

The Expert Committee on Specifications for Pharmaceutical Preparations works towards clear, independent and practical standards and guidelines for the quality assurance of medicines. Standards are developed by the Committee through worldwide consultation and an international consensus-building process. The following new guidelines were adopted and recommended for use: Release procedure for International Chemical Reference Substances; WHO guidelines on quality risk management; WHO guidelines on variations to a prequalified product; and the Collaborative procedure between the World Health Organization Prequalification of Medicines Programme and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products.

WHO Expert Committee on Specifications for Pharmaceutical Preparations • WHO Technical Report Series

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Forty-seventh report



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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 on CD-ROM and online

First supplement: general notices; monographs for pharmaceutical substances; monographs for dosage forms; general and specific monographs; methods of analysis; International Chemical Reference Substances; International Infrared Reference Spectra; reagents, test solutions and volumetric solutions.

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Second supplement: general notices; monographs for pharmaceutical substances and radiopharmaceuticals; monographs for dosage forms; general and specific monographs; methods of analysis; International Chemical Reference Substances; International Infrared Reference Spectra; reagents, test solutions and volumetric solutions.

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Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms

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1991 (134 pages)

Quality Assurance of Pharmaceuticals: a compendium of guidelines and related materials

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Forty-sixth report.

WHO Technical Report Series, No. 970, 2012 (235 pages)

International Nonproprietary Names (INN) for pharmaceutical substances

Cumulative List No. 14

2011 (available on CD-ROM only)

The Selection and Use of Essential Medicines

Report of the WHO Expert Committee (including the 17th WHO Model List of Essential Medicines and the 3rd WHO Model List of Essential Medicines for Children)

WHO Technical Report Series, No. 965, 2011 (263 pages)

WHO Expert Committee on Biological Standardization

Fifty-seventh report.

WHO Technical Report Series, No. 964, 2012 (228 pages)

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WHO Expert Committee on Specifications for Pharmaceutical Preparations

Forty-seventh report

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization



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This publication contains the collective views of an international group of experts and does not necessarily represent the decisions or the policies of the World Health Organization.

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Amsterdam, 9–12 October 2012

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Special acknowledgement and appreciation is given to Dr J.A. Molzon, Associate Director for International Programs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA, who attended as observer in her function as member of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

⁹ Unable to attend.

Declarations of interest

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

Professor S. Bawazir, Professor T. Dekker, Ms N. Guerrero Rivas, Professor J. Hoogmartens, Professor S. Jin, Ms M.Y. Low, Ms C. Munyimba-Yeta, Dr L. Paleshnuik, Ms M.-L. Rabouhans and Dr J.-L. Robert reported no conflicts of interest.

Professor H.G. Kristensen reported that he and his wife, a former employee of Novo Nordisk, hold investment interests in the company. Professor Kristensen has provided an expert opinion and testimony as an independent expert in patent cases regarding the formulation and processing of medicines. The declaration did not conflict with the subjects of the meeting.

Ms G.N. Mahlangu reported that she would receive an out-of-pocket allowance from the Medicines Control Authority of Zimbabwe in accordance with the travel allowances schedule for sponsored travel.

Dr S. Parra reported that she is a full-time employee of a governmental organization (Canadian Ministry of Health) and, as such, is a civil servant receiving remuneration from a regulatory agency. Dr Parra works for the department that approves new medicines for the Canadian market. As an employee of Health Canada she represents her organization in international forums and was present in sessions on topics relevant to her work (i.e. evaluation of the quality part of drug applications) as a stakeholder.

Professor A.J. Nunn reported that he took part in discussions of the paediatric hospital pharmacy practice for Rosemont Pharmaceuticals, for which he personally received payment in 2012. His research unit received a research grant in 2011 of £250 000 from the United Kingdom National Institute for Health Research; a research grant “GRIP” WP5 from EU FP7 for the current year of €6 million (part-consortium); and personal conference costs in 2011 from the European Paediatric Formulations Initiative. He is a member of the European Medicines Agency (EMA) Paediatric Committee (PDCO) and PDCO Formulation Working Party, considering formulation development for paediatric investigation parties and for guidelines (2010–2014). Professor Nunn was not present in any Expert Committee session during which individual products were discussed.

Dr A.J. van Zyl reported that he received the fees for the current year for consulting for the United States Pharmacopeia (USP), the Global Fund, and pharmaceutical companies. He has provided an expert opinion on good manufacturing practices (GMP) in an arbitration case for Norton Rose, Cape Town, South Africa, from August 2011 to date.

