutical product(s) or batch of product(s) supplied by the manufacturer, communicated to WHO, will be investigated in accordance with an SOP established by WHO.

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

A copy of the report will be sent to the DRA of the country where the manufacturing site is located. The DRA could be invited to participate in the investigation of the complaint.

WHO will make a copy of the report available to the manufacturer.

2.12 Cost recovery

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

2.13 Confidentiality undertaking

The evaluators and inspectors will treat all information to which they will gain access during the evaluations and inspections, or otherwise in connection with the discharge of their responsibilities in regard to the above-mentioned project, as confidential and proprietary to WHO or parties

collaborating with WHO in accordance with the terms set forth below and those contained in the attached Provisions for evaluators of product dossiers and inspectors (team members participating in site visits) within the scope of the quality assessment procedure of pharmaceutical products.

Evaluators and inspectors will take all reasonable measures to ensure:

- that confidential information is not used for any other purpose than the evaluation/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.

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

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

2.14 Conflict of interest

Before undertaking the work, each evaluator and inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest. If based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest and it is thus deemed appropriate for the evaluator or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each evaluator and 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:

- (a) may have a vested commercial interest in obtaining access to any confidential information disclosed to him/her in the course of the evaluation/inspection activities described in this document; and/or
- (b) may have a vested interest in the outcome of the evaluation activities/inspection including, but not limited to, parties such as the manufacturers whose products are subject to evaluation or manufacturers of competing products.

Each evaluator and 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 of WHO.

All inspectors furthermore agree, that at the manufacturer's request, WHO will advise the manufacturer 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 manufacturer 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 manufacturer may object to a team member's participation in the site visit. Such an objection must be made known to WHO by the manufacturer within 10 days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel its agreement with the inspector, and the activities to be undertaken by that inspector, in whole or in part.

References

1. *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products. A Manual for a drug regulatory authority.* Geneva, World Health Organization, 1999. Regulatory support Series, No. 5 (WHO/DMP/RGS/98.5).
2. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2, 2nd updated edition. Good manufacturing practices and inspection.* Geneva, World Health Organization, 2007 (in press).
3. *Guidance for industry. Q7A guidance for good manufacturing practice for active pharmaceutical ingredients.* Rockville, MD, Center for Biologics Evaluation and Research, Food and Drug Administration, 2001 (<http://fda.gov/Cber/guidance/index.htm>).
4. *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products.* Geneva, World Health Organization, 1995. Annex 3 (WHO Technical Report Series, No. 850).
5. *Good practices for national pharmaceutical control laboratories.* Geneva, World Health Organization, 2002, Annex 3 (WHO Technical Report Series, No. 902).
6. *Handbook of good laboratory practice (GLP).* UNDP/World Bank/WHO, Special Programme for Research and Training in Tropical Diseases (TDR). Geneva, World Health Organization, 2001.

Appendix

Provisions for evaluators of product dossiers and for inspectors (team members participating in site visits) within the scope of the quality assessment procedure of pharmaceutical products

In the course of discharging your functions as an expert adviser to WHO under the attached Agreement for Performance of Work (APW), you will gain access to certain information, which is proprietary to WHO or entities collaborating with WHO, including the manufacturers of the product(s) 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:

- (a) not to use the Information for any other purpose than discharging your obligations under the above-mentioned APW; and*
- (b) 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 manufacturer(s)); or*
- (ii) was in the public domain at the time of disclosure by or on behalf of WHO (including the manufacturer(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 product(s), in which you will participate (such as the manufacturers of those products or of competing products).*

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 _____

Annex 5

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

Introduction

1. Steps of the procedure

- 1.1 Publication of invitation for Expressions of Interest
- 1.2 Submission of laboratory information
- 1.3 Screening of submitted laboratory information
- 1.4 Evaluation of the laboratory information
- 1.5 Site inspection
- 1.6 Report and outcome of evaluation
- 1.7 Results of assessment
- 1.8 Re-evaluation
- 1.9 Monitoring of complaints
- 1.10 Cost recovery
- 1.11 Confidentiality undertaking
- 1.12 Conflict of interest

References

Appendix

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

Introduction

The World Health Organization (WHO) provides United Nations agencies, on request, with advice on the acceptability, in principle, of quality control laboratories that are found to meet WHO recommended quality standards, i.e. Good Practices for National Pharmaceutical Control Laboratories (1) and good manufacturing practices (GMP) as recommended by WHO (2), for such laboratories. This is done through a standardized quality assessment procedure. The purpose of the quality assessment procedure is to evaluate whether the quality control laboratories to be used for the analysis of pharmaceutical products meet the requirements recommended by WHO for such laboratories.

Participation in the prequalification procedure is voluntary and any laboratory (private or governmental) could participate. Certification such as ISO (in terms of ISO/IEC 17025) is encouraged and will also be considered in the prequalification procedure. It is recommended that laboratories should work towards obtaining certification.

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

- 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 GMP(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 medicines on behalf of United Nations agencies inform the regulatory authorities and other networks (e.g. the Official Medicines Control Laboratories (OMCL) network) of their intention to be pre-qualified and request the regulatory authorities to collaborate with WHO in the quality assessment process.

This procedure describes a process to be followed for prequalification of quality control laboratories for use by the United Nations agencies.

1. Steps of the procedure

WHO requires information related to the activities and quality control of products in laboratories interested in being evaluated under this procedure. Interested

quality control laboratories should submit the required information about their activities as requested by WHO (see point 1.2). 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 of a laboratory when the laboratory is not able, or fails, to provide the required information within a specified time period, or when the information supplied is inadequate to complete the quality assessment effectively.

1.1 Publication of invitation for Expressions of Interest

WHO will publish, and when necessary repeat at regular intervals, an invitation to laboratories to submit an Expression of Interest (EOI) in testing pharmaceutical products as identified in the invitation on behalf of United Nations agencies. Such an invitation will be published widely, i.e. on the WHO web site and possibly also through other media, such as the international press. The invitation should be open and transparent, inviting all laboratories to submit the EOI for the tests listed.

1.2 Submission of laboratory information

Each interested laboratory should provide the specified focal point indicated in the request for EOIs and the relevant laboratory information.

Guidelines developed for the submission of EOIs and relevant information will be available on the WHO web site and be sent to interested laboratories upon request.

WHO will record the receipt of the EOI from each laboratory in a register.

If the laboratory has documented its quality system as a Quality Manual this can be submitted, provided that it is supplemented with the information required for the Laboratory Information File ((LIF), see below) that is not provided in the Quality Manual.

If there is no Quality Manual, the information should be submitted as described in the document *Guidelines for preparing a laboratory information file (LIF)* (3) and contain information on the areas listed below:

- general information
- documentation
- personnel
- handling of samples

- materials
- premises
- equipment
- contract operations and activities
- out-of-specification investigation
- self-inspection
- stability testing
- microbiological testing
- water system.

The laboratory should provide evidence of regular participation in WHO-organized or other appropriate proficiency testing schemes.

1.3 Screening of submitted laboratory information

The information 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 incomplete information has been received, and be requested to complete it within a specified time period. In the event of noncompliance with this request, the laboratory information will in principle be rejected on grounds of incompleteness and returned to the laboratory.

Laboratory information that complies with the requirements set out in section 1.2 above will be retained for evaluation purposes and the laboratory will be considered for a possible site inspection (if this is warranted, based on the outcome of the evaluation of the laboratory information).

1.4 Evaluation of the laboratory information

The laboratory information will be evaluated by WHO in accordance with a standard operating procedure established by WHO to ensure uniformity in evaluation of the information. This information is evaluated against the Guidelines for preparing a laboratory information file as described in Annex 5 of WHO Technical Report Series, No. 917 (3).

1.5 Site inspection

Depending on the outcome of the evaluation of the laboratory information, WHO will plan and coordinate inspections of the laboratory to assess compliance with “Good practices for control laboratories” as recommended

by WHO (1).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 participate in the assessment of the laboratory's compliance with WHO recommended standards for quality control laboratories.

Evaluators and inspectors must have the relevant qualifications and experience.

1.6 Report and outcome of evaluation

The inspector or inspection team will finalize a report describing the findings according to the established WHO format. These will be communicated to the laboratory and a copy will be sent to the national drug regulatory authority.

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).

1.7 Results of assessment

Once WHO is satisfied that the quality assessment process for the laboratory is complete, and that the laboratory is acceptable in principle

¹ Training modules can be found on the Prequalification web site (<http://mednet3.who.int/prequal/>).

for use by United Nations agencies (i.e. it has been found to meet the WHO recommended standards for quality control laboratories), the laboratory at the specified site will be included in a list referred to as “List of prequalified quality control laboratories”.

Laboratories on the list will be considered to be able to test products in compliance with WHO recommended 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 of the prequalified laboratories will be published and will also be included on the WHO web page. The list will be subjected to review at least once a year.