The declarations of interest were presented to the Expert Committee for information. There were no comments from Committee members or temporary advisers.

1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Amsterdam from 9 to 12 October 2012. Mr C. de Joncheere, Director of the Department of Essential Medicines and Health Products (EMP) at the World Health Organization (WHO) opened the meeting. On behalf of the Director-General of WHO, Mr de Joncheere welcomed the participants to the forty-seventh meeting of the Expert Committee. He reminded the members of the Expert Committee of the importance of the Expert Committee system to the work of WHO. The work of the Expert Committee on Specifications for Pharmaceutical Preparations had provided considerable support, among others, to the WHO Prequalification of Medicines Programme (PQP) to the extent that the work of that Programme depended on the Expert Committee. He thanked the members of the Committee for their service to the Organization and its Member States.

Dr L. Rågo, Coordinator of the Quality Assurance and Safety: Medicines (QSM) team added his welcome to that of Mr de Joncheere. He reiterated the value of the contributions to WHO's work made by experts around the world. Such assistance helped WHO to keep abreast of changes in the environment. He noted that for the third time it had been planned to hold an open session during the meeting of the Expert Committee to respond to the interest in the quality of medicines previously demonstrated by Member States during the World Health Assembly. However, as no Member States had confirmed that they would attend, the open session was not to be held on this occasion.

The meeting elected Professor S.A. Bawazir as Chairperson, Ms N.M. Guerrero Rivas as Co-Chairperson, and Professor S. Jin and Ms C. Munyimba-Yeta as Rapporteurs.

2. General policy

2.1 Cross-cutting pharmaceutical quality assurance issues

The Secretary to the Expert Committee gave a short overview of the general principles and working procedures of this Committee. She reminded the members of the Expert Committee that this was one of WHO's oldest Expert Committees and that its work and its reports had long been seen as very significant for the Organization. She presented the report of the forty-sixth meeting of the Expert Committee of October 2011, which had been published during the year. She noted recent activities of the Expert Committees on Biological Standardization and on the Selection and Use of Essential Medicines, and mentioned recent publications on herbal and complementary medicines.

2.2 International collaboration

2.2.1 Collaboration with international organizations and agencies

The Global Fund to Fight AIDS, Tuberculosis and Malaria

The work of the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) was summarized for members of the Expert Committee. GFATM has so far funded antiretroviral (ARV) treatment for 3.6 million people, treatment for 9.3 million people newly diagnosed with infectious tuberculosis, 260 million malaria medicine treatments and has distributed 270 million insecticide-treated bednets. It was noted that there was a continuing need to balance the international standards of GFATM with the standards and requirements of individual countries. Procurement is done according to model quality assurance system (MQAS) principles and according to national and international laws. The Global Fund has a strict selection process, defined in its quality assurance policy, so quality standards must be assured either by WHO/PQP or by a stringent regulatory authority. When no products meet these standards, products reviewed by an Expert Review Panel (ERP) can be considered, but only under strict conditions. Countries are requested to monitor quality throughout the supply chain.

The Global Fund's ERP (hosted by EMP/QSM) reviews the dossiers of products. So far the ERP has performed a risk–benefit assessment of 58 dossiers on ARVs, of which 29 (50%) were successful; 291 dossiers on antituberculosis medicines, of which 96 (33%) were successful, and 68 dossiers on antimalarials, of which 22 (32%) were successful.

QSM's support to the Global Fund is provided through the prequalification programmes for medicines and quality control laboratories (QCLs), QSM technical expertise, the monographs (on ARVs, artemisinin combination therapy (ACT), antituberculosis and anti-infective medicines) of *The International Pharmacopoeia*, and through the development and updating of quality assurance guidelines.

The Expert Committee thanked the Global Fund for its report and expressed appreciation for its strong commitment to ensuring the highest quality standards during the procurement and supply process.

United Nations Children's Fund

The United Nations Children's Fund (UNICEF) is present in some 170 countries. Its Supply Division, located in Copenhagen, Denmark, procures supplies, including medicines, for UNICEF and partners. UNICEF country offices do not carry out procurement of medicines themselves. Ninety per cent of UNICEF supplies are for Africa and Asia.

UNICEF prequalification of medicines applies to both suppliers and products. UNICEF carries out good manufacturing practices (GMP) inspections itself mainly to check compliance with WHO GMP guidelines. Around 100 GMP inspections were carried out in 2007–2012, and 19 companies failed the inspection.