WHO will publish WHO Public Inspection Reports (WHOPIR(s)), in accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, on the laboratories considered to meet WHO standards for quality control laboratories.

1.8 Re-evaluation

Routine follow-up

- Re-inspections of laboratories will be performed at regular intervals, normally at least once every three years.
- Participation in an appropriate external quality assessment scheme is expected of the prequalified laboratories and they should provide evidence of this.

Non-routine re-evaluation

Non-routine re-evaluation may be undertaken 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 prequalification 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 prequalified quality control laboratory from the List when there is evidence of noncompliance with the WHO recommended standards for quality control laboratories.

1.9 Monitoring of complaint(s)

Complaint(s) concerning the results of analysis of pharmaceutical product(s) by the laboratory or concerning the 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 where appropriate include recommendations for action in accordance with a standard operating procedure. WHO will make a copy of the report available to the laboratory under investigation.

A copy of the report will also 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.

1.10 Cost recovery

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

1.11 Confidentiality undertaking

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

Evaluators and inspectors will take all reasonable measures to ensure:

- that confidential information is not used for any purpose other than the 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.

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

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

1.12 Conflict of interest

Before undertaking the work, each evaluator and inspector will (in addition to the above-mentioned confidentiality undertaking) be required to sign a Declaration of Interest in accordance with the terms set out below and those contained in the attached Provisions for evaluators and 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 interests and it is thus deemed appropriate for the evaluator or inspector in question to undertake this work, he or she will discharge his or her functions exclusively as adviser to WHO.

In this connection, each evaluator and inspector is required to confirm that the information disclosed by him or her in the Declaration of Interest is correct and that no situation of real, potential or apparent conflict of interests is known to him or her, including that he or 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 or her in the course of the evaluation or inspection activities described in this document; and/or
- may have a vested interest in the outcome of the evaluation or inspection.

Each evaluator and inspector will undertake to advise WHO promptly of any change in the above circumstances, including if an issue arises during the course of his or 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 10 days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel its agreement with the inspector and the activities to be undertaken by that inspector, in whole or in part.

References

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), Annex 3.
2. WHO good manufacturing practices: main principles for pharmaceutical products. In: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2*, 2nd updated edition. *Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007 (in press).
3. Guidelines for preparing a laboratory information file. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 917), Annex 5.

Appendix

Provisions for evaluators and inspectors 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 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 (herein after referred to as "the Information") as confidential and proprietary to WHO or the aforesaid parties collaborating with WHO. In this connection, you agree:

- (a) not to use the Information for any other purpose than discharging your obligations under the above-mentioned APW; and*
- (b) 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 advise WHO promptly 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 _____

Annex 6

Guidance on variations to a prequalified product dossier

Preface

This guidance document was technically and structurally inspired by the *Guideline on dossier requirements for type IA and IB notifications*.¹ It is intended to provide information on how to present an application to implement a change to a prequalified product.

References to compendial monographs (*British Pharmacopoeia* (BP), *International Pharmacopoeia* (Ph Int), *Japanese Pharmacopoeia* (JP), *European Pharmacopoeia* (Ph Eur) or *United States Pharmacopoeia* (USP)) or to guidelines (WHO, International Conference on Harmonisation (ICH)-region and associated countries) are included to assist applicants. However, it remains the applicant's responsibility to ensure that the most recent revisions of all relevant legislation and guidelines are taken into account in the preparation of each part of their dossier. The guidelines referred to in each section provide useful information on the content expected in that section. However, this list should not be regarded as exhaustive.

Where a variation requires consequential revision of the summary of product characteristics (SmPC), labelling and package leaflet or insert, this is considered as part of the variation.

This guidance document is applicable only to active pharmaceutical ingredients (APIs) and excipients manufactured by chemical synthesis or semisynthetic processes and finished pharmaceutical products (FPPs) containing such APIs and excipients. Variations to a biological API and/or biological excipient, or to biological finished products are assessed as major changes. In such a case the applicant should refer to guidance documents

¹ Guideline on dossier requirements for type IA and IB notifications (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/var_type_1a1b_guideline_06-2006.pdf).

that specifically address biological APIs, excipients and finished products (e.g. ICH Q5A (R1), Q5B, Q5C, Q5D, Q5E, Q6B).²

This guidance document applies to multisource (generic) FPPs that have been prequalified by WHO. Whenever FPPs have been prequalified on the basis of approval by a drug regulatory authority of the ICH region and associated countries (innovator products or generic products) subsequent applications for variations also need to be approved by the same drug regulatory authorities and WHO should be notified of the approval of the changes. Applicants are advised to refer to the Letters of Prequalification.

Introduction

The listing of a product on the list of prequalified products that have been found acceptable, in principle, for procurement by United Nations agencies, is a temporary status given for a defined period of time as described in detail in the general procedure.³ An application for renewal is required before expiry, resulting in a submission and a review of an updated dossier as part of the procedure within the prequalification project.

Irrespective of these regular reviews by WHO a prequalified supplier is responsible for the prequalified product throughout its life and is, therefore,

² ICH Q5A (R1): *Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin* (<http://www.ich.org/LOB/media/MEDIA425.pdf>).

ICH Q5B: *Quality of biotechnological products: analysis of the expression construct in cells used for production of r-DNA derived protein products* (<http://www.ich.org/LOB/media/MEDIA426.pdf>).

ICH Q5C: *Quality of biotechnological products: stability testing of biotechnological/biological products* (<http://www.ich.org/LOB/media/MEDIA427.pdf>).

ICH Q5D: *Derivation and characterisation of cell substrates used for production of biotechnological/biological products* (<http://www.ich.org/LOB/media/MEDIA429.pdf>).

ICH Q5E: *Comparability of biotechnological/biological products subject to changes in their manufacturing process* (<http://www.ich.org/LOB/media/MEDIA1196.pdf>).

ICH Q6B: *Specifications: test procedures and acceptance criteria for biotechnological/biological products* (<http://www.ich.org/LOB/media/MEDIA432.pdf>).

³ *Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies Revised Procedure.* in: *Forty-first report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.* Geneva, World Health Organization, 2007, Annex 4. (http://mednet3.who.int/prequal/info_general/documents/ppdoc2.pdf).

required to take into account technical and scientific progress. He or she is required to make any amendment that may be required to enable the prequalified product to be manufactured and checked by means of generally accepted scientific methods. Suppliers of prequalified products may also wish to alter or to improve the medicinal product or to introduce an additional safeguard.

The prequalification project is, therefore, considered dynamic, taking into account that changes to the original dossier that was used for prequalification of the product may become necessary during the lifetime of the product. Any changes to prequalified products (variations) may involve administrative and/or more substantial changes and are subject to approval by WHO.

Procedures for the implementation of the different types of variations need to be set out to facilitate the task of both suppliers and WHO and to guarantee that variations to the medicinal product do not give rise to public health concerns.

The following definitions may be used to classify changes:

- A *minor change* is one of the variations listed in Appendix 1 of this guidance.
- A *major change* is a change to the documentation which can neither be deemed to be a minor variation within the meaning of the above definition (being of greater significance than a minor change) nor to be a change for which the submission of a new dossier would be necessary (Appendix 2).

Approval of changes

Of the minor changes listed in Appendix 1 of this document, some are classified by the letter N and can be considered as notifications. Applications for minor changes that are so classified must provide evidence to fulfil the conditions and documentation requirements listed. These notifications will be evaluated by WHO within a period of 3 months and can be considered approved if no correspondence with the applicant has been initiated by WHO within that time. If the validity of the notification cannot be acknowledged by WHO, correspondence with the applicant will be started and a further period of 3 months must be allowed to elapse by the applicant upon submission of his or her response documents.

For all other change applications that are not considered as notifications, prior approval by WHO is always necessary before the changes can be implemented.

Certain changes are so fundamental that they alter the terms of the prequalified dossier and consequently cannot be considered as a “change”. In such cases a new dossier must be submitted (Appendix 3).

In order to facilitate the classification of changes, the appendices explicitly define the various types of changes:

- Appendix 1 lists minor changes classified by the type of change and the conditions which frame the type of change. When the conditions are not met, the change may either be classified as a major change or may make a new application necessary.
- Appendix 2 lists examples of major changes.
- Appendix 3 lists the types of changes which make a new application necessary.
- Appendix 4 lists the stability requirements for variations and changes to prequalified FPPs.

Glossary

Biological pharmaceutical product

A product, the API of which is a biological substance.

Biological API

A substance that is produced by or extracted from a biological source and for which a combination of physicochemical–biological testing and the production process and its control is needed for its characterization and the determination of its quality.

Finished pharmaceutical product (FPP)

The acronym FPP always represents a pharmaceutical product after final release (manufacturing control release, quality control release, packaging control release).