Virtually all pharmaceutical products supplied by UNICEF are on the WHO Model List of Essential Medicines. Vaccines, human immunodeficiency virus (HIV), antimalarial and antituberculosis medicines must be prequalified by WHO and listed on the WHO Prequalification web site.

The Expert Committee thanked UNICEF for its report and expressed appreciation for its strong commitment to ensuring the highest quality standards during the procurement and supply process.

2.2.2 Pharmacopoeial Discussion Group

The Expert Committee received a report on the Pharmacopoeial Discussion Group (PDG), of which WHO is an observer. At present, 28 of the 35 general chapters and 43 of the 62 excipient monographs of the current work programme have been harmonized. Representatives of the three pharmacopoeias that make up the PDG discussed ways to improve and speed up the harmonization process and proposed a number of options. Test procedures concerning excipient adulteration were also discussed. The Expert Committee took note of the report.

2.2.3 International Conference on Harmonisation

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is reviewing its work and making plans for the future. The ICH Steering Committee has agreed to set up a quality brainstorming group, working chiefly by teleconference, to advise ICH parties. Current plans include revision of guidelines, such as those on specifications, and it is expected to proactively review which new guidelines may be needed in the future. ICH has plans to develop training on its guidelines, both within the ICH regions and outside. The following topics are currently being pursued in the area of quality: Q3D (residual metals); M7 (genotoxic

impurities); and a question and answer (Q&A) document on Q7 (GMP for active pharmaceutical ingredients (APIs)).

The Expert Committee expressed its thanks for the report.

2.2.4 International Conference of Drug Regulatory Authorities

The International Conference of Drug Regulatory Authorities (ICDRA) provides medicines regulatory authorities of WHO Member States with a forum to meet and discuss ways to strengthen collaboration. The ICDRAs have been instrumental in guiding regulatory authorities, WHO and interested stakeholders and in determining priorities for action in the national and international regulation of medicines, vaccines, biomedicines and herbals.

The programme of the 15th ICDRA, scheduled for 23–26 October 2012 in Tallinn, Estonia, was outlined for the Expert Committee. The Committee's attention was also drawn to a pre-conference meeting on “The quality of medicines in a globalized world: focus on active pharmaceutical ingredients” organized jointly by the State Agency of Medicines of Estonia, the European Directorate for the Quality of Medicines & HealthCare (EDQM) and WHO.

The Expert Committee noted the programme for both the conference and the pre-conference meeting.

2.2.5 World Health Assembly resolution on new Member States' mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit medical products

The Secretary to the Expert Committee described the creation of a new Member States' mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products. This mechanism was agreed upon at the Sixty-fifth World Health Assembly in 2012 following the recommendation of a working group of Member States on SSFFC medical products which met twice in 2011.

The mechanism, which is set to meet at least once each year, is open to representation by all WHO Member States and, where applicable, by regional economic integration organizations. The goal of the mechanism is “to protect public health and promote access to affordable, safe, efficacious and quality medical products, promote, through effective collaboration among Member States and the Secretariat, the prevention and control of substandard/spurious/falsely-labelled/falsified/counterfeit medical products and associated activities”. The first meeting of this new mechanism would discuss the structure, governance and a work plan in November 2012 in Argentina.

It was recognized that the Expert Committee might have a role in supporting the mechanism.

3. Quality control – specifications and tests

3.1 *The International Pharmacopoeia*

3.1.1 Fourth Edition update

The Expert Committee was informed that the Third Supplement to the Fourth Edition would be published as a CD-ROM. The Expert Committee urged the rapid publication and placing of adopted monographs on the WHO web site.

3.1.2 Annotated work plan

The annotated work plan for 2011, which remained valid, was presented to the Expert Committee. Members commented on the work plan and noted it.

3.2 Specifications for medicines, including children's medicines

3.2.1 Medicines for human immunodeficiency virus and related conditions

Abacavir sulfate

The Expert Committee discussed a proposal for revision of the monograph on abacavir sulfate. Following discussion at the consultation on specifications for medicines and quality control laboratory issues in May 2012, a draft of the revised monograph had been sent out for comments, which had been consolidated by the secretariat. It was proposed to revise the solubility of abacavir sulfate from “freely soluble in water” to “soluble in water”. The Expert Committee noted that solubility is not a specification but is included for information. The Expert Committee endorsed the monograph, subject to the amendments proposed.