GuideGeneric

Guideline on submission of documentation for prequalification of multisource (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis (GuideGenericRev1_Final.doc). Available at: http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

GuideGeneric supplement 1

Supplementary, separate document 1 (dissolution requirements) to the Guideline on submission of documentation for prequalification of multisource (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis (GuideGeneric-Dissolution_Suppl1.doc). Available at: http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_Supplement1_08_2005.pdf

GuideGeneric supplement 2

Supplementary, separate document 2 (stability implications) to the Guideline on submission of documentation for prequalification of multisource (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis (GuideGeneric_Suppl2.doc). Available at: http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_Supplement2.pdf

Test procedure

Analytical procedure.

Limits

Acceptance criteria.

Validation protocol

Validation scheme, validation plan.

Appendix I

Dossier requirements for minor changes to prequalified products

This guide has been prepared to clarify what documentation should be submitted with regard to each type of minor change. The applicant is also asked to check whether other guidance documents (Prequalification guidelines, WHO guidelines, guidelines of the ICH region and associated countries) are also applicable. If the change also implies a change in the pharmaceutical particulars in the SmPC, labelling and/or package leaflet or insert, this also forms part of the change.

The titles of the changes are numbered and subcategories are depicted by letters and numbers. The conditions necessary for a given change are outlined for each subcategory and listed below each change.

In principle, all parts of the dossier that are affected by a variation need to be resubmitted according to the structure of the pharmaceutical quality information form (PQIF)⁴ (the structure/relevant parts of the dossier is/are also covered in the “*Guideline on submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis*”)⁵. Moreover, any further documentation required for a particular change is identified.

Applicants should present a summary of the intended change in tabular form in which the current state/situation and the situation after the intended change are compared to outline the scope of the change in a transparent manner. A justification for the introduction of the change should always follow.

Applicants should be aware that submitting redundant or irrelevant information may hamper approval procedures. Deficient documentation can lead to non-validation or rejection of the change.

1	Change in the name and/or address of the supplier of the prequalified product	Conditions to be fulfilled	Documentation to be supplied	
		1	1	N

⁴ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

⁵ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

Conditions

1. The supplier of the prequalified product shall remain the same legal entity.

Documentation

1. A formal document from a relevant official body (e.g. the national drug regulatory authority (DRA)) in which the new name and/or address is mentioned.

2	Change in the name of the finished pharmaceutical product (FPP)	Conditions to be fulfilled	Documentation to be supplied
		1	1, 2

Conditions

1. No confusion with the International Nonproprietary Name (INN).

Documentation

1. A formal document from the national drug regulatory authority (DRA) in which the new name is approved.
2. Replacement of the relevant pages of the dossier according to the structure as listed in the PQIF.⁶

3	Change in the name and/or address of a manufacturer of the active pharmaceutical ingredient (API) where no European Pharmacopoeia certificate of suitability (CEP) is available	Conditions to be fulfilled	Documentation to be supplied	
		1	1, 2	N

Conditions

1. The manufacturing site shall remain the same.

Documentation

1. A formal document from a relevant official body (e.g. DRA) in which the new name and/or address is mentioned.

⁶ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

2. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.

4	Change in the name and/or address of a manufacturer of the finished pharmaceutical product (FPP)	Conditions to be fulfilled	Documentation to be supplied	
		1	1, 2	N

Conditions

1. The manufacturing site shall remain the same.

Documentation

1. Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. DRA) in which the new name and/or address is mentioned.
2. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.⁷

5	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FPP	Conditions to be fulfilled	Documentation to be supplied	
a)	Secondary packaging for all types of pharmaceutical forms	1, 2	1, 2, 5	N
b)	Primary packaging site			
	1. Solid pharmaceutical forms, e.g. tablets and capsules	1, 2, 3	1, 2, 5	N
	2. Semisolid or liquid pharmaceutical forms	1, 2, 3	1, 2, 5	
	3. Liquid pharmaceutical forms (suspensions, emulsions)	1, 2, 3, 4	1, 2, 4, 5	
c)	All other manufacturing operations except batch release	1, 2, 4	1, 3, 4, 5, 6, 7, 8, 9	

⁷ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

Conditions

1. Satisfactory inspection in the last 3 years either by WHO or a drug regulatory authority (DRA) in the International Conference on Harmonisation (ICH) region and associated countries.
2. Site appropriately authorized by a DRA (to manufacture the pharmaceutical form and the product concerned).
3. Product concerned is not a sterile product.
4. Validation protocol is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production-scale batches.

Documentation

1. Proof that the proposed site is appropriately authorized for the pharmaceutical form and the product concerned:
 - a copy of the current manufacturing authorization, a GMP certificate or equivalent document issued by the DRA; and
 - a GMP statement or equivalent issued by WHO or a drug regulatory authority (DRA) in the International Conference on Harmonisation (ICH) region and associated countries.
2. The date of the last satisfactory inspection of the packaging facilities by WHO or the drug regulatory authority (DRA) in the International Conference on Harmonisation (ICH) region and associated countries must have taken place within the last 3 years.
3. Date and scope (indicate if product-specific, if related to a specific pharmaceutical form, etc.) of the last satisfactory inspection.
4. The batch numbers of batches (≥ 3) used in the validation study and the validation protocol (scheme).
5. Clear identification of the “prequalified” and “proposed” finished product manufacturers in the variation application.
6. Copy of prequalified release and end-of-shelf-life specifications.
7. Batch analysis data of three production batches and comparative data on the last three batches from the previous site.
8. For semi-solid and liquid formulations in which the API is present in a non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.

9. For solid dosage forms, data from comparative dissolution tests (refer to Supplement 1⁸ of the *Guideline on submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis*) with demonstration of similarity of dissolution profile, performed on the last three batches from the previous site and the first three batches from the new site should be submitted.

6	Change to quality control testing of the finished product	Conditions to be fulfilled	Documentation to be supplied	
	Replacement or addition of a site where batch control/testing takes place	1, 2	1, 2, 3	N

Conditions

1. The site is appropriately authorized by the DRA.
2. Transfer of the method from the old to the new site or to the new test laboratory has been successfully completed.

Documentation

1. The letter that accompanies the application for approval should clearly outline the “prequalified” and “proposed” quality control sites.
2. Documented evidence that the site is appropriately authorized by the DRA.
3. Documented evidence that the transfer of the method from the old to the new site or to the new test laboratory has been successfully completed.

7	Deletion of any manufacturing site (including for an API, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place)	Conditions to be fulfilled	Documentation to be supplied	
		None	1	N

Conditions

None

⁸ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_Supplement1_08_2005.pdf

Documentation

1. The letter that accompanies the application for approval should clearly name the manufacturer to be deleted.

8	Minor change in the manufacturing process of the API	Conditions to be fulfilled	Documentation to be supplied
		1, 2	1, 2, 3

Conditions

1. No change in qualitative and quantitative impurity profile or in physicochemical properties.
2. The route of synthesis remains the same, i.e. intermediates remain the same.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF⁹ and of the prequalified drug master file (where applicable), including a direct comparison of the prequalified process with the new process.
2. Batch analysis data (in comparative tabular format) from at least two batches (minimum pilot scale) manufactured according to the prequalified and the proposed process.
3. Copy of prequalified specifications of the API.

9	Change in batch size of API or intermediate	Conditions to be fulfilled	Documentation to be supplied	
a)	Up to 10-fold increase compared to the prequalified batch size	1, 2, 3	1, 2	N
b)	Downscaling	1, 2, 3, 4	1, 2	N
c)	More than 10-fold increase compared to the prequalified batch size	1, 2, 3	1, 3, 4	

⁹ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

Conditions

1. No changes to the manufacturing methods other than those necessitated by scale-up, e.g. use of different sized equipment.
2. Test results of at least two batches according to the specifications should be available for the proposed batch size.
3. The change does not affect the reproducibility of the process.
4. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.¹⁰
2. The batch numbers of the tested batches that have the proposed batch size.
3. Batch analysis data (in a comparative tabular format) on a minimum of one production batch manufactured to both the prequalified and the proposed size. Batch data on the next two full production batches should be available on request and reported immediately to WHO if outside specifications (OoS) with details of proposed action.
4. Copy of prequalified specifications of the API (and of the intermediate, if applicable).