Abacavir oral solution

Following notification from collaborating quality laboratories, manufacturers and assessment specialists, of plans to revise the requirement for the pH test in the published monograph on abacavir oral solution, a draft revision was circulated for comments in July 2012. The Expert Committee discussed the proposed revision, which involved an extension of the pH range, in light of the comments received and endorsed the change. The Expert Committee adopted the monograph, subject to the amendments proposed.

Nevirapine monographs

The Expert Committee discussed proposals for correction of the monographs on nevirapine, nevirapine oral suspension and nevirapine tablets. It was noted that the nomenclature would follow the new policy on naming International Chemical Reference Substances (ICRS) (see 4.1.6). Copies of the current monographs were circulated showing the proposed changes. The Expert Committee adopted the monographs, subject to the amendments proposed.

Tenofovir disoproxil fumarate

Following the adoption of the monograph on tenofovir disoproxil fumarate in October 2009, the secretariat was informed by users about difficulties encountered with the specific optical rotation test. The collaborating laboratory which was assigned the development of the monograph investigated the issue, and new acceptance limits for this test were proposed. A draft revision of the monograph was discussed at the consultation in May 2012, following which a further draft of the monograph was sent out for public consultation. The comments received were subsequently consolidated and the draft was revised accordingly.

The Expert Committee discussed the revised draft. The monograph was adopted subject to the changes proposed.

3.2.2 Antituberculosis medicines

Cycloserine

Following a request from a user of *The International Pharmacopoeia*, it had been proposed to change the system suitability criterion of the test for related substances in the monograph on cycloserine. A revision of the monograph was sent out for public consultation and further proposals for changes were received.

The Expert Committee reviewed the proposals for the revision of the monograph on cycloserine and adopted the monograph, subject to the amendments proposed.

Cycloserine capsules

As in the case of the cycloserine monograph, it was proposed to change the system suitability criterion of the test for related substances in the monograph on cycloserine capsules following a request from a user of *The International Pharmacopoeia*. A revision of the monograph was sent out for public consultation and further proposals for changes were received.

The Expert Committee reviewed the proposals for the revision of the monographs on cycloserine capsules and adopted the monograph, subject to the amendments proposed.

3.2.3 Antimalarial medicines

Artesunate

The revision of the monograph on artesunate had been adopted by the Expert Committee in 2011 and included the correction of information related to the stereochemistry of artesunate impurity A (artenimol). Further to the changes already agreed, it was proposed to align the conditions for identity tests C and D to the test descriptions given in the document *New basic tests for antimalarials*.

The Expert Committee adopted the monograph, subject to the amendments proposed.

Artesunate tablets

A user of *The International Pharmacopoeia* had reported a problem with the chromatography described in the dissolution testing of artesunate tablets. A collaborating centre investigated the issue, advised corrections to the monograph and recommended aligning the conditions for identity tests C and D to the test descriptions given in the document *New basic tests for antimalarials*.

The Expert Committee adopted the monograph subject to the amendments proposed.

Artesunate for injection

In view of the proposed changes to the monographs on artesunate and artesunate tablets, it was also proposed to change the monograph on artesunate for injection accordingly.

The Expert Committee discussed the revised monograph, and adopted the monograph subject to the amendments proposed.

Artemisinin

In October 2011 the Expert Committee adopted the document *Recommendations for quality requirements when artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients*, including a specification for artemisinin used as a starting material. The Committee further advised that the monograph on artemisinin in *The International Pharmacopoeia* should be aligned with the new specification of artemisinin used as a starting material. Consequently a draft revision of the monograph on artemisinin was discussed at the consultation in May 2012 and circulated for public consultation in August 2012.

The Expert Committee reviewed the proposed draft of the monograph. The monograph was adopted subject to the amendments proposed. It was noted that certain proposed changes would require that the same changes should be made to the specification on artemisinin used as a starting material. The Expert Committee therefore requested the secretariat to make the changes to the specification on artemisinin as a starting material, provided they are confirmed by one of the WHO collaborating centres, and to publish the revised *Recommendations for quality requirements when artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients* as an annex to the report of the current meeting.¹

¹ During the compilation of the report it was unfortunately revealed that further investigations would be necessary.

Artemisinin tablets and artemisinin capsules

The International Pharmacopoeia contains monographs on artemisinin tablets and artemisinin capsules. However, according to WHO guidelines for the treatment of malaria, artemisinin and its derivatives should no longer be used as monotherapy since fixed-dose combination formulations are recommended. It was therefore proposed to suppress the monographs on artemisinin tablets and artemisinin capsules.