10	Change in the specification of an API, a starting chemical material/intermediate/reagent used in the manufacturing process of the API	Conditions to be fulfilled	Documentation to be supplied	
a)	Tightening of specification limits	1, 2, 3	1, 2	N
		2, 3	1, 2	
b)	Addition of a new test parameter to the specification of:			
	1. an API	2, 4	1, 2, 3, 4, 5, 6	
	2. a starting chemical material/intermediate/reagent	2, 4	1, 2, 3, 4	

¹⁰ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPs_08_2005_ANNEX8.doc

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the assessment procedure prior to prequalification or *a major change* procedure after prequalification).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of prequalified limits.
4. Any new test method does not concern a novel nonstandard technique or a standard technique used in a novel way.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.¹¹
2. Comparative table of prequalified and proposed specifications.
3. Details of any new analytical method and validation data.
4. Batch analysis data (in a comparative tabular format) on a minimum of two production batches of the relevant substance for all tests in the new specification manufactured to both the prequalified and the proposed specifications. (Batch data on the next two full production batches should be available on request or reported if outside specification (OoS) with details of the proposed action.)
5. Where appropriate, comparative dissolution profile data for the finished product on at least one batch containing the API complying with the prequalified and the proposed specification.
6. Justification for not submitting a new bioequivalence study according to the current WHO guideline, in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, 2006, Annex 7* (WHO Technical Report Series, No. 937) and Good Clinical Practices.¹²

¹¹ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

¹² http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=359.

11	Change in test procedure for API or starting chemical material, intermediate, or reagent used in the manufacturing process of the API	Conditions to be fulfilled	Documentation to be supplied	
a)	Minor changes to a prequalified test procedure	1, 2, 3	1	N
b)	Other changes to a test procedure, including replacement or addition of a test procedure	2, 3, 4	1, 2	

Conditions

1. The method of analysis should remain the same (e.g. a change in column length or temperature is acceptable, but a different type of column or method is not); no new impurities are detected.
2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.
3. The results of method validation show the new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel nonstandard technique or a standard technique used in a novel way.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF,¹³ which includes a description of the analytical methodology, a summary of validation data and revised specifications for impurities (if applicable).
2. Comparative validation results showing that the prequalified test and the proposed one are equivalent (please refer to guideline ICH Q2 (R1)).¹⁴

¹³ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

¹⁴ ICH Q2 (R1): *Validation of analytical procedures: text and methodology* (<http://www.ich.org/LOB/media/MEDIA417.pdf>).

12	Change in the manufacturer of the API or final (ultimate) key intermediate in the manufacturing process of the API	Conditions to be fulfilled	Documentation to be supplied
a)	Change in site of the already prequalified manufacturer (replacement or addition)	1, 2	1, 2, 3, 4, 5
b)	New manufacturer (replacement or addition)	1, 2	1, 2, 3, 4, 5

Conditions

1. The specifications (including in-process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already prequalified.
2. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current WHO *Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products*¹⁵ or the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*¹⁶ or an equivalent guideline of the ICH region and associated countries.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.
2. A declaration from the supplier of the prequalified FPP that the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already prequalified.
3. Either a transmissible spongiform encephalopathy (TSE) European Pharmacopoeia certificate of suitability for any new source of material or, where applicable, documentary evidence that the specific source of the material that carries a risk of TSE has previously been assessed by the competent authority and shown to comply with the current WHO

¹⁵ http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

¹⁶ (EMA/410/01rev 2; note that rev 3 is in the consultation phase) <http://www.emea.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf>

*Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products*¹⁷ or the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*¹⁸ or an equivalent guideline of the ICH region and associated countries.

4. Batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the API from the prequalified and proposed manufacturers/sites.
5. The application should clearly outline the “prequalified” and “proposed” manufacturers.

13	Submission of a new or updated European Pharmacopoeia certificate of suitability for an API or starting chemical material/reagent/intermediate in the manufacturing process of the API	Conditions to be fulfilled	Documentation to be supplied	
a)	From a prequalified manufacturer	1, 2, 4	1, 2, 3, 4	N
b)	From a new manufacturer (replacement or addition)			
	1. Sterile substance	1, 2, 3, 4	1, 2, 3, 4	
	2. Other substances	1, 2, 3, 4	1, 2, 3, 4	N

Conditions

1. The finished product release and end-of-shelf-life specifications remain the same.
2. Unchanged additional (to European Pharmacopoeia) specifications for impurities and product-specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3. The API will be tested immediately prior to use if no retest period is included in the European Pharmacopoeia certificate of suitability or if data to support a retest period is not provided.
4. The manufacturing process of the API, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.

¹⁷ http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

¹⁸ (EMA/410/01 rev 2; note that rev 3 is in the consultation phase) <http://www.emea.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf>

Documentation

1. Copy of the current (updated) European Pharmacopoeia certificate of suitability.
2. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.¹⁹
3. Where applicable, a document providing information on any materials falling within the scope of the WHO *Guideline on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products* or the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* or an equivalent guideline of the ICH region and associated countries including those which are used in the manufacture of the API. The following information should be included for each such material:
 - name of manufacturer;
 - species and tissues from which the material is derived;
 - country of origin of the source animals; and
 - its use.
4. The variation application should clearly outline the “prequalified” and “proposed” manufacturers.

Note

The reference to unchanged specifications for impurities, if applicable, in condition no. 2 should refer to new additional impurities. In change no. 8: minor change in the manufacturing process of the API, condition no. 1 stipulates that there is no change in the qualitative and quantitative impurity profile or in the physicochemical properties. In change no. 10: change in specification of API tightening of specification limits or addition of new test parameters are allowed. One of the conditions to be met for these changes to qualify as a minor change is that the change should not be the result of unexpected events during manufacture. The conditions of these changes should be borne in mind in the fulfilment of the conditions of change no. 13.

¹⁹ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

14	Submission of a new or updated TSE European Pharmacopoeia certificate of suitability for an API or starting chemical material/reagent/intermediate in the manufacturing process of the API for a prequalified manufacturer and prequalified manufacturing process	Conditions to be fulfilled	Documentation to be supplied	N
		None	1, 2, 3	

Conditions

None

Documentation

1. Copy of the current (updated) European Pharmacopoeia TSE certificate of suitability.
2. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.²⁰
3. A document providing information on any materials falling within the scope of the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*²¹ including those which are used in the manufacture of the API. The following information should be included for each such material:
 - name of manufacturer;
 - species and tissues from which the material is a derivative;
 - country of origin of the source animals; and
 - its use.

15	Change in:	Conditions to be fulfilled	Documentation to be supplied
a)	the re-test period of the API	1, 2	1, 2
b)	the storage conditions for the API	1, 2	1, 2

²⁰ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

²¹ (EMA/410/01rev 2; note that rev 3 is in the consultation phase) <http://www.emea.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf>

Conditions

1. Stability studies have been done according to the prequalified protocol (*Guideline on submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis*,²² Section 2.7.2). The studies must show that the agreed relevant specifications are still met.
2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.²³ These must contain results of appropriate real-time stability studies conducted in accordance with the relevant stability guidelines on at least two pilot or production-scale batches of the API in the prequalified packaging material and covering the duration of the requested re-test period or requested storage conditions.
2. Copy of approved specifications of the API.

16	Replacement of an excipient with a comparable excipient	Conditions to be fulfilled	Documentation to be supplied
		1, 2, 3, 4	1, 2, 3, 4, 5, 6, 7

Conditions

1. Same functional characteristics of the excipient.
2. The dissolution profile of the new product determined on a minimum of two pilot-scale batches is comparable to the old one (no significant differences regarding comparability according to the WHO Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, 2006, Annex 7* (WHO Technical Report Series, No. 937) and good clinical practices.²⁴

²² http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

²³ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

²⁴ http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=359

3. The new excipient does not include the use of materials of human or animal origin for which assessment of viral safety data is required.
4. Stability studies in accordance with the relevant guidelines have been started with at least two pilot-scale or production-scale batches and satisfactory stability data for at least 3 months (accelerated and real-time) are at the disposal of the applicant together with the assurance that these studies will be finalized. Data will be provided immediately to WHO if outside specifications or potentially outside specification at the end of the prequalified shelf-life (with details of proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF (as applicable).
2. Justification for the change/choice of excipients, etc. must be given by appropriate information from pharmaceutical development including stability aspects and antimicrobial preservation where appropriate).
3. For solid dosage forms, comparative dissolution profile data on at least two pilot-scale batches of the finished product in the new and old composition.
4. Justification for not submitting a new bioequivalence study according to the WHO Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, 2006, Annex 7 (WHO Technical Report Series, No. 937) and good clinical practices.*²⁵
5. Either a European Pharmacopoeia certificate of suitability for any new component of animal origin susceptible to TSE risk or, where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by a DRA of the ICH region and associated countries and shown to comply with the scope of the current WHO *Guideline on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products*²⁶ or the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*²⁷

²⁵ http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

²⁶ http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

²⁷ http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

or an equivalent guide of the ICH region and associated countries. The information should include the following:

- name of manufacturer;
- species and tissues from which the material is derived;
- country of origin of the source animals;
- its use; and
- evidence of its previous acceptance.

6. Data to demonstrate that the new excipient does not interfere with the finished product specification test method (if appropriate).

7. The batch numbers of the batches used in the stability studies should be given.

17	Change in specification of an excipient	Conditions to be fulfilled	Documentation to be supplied	
a)	Tightening of specification limits	1, 2, 3	1, 2	N
		2, 3	1, 2	
b)	Addition of a new test parameter to the specification	2, 4	1, 2, 3, 4, 5, 6	

Conditions

1. The change is not a consequence of any commitment from previous assessments (e.g. made during the assessment procedure prior to prequalification of the product or a major change in procedure after prequalification).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of prequalified limits.
4. Any new test method does not concern a novel nonstandard technique or a standard technique used in a novel way.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the PQIF.²⁸

²⁸ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

2. Comparative table of prequalified and proposed specifications.
3. Details of any new analytical method and summary of validation data (please refer to guideline ICH Q2 (R1)).²⁹
4. Batch analysis data on two production batches for all tests in the new specification.
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot-scale batch containing the excipient complying with the prequalified and proposed specification.
6. Justification for not submitting a new bioequivalence study according to the current WHO Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, 2006, Annex 7 (WHO Technical Report Series, No. 937) and Good Clinical Practices.*³⁰

18	Change in test procedure for an excipient	Conditions to be fulfilled	Documentation to be supplied	
a)	Minor changes to an approved test procedure	1, 2, 3	1	N
b)	Other changes to a test procedure, including replacement of a prequalified test procedure by a new test procedure	2, 3, 4	1, 2	

Conditions

1. The method of analysis should remain the same (e.g. a change in column length or temperature is acceptable, but a different type of column or method is not); no new impurities are detected.
2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.
3. Results of method validation show the new test procedure to be at least equivalent to the former procedure.

²⁹ (EMA/410/01 rev2; note that rev 3 is in the consultation phase) <http://www.ema.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf>

³⁰ ICH Q2 (R1): *Validation of analytical procedures: text and methodology* (<http://www.ich.org/LOB/media/MEDIA417.pdf>).

- Any new test method does not concern a novel nonstandard technique or a standard technique used in a novel way.

Documentation

- Replacement of the relevant pages of the dossier according to the structure listed in the PQIF³¹ which includes a description of the analytical methodology, a summary of validation data and revised specifications for impurities (if applicable).
- Comparative validation results showing that the current test and the proposed one are equivalent (please refer to guideline ICH Q2 (R1)).³²

19	Submission of a new or updated European Pharmacopoeia certificate of suitability for an excipient	Conditions to be fulfilled	Documentation to be supplied	
a)	From a manufacturer prequalified	1, 2, 3	1, 2, 3	N
b)	From a new manufacturer (replacement or addition)			
	1. Sterile substance	1, 2, 3	1, 2, 3	
	2. Other substances	1, 2, 3	1, 2, 3	N

Conditions

- The finished product release and end-of-shelf-life specifications remain the same.
- Unchanged additional (to European Pharmacopoeia) specifications for product-specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
- The manufacturing process of the excipient does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.

Documentation

- Copy of the current (updated) European Pharmacopoeia certificate of suitability.

³¹ http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=359

³² http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

2. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.
3. Where applicable, a document providing information on any materials falling within the scope of the WHO *Guideline on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products*³³ or the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*³⁴ or an equivalent guideline of the ICH region and associated countries including those which are used in the manufacture of the excipient. The following information should be included for each such material:
 - name of manufacturer;
 - species and tissues from which the material is derived;
 - country of origin of the source animals; and
 - its use.

20	Submission of a new or updated TSE European Pharmacopoeia certificate of suitability for an excipient	Conditions to be fulfilled	Documentation to be supplied	N
	From a manufacturer prequalified or a new manufacturer (replacement or addition)	None	1, 2, 3	

Conditions

None.

Documentation

1. Copy of the current (updated) TSE European Pharmacopoeia certificate of suitability.
2. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.³⁵
3. A document providing information on any materials falling within the scope of the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*.

³³ ICH Q2 (R1): *Validation of analytical procedures: text and methodology* (<http://www.ich.org/LOB/media/MEDIA417.pdf>).

³⁴ http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

³⁵ http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

*medicinal products*³⁶ including those which are used in the manufacture of the excipient. The following information should be included for each such material:

- name of manufacturer;
- species and tissues from which the material is derived;
- country of origin of the source animals; and
- its use.

21	Change in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material	Conditions to be fulfilled	Documentation to be supplied	N
		1	1, 2	

Conditions

1. Excipient and finished product release and end-of-shelf-life specifications remain the same.

Documentation

1. Declaration from the manufacturer of the material that it is purely of vegetable or synthetic origin.
2. Study of equivalence of the materials and the impact on production of the pharmaceutical product.

22	Change to comply with a major international pharmacopoeia (BP, Ph Int, JP, Ph Eur, USP)	Conditions to be fulfilled	Documentation to be supplied
	Change of specifications of a substance from a former non-major pharmacopoeia to comply with a monograph of a major international pharmacopoeia		
	a) API	1, 2	1, 2, 3, 4, 5
	b) Excipient	1, 2	1, 2, 3, 4, 5

Conditions

1. The change is made exclusively to comply with a major international pharmacopoeia.

³⁶ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

2. Unchanged specifications (additional to the pharmacopoeia) for product-specific properties (e.g. particle size profiles, polymorphic form), if applicable.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.³⁷
2. Comparative table of prequalified and proposed specifications.
3. Batch analysis data on two production batches of the relevant substance for all tests in the new specification.
4. Analysis of the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities.
5. Where appropriate, batch analysis data (in a comparative tabular format) on two production batches of the finished product containing the substance complying with the prequalified and proposed specification and additionally, where appropriate, comparative dissolution profile data for the finished product obtained on at least one pilot batch.

23	Change in the specifications of the immediate packaging of the finished product	Conditions to be fulfilled	Documentation to be supplied	
a)	Tightening of specification limits	1, 2, 3	1, 2	N
		2, 3	1, 2	
b)	Addition of a new test parameter	2, 4	1, 2, 3, 4	

Conditions

1. The change is not a consequence of any commitments from previous assessments to review specification limits (e.g. made during the assessment procedure prior to prequalification of the product or a major change procedure after prequalification).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of prequalified limits.
4. Any new test method does not concern a novel nonstandard technique or a standard technique used in a novel way.

³⁷ (EMA/410/01 rev 2; note that rev 3 is in the consultation phase) <http://www.emea.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf>

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.
2. Comparative table of prequalified and proposed specifications.
3. Details of any new analytical method and validation data (please refer to guideline ICH Q2 (R1)).³⁸
4. Batch analysis data on two batches for all tests in the new specification.

24	Change to a test procedure on the immediate packaging of the finished product	Conditions to be fulfilled	Documentation to be supplied	
a)	Minor change to a prequalified test procedure	1, 2, 3	1	N
b)	Other changes to a test procedure, including replacement or addition of a test procedure	2, 3, 4	1, 2	

Conditions

1. The method of analysis should remain the same (e.g. a change in column length or temperature is acceptable, but a different type of column or method is not).
2. Appropriate (re-)validation studies were performed in accordance with relevant guidelines.
3. Results of method validation show the new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel nonstandard technique or a standard technique used in a novel way.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF,³⁹ which includes a description of the analytical methodology and a summary of validation data.

³⁸ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

³⁹ ICH Q2 (R1): *Validation of analytical procedures: text and methodology* (<http://www.ich.org/LOB/media/MEDIA417.pdf>).

2. Comparative validation results showing that the prequalified test and the proposed one are at least equivalent (please refer to guideline ICH Q2 (R1)).

25	Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (i.e. different plastic used))	Conditions to be fulfilled	Documentation to be supplied	
		1	1	N

Conditions

1. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished product.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.⁴⁰

26	Change in the qualitative and/or quantitative composition of the immediate packaging material	Conditions to be fulfilled	Documentation to be supplied	
a)	Semisolid and liquid pharmaceutical forms	1, 2, 3, 4	1, 2, 3, 4, 5	
b)	All other pharmaceutical forms	1, 2, 3, 4	1, 4, 5	N
		1, 3, 4	1, 2, 3, 4, 5	

Conditions

1. The product concerned is not a sterile product.
2. The packaging type and material remain the same (e.g. a different blister, but same type).

⁴⁰ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

3. The relevant properties of the proposed packaging material must be at least equivalent to those of the prequalified material.
4. Relevant stability studies in accordance with the relevant guidelines have been started with at least two pilot-scale or production-scale batches, and at least 3 months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to WHO if outside specifications or potentially outside specifications at the end of the prequalified shelf-life (with details of proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.
2. Appropriate data on the new packaging (comparative data on permeability e.g. for oxygen, carbon dioxide and moisture).
3. Proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack).
4. The batch numbers of batches used in the stability studies should be indicated.
5. Comparison of the prequalified and proposed specifications, if applicable.