The Expert Committee agreed that the monographs were no longer in line with WHO policy and they should not appear in future editions of *The International Pharmacopoeia*. The secretariat was asked to find a means to suppress the monographs, i.e. by removing them from the current edition of *The International Pharmacopoeia* and by explaining why this action has been taken.

Mefloquine hydrochloride

Following the Expert Committee's adoption of the monograph on mefloquine tablets in October 2010, a revision of the monograph on mefloquine API was begun. A draft text for revision was discussed by the Expert Committee in October 2011 and at the consultation in May 2012. The draft was subsequently revised in light of comments made during the consultation and was then circulated for public consultation in July–August 2012.

The Expert Committee adopted the monograph, subject to the amendments proposed.

3.2.4 Anti-infectives

Cloxacillin

A user of *The International Pharmacopoeia* had reported that the specified limit for bacterial endotoxins in the monograph on cloxacillin sodium for sterile use was high compared to the limit specified in other pharmacopoeias. This was discussed with selected experts and, in consequence, the monograph was corrected to bring it in line with the limits specified in other pharmacopoeias.

The Expert Committee noted the amendment.

Fluconazole

A proposed draft of the monograph on fluconazole was first discussed at the consultation in May 2012. The draft monograph was then sent out for public consultation. Comments received were consolidated by the secretariat, and the monograph was further revised in light of the comments received.

The Expert Committee reviewed the draft, noted progress in the development of the monograph, and proposed further amendments.

Fluconazole capsules

A proposed draft of the monograph on fluconazole capsules was discussed at the consultation in May 2012. The draft monograph was then circulated for public consultation. Comments received were consolidated by the secretariat, and the monograph was further revised in light of the comments received.

The Expert Committee reviewed the draft. After noting progress in the development of the monograph, the Expert Committee proposed a number of further changes.

Fluconazole for injection

A proposed draft of the monograph on fluconazole for injection was discussed at the consultation in May 2012. The draft monograph was then circulated for public consultation. Comments received were consolidated by the secretariat, and the monograph was further revised in light of the comments received.

The Expert Committee reviewed the draft. Progress in the development of the monograph was noted and the Expert Committee proposed a number of further changes.

Pyrantel oral suspension

A draft proposal for the monograph on pyrantel oral suspension was discussed by the Expert Committee in October 2011 and at the consultation in May 2012. Following the consultation, the draft revision was circulated for public consultation and comments received were subsequently consolidated by the secretariat.

The Expert Committee adopted the monograph subject to the amendments proposed.

Sulfamethoxazole and trimethoprim intravenous infusion and oral suspension

The draft monographs on sulfamethoxazole and trimethoprim intravenous infusion and oral suspension, which had been proposed for inclusion in *The International Pharmacopoeia*, were discussed at the consultation in May 2012 and circulated for public consultation in the same month. Revised drafts of the two documents were circulated widely for further comment in August 2012. Comments subsequently received were consolidated by the secretariat.

The Expert Committee noted progress in the development of the monographs and proposed a number of changes.

3.2.5 Other medicines

Levonorgestrel and ethinylestradiol tablets

A draft proposal for the monograph on levonorgestrel and ethinylestradiol tablets was circulated for public consultation in February 2012 and comments received

were collated by the secretariat prior to discussion at the consultation in May 2012, where it was proposed to align the conditions for the dissolution testing to the respective test described in the monograph on levonorgestrel tablets. The collaborating centre investigated the possibility and subsequently revised the proposal.

The Expert Committee adopted the monograph, subject to the amendments proposed.

Zinc acetate and zinc gluconate

Draft proposals for the monographs on zinc acetate and zinc gluconate were first discussed at the consultation in May 2012. The documents were sent out for public consultation in August 2012 and were subsequently revised taking into account the comments received.

It was agreed that limits to microbial contamination should be included in the monograph on zinc gluconate.

The Expert Committee adopted the monographs on zinc acetate and zinc gluconate subject to the amendments proposed.

3.3 Harmonized texts

3.3.1 Revision of monograph on General method 5.5 Dissolution test for solid oral dosage forms

In October 2010 the Expert Committee recommended revision of the dissolution test for solid oral dosage forms. Following discussion of a draft with comments by the Expert Committee in October 2011 and at the consultation in May 2012, a revised draft was circulated for public consultation in July 2012. Comments received were collated by the secretariat for consideration by the Expert Committee.

The Expert Committee noted that the text was based on the internationally harmonized texts developed by the PDG. It was developed in line with the style and requirements used in *The International Pharmacopoeia*, and the chapter on “Test conditions and dissolution media” was added to the original PDG text.