27	Change (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the dossier); spacer devices for metered dose inhalers are excluded	Conditions to be fulfilled	Documentation to be supplied	
a)	Deletion of a supplier	1	1	N
b)	Replacement or addition of a supplier	1, 2, 3, 4	1, 2, 3	

Conditions

1. No deletion of packaging component or device.
2. The qualitative and quantitative composition of the packaging components or device remain the same.
3. The specifications and quality control method are at least equivalent.
4. The sterilization method and conditions remain the same, if applicable.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.⁴¹
2. Data to demonstrate accuracy, precision and compatibility of the device or certification to this effect.
3. Tabulated comparison of prequalified and proposed specifications, if applicable.

28	Change to in-process tests or limits applied during the manufacture of the product	Conditions to be fulfilled	Documentation to be supplied	
a)	Tightening of in-process limits	1, 2, 3	1, 2	N
		2, 3	1, 2	
b)	Addition of new tests and limits	2, 4	1, 2, 3, 4, 5	

Conditions

1. The change is not a consequence of any commitment from previous assessments (e.g. made during the assessment procedure prior to prequalification of the product or a major change procedure after prequalification).
2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
3. Any change should be within the range of prequalified limits.
4. Any new test method does not concern a novel nonstandard technique or a standard technique used in a novel way.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.
2. Tabulated comparison of prequalified and proposed specifications.
3. Details of any new analytical method and validation data (please refer to guideline ICH Q2 (R1)).⁴²

⁴¹ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

⁴² http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

4. Batch analysis data on two production batches of the finished product for all tests in the new specification.
5. Justification for addition of new tests and limits.

29	Change in the batch size of the finished product	Conditions to be fulfilled	Documentation to be supplied	
a)	Up to 10-fold compared to the prequalified batch size	1, 2, 3, 4	1, 4	N
b)	Downscaling to 10-fold	1, 2, 3, 4, 5	1, 4	N
c)	Other situations	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5, 6	

Conditions

1. The change does not affect the reproducibility and/or consistency of the product.
2. The change relates only to standard immediate-release oral pharmaceutical forms and to non-sterile liquid forms.
3. Any changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch size, e.g. use of different sized equipment.
4. A validation protocol is available or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size in accordance with the WHO guideline on validation of manufacturing processes (Supplementary guideline on good manufacturing practices for Pharmaceutical Products: validation. Annex 4, WHO Technical Report Series, No. 937, 2006).⁴³
5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
6. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot-scale or production-scale batch and at least 3 months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to WHO if outside specifications or

⁴³ ICH Q2 (R1): *Validation of analytical procedures: text and methodology* (<http://www.ich.org/LOB/media/MEDIA417.pdf>)

potentially outside specifications at the end of the prequalified shelf-life (with details of proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.⁴⁴
2. Batch analysis data (in a comparative tabular format) on a minimum of one production batch manufactured to both the prequalified and the proposed sizes. Batch data on the next two full production batches should be available on request and should be reported immediately by the supplier of the prequalified product if outside specifications (with details of proposed action).
3. Copy of prequalified release and end-of-shelf-life specifications.
4. The batch numbers (≥ 3) used in the validation study should be indicated or validation protocol (scheme) be submitted.
5. The batch numbers of batches used in the stability studies should be indicated.
6. For solid dosage forms: dissolution profile data on a minimum of one representative production batch and comparative data on the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside dissolution profile similarity requirements.

30	Minor change in the manufacture of the finished product	Conditions to be fulfilled	Documentation to be supplied
		1, 2, 3, 4	1, 2, 3, 4, 5, 6, 7, 8

Conditions

1. The overall manufacturing principle remains the same.
2. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.
3. In case of a change in the sterilization process, the change is to a standard pharmacopoeial cycle only.

⁴⁴ http://whqlibdoc.who.int/trs/WHO_TRS_937.pdf#page=119

4. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot-scale or production-scale batch and at least 3 months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to WHO if outside specifications or potentially outside specifications at the end of the prequalified shelf-life (with details of proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.⁴⁵
2. *For semisolid and liquid products in which the API is present in non-dissolved form:* appropriate validation of the change including microscopic imaging of particles to check for visible changes in morphology, and comparative size distribution data obtained by an appropriate method.
3. *For solid dosage forms:* dissolution profile data on one representative production batch and comparative data on the last three batches from the previous process. Batch data on the next two full production batches should be available on request and should be reported immediately by the supplier of the prequalified product if outside specifications (with details of proposed action).
4. Justification for not submitting a new bioequivalence study according to the WHO Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, 2006, Annex 7* (WHO Technical Report Series, No. 937) and Good Clinical Practices.⁴⁶
5. In case of a change to the sterilization process, validation data should be provided.
6. Copy of prequalified release and end-of-shelf-life specifications.
7. Batch analysis data (in a comparative tabular format) on a minimum of one batch each, manufactured according to the prequalified and the

⁴⁵ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

⁴⁶ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

proposed process. Batch data on the next two full production batches should be made available upon request and reported immediately by the supplier of the prequalified product if outside specifications (with details of proposed action).

8. The batch numbers of batches used in the stability studies should be indicated.

31	Change in the colouring system or the flavouring system currently used in the finished product	Conditions to be fulfilled	Documentation to be supplied	
a)	Reduction or deletion of one or more components of the			
	1. colouring system	1, 2, 3, 4	1, 2, 3	N
	2. flavouring system	1, 2, 3, 4	1, 2, 3	N
b)	Increase, addition or replacement of one or more components of the			
	1. colouring system	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5	
	2. flavouring system	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5	

Conditions

1. No change in functional characteristics of the pharmaceutical form e.g. disintegration time, dissolution profile.
2. Any minor adjustment to the formulation to maintain the total weight should be made by changing the quantity of an excipient which currently makes up a major part of the finished product formulation.
3. The finished product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion or addition of an identification test.
4. Stability studies (long-term and accelerated) in accordance with relevant guidelines have been started with at least two pilot-scale or production-scale batches and at least 3 months' satisfactory stability data are at the disposal of the applicant, together with assurance that these studies will be finalized. Data should be provided immediately to WHO if outside specifications or potentially outside specifications at the end of the prequalified shelf-life (with details of proposed action). In addition, where relevant, photostability testing should be performed.

5. Any proposed new components must comply with section 3.8 of the *Guideline on submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis*.⁴⁷
6. Any new component does not involve the use of materials of human or animal origin which requires:
 - assessment of viral safety data; or
 - compliance with the current WHO Guideline on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products;⁴⁸ or
 - compliance with the note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products;⁴⁹ or
 - compliance with an equivalent guide of the ICH region and associated countries.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF⁵⁰ (if appropriate, where the end-of-shelf-life specifications have been updated).
2. The batch numbers of the batches used in the stability studies should be indicated.
3. Sample of the new product.
4. Either a European Pharmacopoeia certificate of suitability for any new component originating from an animal susceptible to TSE risk or, where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by a DRA in the ICH region or associated countries and shown to comply with the scope of the current guideline in the countries of the ICH region or associated countries. The following information should be included for each such material:
 - name of manufacturer;
 - species and tissues from which the material is a derivative;

⁴⁷ http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=359

⁴⁸ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

⁴⁹ http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

⁵⁰ (EMA/410/01 rev2; note that rev 3 is in the consultation phase) <http://www.emea.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf>

- country of origin of the source animals; and
- its use.

5. Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate.

32	Change in coating weight of tablets or change in weight of capsule shells	Conditions to be fulfilled	Documentation to be supplied	
a)	Immediate-release oral pharmaceutical forms	1, 3, 4	1, 4	N
b)	Gastroresistant, modified or prolonged release pharmaceutical forms	1, 2, 3, 4	1, 2, 3, 4	

Conditions

1. The dissolution profile of the new product determined on a minimum of two pilot-scale batches is comparable to the old one.
2. The coating is not a critical factor for the release mechanism.
3. The finished product specification has only been updated in respect of weight and dimensions, if applicable.
4. Stability studies in accordance with the relevant guidelines have been started with at least two pilot-scale or production-scale batches and at least 3 months' satisfactory stability data are at the disposal of the applicant with assurance that these studies will be finalized. Data will be provided immediately to WHO if outside specifications or potentially outside specifications at the end of the prequalified shelf-life (with details of proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.⁵¹
2. Comparative dissolution profile data on at least two pilot-scale batches of the new formulation and two production batches of the prequalified formulation (no significant differences regarding comparability to WHO Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO*

⁵¹ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

*Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, 2006, Annex 7 (WHO Technical Report Series, No. 937) and good clinical practices.*⁵²

3. Justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.
4. The batch numbers of the batches used in the stability studies should be indicated.

33	Change in shape or dimensions of the container or closure	Conditions to be fulfilled	Documentation to be supplied	
a)	Sterile pharmaceutical forms	1, 2, 3	1, 2, 3	
b)	Other pharmaceutical forms	1, 2, 3	1, 2, 3	N

Conditions

1. No change in the qualitative or quantitative composition of the container and/or closure.
2. The change does not concern a fundamental part of the packaging material, which could affect the delivery, use, safety or stability of the finished product.
3. In case of a change in the headspace or a change in the surface:volume ratio, stability studies in accordance with the relevant guidelines have been started with at least two pilot-scale or production-scale batches, and at least 3 months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that data will be provided immediately to WHO if outside specifications or potentially outside specifications at the end of the prequalified shelf-life (with details of proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF (including description, detailed drawing and composition of the container or closure material).
2. The batch numbers of the batches used in the stability studies should be indicated, where applicable.
3. Samples of the new container or closure.

⁵² http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

34	Change in the specification of the finished product	Conditions to be fulfilled	Documentation to be supplied	
a)	Tightening of specification limits	1, 2, 3	1, 2	N
		2, 3	1, 2	
b)	Addition of a new test parameter	2, 4	1, 2, 3, 4	

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the assessment procedure prior to prequalification of the product or a major change procedure after prequalification).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of prequalified limits.
4. Any new test method does not concern a novel nonstandard technique or a standard technique used in a novel way.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.⁵³
2. Tabulated comparison of prequalified and proposed specifications.
3. Details of any new analytical method and validation data (please refer to guideline ICH Q2 (R1)).⁵⁴
4. Batch analysis data on two production batches of the finished product for all tests in the new specification.

35	Change in test procedure of the finished product	Conditions to be fulfilled	Documentation to be supplied	
a)	Minor change to a prequalified test procedure	1, 2, 3, 4	1	N
b)	Other changes to a test procedure, including replacement or addition of a test procedure	2, 3, 4	1, 2	

⁵³ http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=359

⁵⁴ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

Conditions

1. The method of analysis should remain the same (e.g. a change in column length or temperature is acceptable, but a different type of column or method is not).
2. Appropriate (re-)validation studies have been performed in accordance with the relevant guidelines.
3. The results of method validation show the new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel nonstandard technique or a standard technique used in a novel way.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure in the PQIF,⁵⁵ which includes a description of the analytical methodology, a summary of validation data and revised specifications for impurities (if applicable).
2. Comparative validation results showing that the prequalified test and the proposed one are at least equivalent (please refer to guideline ICH Q2 (R1)).⁵⁶

36	Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking	Conditions to be fulfilled	Documentation to be supplied	
		1, 2	1, 2	N

Conditions

1. Finished product release and end-of-shelf-life specifications have not been changed (except those for physical appearance).
2. Any ink must comply with the relevant section (3.8 excipients) of the Guideline on submission of documentation for prequalification of

⁵⁵ ICH Q2 (R1): *Validation of analytical procedures: text and methodology* (<http://www.ich.org/LOB/media/MEDIA417.pdf>).

⁵⁶ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis.⁵⁷

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF (including a detailed drawing or written description of the current and proposed new appearance).
2. Submit a sample of the product.

37	Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass	Conditions to be fulfilled	Documentation to be supplied	
a)	Gastroresistant, modified or prolonged release pharmaceutical forms and scored tablets	1, 2	1, 2, 3, 4, 5	
b)	All other tablets, capsules, suppositories and pessaries	1, 2	1, 4	N

Conditions

1. The dissolution profile of the reformulated product is comparable to the old one.
2. Release and end-of-shelf-life specifications of the product have not been changed (except for dimensions).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF⁵⁸ (including a detailed drawing of the current and proposed situation).
2. Comparative dissolution data on at least one pilot-scale batch of the current and proposed dimensions (with no significant differences regarding comparability according to the WHO Multisource (generic)

⁵⁷ ICH Q2 (R1): *Validation of analytical procedures: text and methodology* (<http://www.ich.org/LOB/media/MEDIA417.pdf>).

⁵⁸ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, 2006, Annex 7* (WHO Technical Report Series, No. 937) and good clinical practices.⁵⁹

3. Justification for not submitting a new bioequivalence study according to the current WHO Guideline on bioequivalence.
4. Samples of the finished product.
5. Where applicable, data on breakability test of tablets at release must be given together with a commitment to submit data on breakability at the end of the shelf-life.

38	Change in pack size of the FPP	Conditions to be fulfilled	Documentation to be supplied	
a)	Change in the number of units (e.g. tablets, ampoules, etc.) in a pack			
	1. Change within the range of the prequalified pack sizes	1, 2	1, 3	N
	2. Change outside the range of the prequalified pack sizes	1, 2	1, 2, 3	
b)	Change in the fill weight/fill volume of non-parenteral multidose products	1, 2	1, 2, 3	

Conditions

1. The new pack size should be consistent with the posology and treatment duration as prequalified in the SmPC.
2. The primary packaging material remains the same.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF.⁶⁰

⁵⁹ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

⁶⁰ http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=359

2. Justification for the new pack-size, showing that the new size is consistent with the dosage regimen and duration of use as prequalified in the SmPC.
3. Written commitment that stability studies will be conducted in accordance with the WHO guidelines for products where stability parameters could be affected. Data are to be reported immediately if outside specifications (with details of proposed action).

39	Change in:	Conditions to be fulfilled	Documentation to be supplied
	a) the shelf-life of the finished product		
	1. As packaged for sale	1, 2, 3	1, 2
	2. After first opening	1, 2	1, 2
	3. After dilution or reconstitution	1, 2	1, 2
	b) the storage conditions of the finished product or the diluted/reconstituted product	1, 2	1, 2

Conditions

1. Stability studies have been done according to the prequalified protocol. The studies must show that the agreed relevant specifications are still met.
2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
3. The shelf-life does not exceed 5 years.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF. Replacement pages must contain the results of appropriate real-time stability studies conducted in accordance with the relevant stability guidelines on at least two production-scale batches of the finished product in the prequalified packaging material and/or after first opening or reconstitution, as appropriate; where applicable, the results of appropriate microbiological testing should be included.
2. A copy of the prequalified end-of-shelf-life finished product specification and, where applicable, specifications after dilution/reconstitution or first opening.

40	Addition, replacement or deletion of a measuring or administration device that is not an integrated part of the primary packaging (spacer devices for metered-dose inhalers are excluded)	Conditions to be fulfilled	Documentation to be supplied	
a)	Addition or replacement	1, 2	1, 2, 3	N
b)	Deletion	3		

Conditions

1. The proposed measuring device must accurately deliver the required dose for the product concerned in line with the prequalified posology, and results of such studies should be available.
2. The new device is compatible with the FPP.
3. The FPP can still be accurately delivered.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure listed in the PQIF⁶¹ (including description, detailed drawing and composition of the device material and supplier where appropriate).
2. Reference to CE marking for device, where applicable, or data to demonstrate accuracy, precision and compatibility of the device.
3. Samples of the new device.

⁶¹ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

Appendix 2

Major changes (examples)

Major changes exceed the scope of the minor changes listed in Appendix 1, e.g. they exceed or do not comply with the conditions to be fulfilled along with the change, but are not covered by the changes listed in Appendix 3.

They most likely consist of:

- a change in the manufacturing process of the API;
- a change in the composition of the finished product; or
- a change to the immediate (primary) packaging of the product.

It remains the applicant's responsibility to provide the relevant documentation (relevant parts of the dossier) intended to prove that the intended major change will not have an impact on the quality of the product that has been prequalified.

Appendix 3

Changes that make a new application or an extension application necessary

Changes that make a new application necessary are as follows:

Changes to the API

- change of the API to a different API;
- inclusion of an additional API in a multicomponent product;
- removal of one API from a multicomponent product;
- change in the dose of one or more APIs.

Changes to the pharmaceutical form/dosage form

- change from an immediate-release product to a slow- or delayed-release dosage form and vice versa;
- change from a liquid to a powder for reconstitution, or vice versa.

Changes in the route of administration

Appendix 4

Stability requirements for variations and changes to prequalified finished pharmaceutical products (FPPs)

It is the purpose of this Appendix to outline the stability data which have to be generated in case of changes.

The scope and design of stability studies for variations and changes are based on the knowledge and experience acquired on APIs and FPPs. The available information that must be taken into account includes:

- For APIs:
 - the stability profile including the results of stress testing;
 - the supportive data;
 - the primary data on accelerated and long-term testing.
- For FPPs:
 - the supportive data;
 - the primary data on accelerated and long-term testing.

In all cases of variations and changes, the prequalified supplier has to investigate whether or not the intended change will have an impact on the quality characteristics of the APIs and/or FPPs and consequently on their stability.

When stability data are required, the choice of test conditions defined in this Appendix refers to the *Guideline on the submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis*,⁶² the Guidelines for stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms, Annex 5, *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth Report*. Geneva, World Health Organization, 1996: 65–79 (WHO Technical Report Series, No. 863); modification of storage conditions (WHO Technical Report Series, No. 908) and amended stability testing conditions (WHO Technical Report Series, No. 937)⁶³ as well as *Stability testing of new drug substances and products (ICH Q1A (R2))*.⁶⁴

⁶² http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

⁶³ http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

⁶⁴ [http://whqlibdoc.who.int/trs/WHO_TRS_863_\(p1-p98\).pdf](http://whqlibdoc.who.int/trs/WHO_TRS_863_(p1-p98).pdf) http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=23; http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=24

In all cases of variations which require generation of stability data on the FPP, the stability studies required, including commitment batches, should always be continued up to the end of the prequalified shelf-life and WHO should be informed immediately if any problems with the stability occur during storage, e.g. if outside specifications or potentially outside specifications.

Minor changes

In the case of minor changes, as listed in Appendix 1 of this guide, which require generation of stability data on the FPP, the minimum set of data to be submitted with the variation application is defined in Appendix 1. The results of these studies covering the requested time period as defined in Appendix 1, using accelerated and long-term testing conditions, should be compared to the results of studies performed on the unchanged API/FPP to ensure that the change does not have any negative impact on the stability profile, i.e. that the specification limits of the API/FPP are still met at the end of the proposed re-test period/shelf-life. The comparison data may come from earlier studies and need not necessarily be collected in combination with the study on the unchanged product.

Major changes

The following are commonly encountered examples of major changes:

- change in the manufacturing process of the API;
- change in composition of the FPP;
- change of immediate packaging of the FPP.

Change in the manufacturing process of the API

If the quality characteristics (e.g. physical characteristics, impurity profile) of the API are changed in such a way, that stability may be compromised, comparative stability data are required from studies under accelerated and long-term testing conditions conducted on the API before and after the change:

APIs known to be stable ⁶⁵	3 months on one batch of at least pilot-scale
APIs known to be unstable	6 months on three batches of at least pilot-scale

If the quality characteristics of the API are changed in such a way that it may have an impact on the stability of the FPP, additional stability data on the FPP, obtained in studies under accelerated and long-term testing conditions, over 3 months on two batches on at least pilot-scale, may be required.

⁶⁵ ICH Q1A (R2) *Stability testing of new drug substances and products* (<http://www.ich.org/LOB/media/MEDIA419.pdf>)

Physical quality characteristics: crystallinity and/or polymorphic state, if applicable, and characteristics derived from crystallinity such as solubility and hygroscopicity. Chemical quality characteristics: impurity profile and degradation products.

Change in composition of the finished product

- *For conventional dosage forms* (e.g. conventional release solid dosage forms, solutions) *and* when the API is known to be stable, comparative stability data from a study of 6 months duration, under long-term and accelerated testing conditions on two pilot-scale batches⁶⁶ are required.
- *For critical dosage forms* (e.g. prolonged release form) *or* when the API is known to be unstable, comparative stability data, from a study of 6 months duration, under long-term and accelerated stability testing conditions on three pilot-scale batches are required.

Change to immediate packaging of the finished product

In the case of less protective packaging or when a risk of interaction occurs, mainly for semisolid or liquid dosage forms, comparative stability data are required from a study of 6 months duration, using accelerated and long-term testing conditions, on three pilot-scale batches of the finished product.

Commitment batches

Minor changes

For all minor changes that require the generation of stability data on the FPP, adequate follow-up studies on commitment batches need to be performed.

Major changes

For all major changes that require the generation of stability data on the FPP, at least the first production-scale batch manufactured according to the prequalified variation should undergo long-term stability testing using the same stability testing protocol as described above unless the respective data on stability testing have already been submitted as part of the variation application.

Stability studies need to be continued to cover the entire shelf-life. The results of these stability studies should be made available on request and WHO should be informed immediately if any problems occur during the stability studies.

⁶⁶ *Definition of stable APIs:* An API is considered as stable if it is within the initial specifications when stored at 25 °C at 60% relative humidity (RH) or 30 °C/60% RH or 65% RH, respectively, for 2 years and at 40 °C/75% RH for 6 months, and such data are available from the API manufacturer that is applying for approval of change in the manufacturing process. Please refer also to Supplement 2 of the GuideGeneric for a specific list of stable APIs.

Web links

Guideline on dossier requirements for type IA and IB notifications.

Available at: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/var_type_1a1b_guideline_06-2006.pdf

Pharmaceutical quality information form (PQIF). Available at:

http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc

Guideline on submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis [GuideGeneric].

Available at: http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

Supplement 1 of the GuideGeneric. Available at:

http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_Supplement1_08_2005.pdf

Supplement 2 of the GuideGeneric. Available at:

http://mednet3.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_Supplement2.pdf

WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report. Geneva, World Health Organization, 2006, Annex 7 (WHO Technical Report Series, No. 937) and good clinical practices. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=359

ICH Q2 (R1) *Validation of analytical procedures: text and methodology.*

Available at: <http://www.ich.org/LOB/media/MEDIA417.pdf>

ICH Q5A (R1) *Quality of biotechnological products: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin* (CPMP/ICH/295/95). Available at: <http://www.ich.org/LOB/media/MEDIA425.pdf>

ICH Q5B *Quality of biotechnological products: analysis of the expression construct in cell lines used for production of r-DNA derived protein products* (CPMP/ICH/139/95). Available at: <http://www.ich.org/LOB/media/MEDIA426.pdf>

ICH Q5C *Quality of biotechnological products: stability testing of biotechnological/biological products* (CPMP/ICH/138/95). Available at: <http://www.ich.org/LOB/media/MEDIA427.pdf>

ICH Q5D *Quality of biotechnological products: derivation and characterization of cell substrates used for production of biotechnological/biological products* (CPMP/ICH/294/95). Available at: <http://www.ich.org/LOB/media/MEDIA429.pdf>

ICH Q5E *Guidance on biotechnological/biological products subject to changes in their manufacturing process* (CPMP/ICH/5721/03). Available at: <http://www.ich.org/LOB/media/MEDIA1196.pdf>

ICH Q6B *Specifications: test procedures and acceptance criteria for biotechnological/biological products* (CPMP/ICH/365/96). Available at: <http://www.ich.org/LOB/media/MEDIA432.pdf>

WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products. Geneva, World Health Organization, 2003. Available at: http://www.who.int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf

Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev2). Available at: <http://www.emea.eu.int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf>

Good manufacturing practices for pharmaceutical products: main principles. Geneva, World Health Organization, 2003, Annex 4 (WHO Technical Report Series, No. 908), Available at: http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=46

Supplementary guidelines on good manufacturing practices: validation. Geneva, World Health Organization, 2006, Annex 4 (WHO Technical Report Series, No. 937). Available at: http://www.who.int/medicines/publications/pharmprep/TRS_937.pdf#page=119

and *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Good manufacturing practices and inspection*, Vol. 2, 2nd updated edition, Geneva, World Health Organization, 2006 (in press). Available at: http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html

Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies. Geneva, World Health Organization, 2004. Available at: http://mednet3.who.int/prequal/info_general/documents/ppdoc2.pdf

Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth Report. Annex 5. Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 863): 65–79. Available at: [http://whqlibdoc.who.int/trs/WHO_TRS_863_\(p1-p98\).pdf](http://whqlibdoc.who.int/trs/WHO_TRS_863_(p1-p98).pdf)

and modification of storage conditions in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh Report. Geneva, World Health Organization 2003 (WHO Technical Report Series, No. 908)* and amended stability testing conditions in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization 2006 (WHO Technical Report Series, No. 937)*. Available at:
http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=23
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=24

ICH guidance on stability testing of new drug substances and products (ICH Q1A (R2), CPMP/ICH/2736/99). Available at: <http://www.ich.org/LOB/media/MEDIA419.pdf>

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The International Pharmacopoeia, fourth edition.

Volume 1: general notices; monographs for pharmaceutical substances (A–O)

Volume 2: monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents.

2006 (1500 pages), also available in CD-ROM format

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.

2nd updated edition, 2007 (in print)

WHO Expert Committee on Specifications for Pharmaceutical Preparations.

Fortieth report.

WHO Technical Report Series, No. 937, 2006 (461 pages)

International nonproprietary names (INN) for pharmaceutical substances. Cumulative list no. 11.

2004 (available in CD-ROM format only)

The use of essential medicines

Report of the WHO Expert Committee (including the 13th Model List of Essential Drugs).

WHO Technical Report Series, No. 933, 2007 (in print)

WHO Expert Committee on Biological Standardization.

Fifty-fifth report.

WHO Technical Report Series, No. 932, 2006 (146 pages)

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.

The report is complemented by a number of annexes. These include: guidance notes on related substances tests concerning the dosage form monographs of *The International Pharmacopoeia*; a list of available International Chemical Reference Substances and International Infrared Reference Spectra; a revision of the general guidelines for the establishment, maintenance and distribution of chemical reference substances; the procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies; the procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies; and guidance on variations to a prequalified product dossier.

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