In its review of the draft text, the Expert Committee made a number of further proposals for change. The monograph was adopted subject to implementation of the amendments proposed.

3.4 Preface, general notices and supplementary information sections of *The International Pharmacopoeia*

3.4.1 Proposal for revision of monograph on capsules

The draft of a revised monograph on capsules was considered in May 2012 at the Consultation on specifications for medicines and quality control laboratory

issues and was subsequently mailed out for public consultation. The comments received were collated by the secretariat for submission to the Expert Committee.

It had been noted that the requirements of the monograph did not necessarily apply to preparations that were intended for any use other than by oral administration. It was pointed out that such non-oral preparations, for example, vaginal or rectal capsules, might require a special formulation, method of manufacture, or form of presentation appropriate to their particular use. Starch capsules (often known as cachets) are also not included in the monograph.

The Expert Committee adopted the text as proposed.

3.4.2 **Proposal for revision of general monographs: parenteral preparations**

Following discussion at the May 2012 consultation, the draft general monograph on parenteral preparations was circulated for public consultation. The comments received were then collated by the secretariat in August and September 2012 in preparation for consideration by the Expert Committee.

The proposed revisions of this general monograph were part of the review of general monographs endorsed by the Expert Committee at its forty-second meeting. Account was taken of recently adopted revised texts for 3.2 Test for sterility, 3.4 Test for bacterial endotoxins, 5.6 Extractable volume and 5.7 Test for particulate contamination.

One of the major changes proposed in the revision was the required compliance of all parenteral preparations with tests for bacterial endotoxins (or, where justified, pyrogens). Consequently, a review of the individual monographs for injections is necessary, with the addition of a test and limit for bacterial endotoxins to each monograph that currently does not include such a requirement. It was noted that the requirements of the monograph did not necessarily apply to human blood and products derived from human blood, to immunological preparations, to peritoneal dialysis solutions or to radiopharmaceutical preparations.

The Expert Committee proposed a number of changes to the draft and adopted the monograph subject to the amendments proposed.

3.4.3 **Proposal for revision of 5.1 Uniformity of content for single-dose preparations**

The preliminary draft of the revision of the chapter of *The International Pharmacopoeia* on uniformity of content for single-dose preparations was discussed at the consultation in May 2012. It was subsequently circulated for public consultation. Comments received were collated by the secretariat prior to the meeting of the Expert Committee.

The Expert Committee noted that it was proposed to revise the text to bring it in line with the draft proposal for revision of the general monograph on

parenteral preparations. The Expert Committee adopted the text subject to the amendments proposed.

3.4.4 **Proposal for revision of high-performance liquid chromatography**

A preliminary draft of the revision of the document on high-performance liquid chromatography (HPLC) was reviewed at the consultation in May 2012. The document was then sent out for public consultation in July 2012 and the comments received were subsequently collated by the secretariat. It was pointed out that it was proposed to revise the chapter of *The International Pharmacopoeia* on HPLC to include, among other additions, a description of the dwell volume and the peak-to-valley ratio.

The Expert Committee adopted the text, subject to the amendments proposed.

3.4.5 **General method for the supplementary information section of the Fourth Edition of *The International Pharmacopoeia*: Resistance to crushing of tablets**

At its meeting in October 2007 the Expert Committee recommended that a general method text on the resistance to crushing of tablets should be included in the supplementary information section of *The International Pharmacopoeia*. Subsequently, at the Committee's meeting in October 2009, a revision of the general monograph on tablets was adopted in which, in the section on "Manufacturing", reference is made to a general method for resistance to crushing of tablets.

The draft text on resistance to crushing of tablets, which is based on the text in the *European Pharmacopoeia*, was discussed at the May 2012 consultation and was subsequently circulated for public consultation, with comments received being collated in September and October 2012. This test is intended to determine, under defined conditions, the resistance to crushing of tablets, measured by the force needed to disrupt them by crushing. It was noted that the *European Pharmacopoeia* had granted permission for the text to be reproduced in *The International Pharmacopoeia*.

The Expert Committee adopted the text as proposed.

3.4.6 **General method for the supplementary information section of the Fourth Edition of *The International Pharmacopoeia*: Measurement of consistency by penetrometry**

In October 2007 the Expert Committee recommended that a general method text on the measurement of consistency by penetrometry should be included in the supplementary information section of *The International Pharmacopoeia*. A preliminary draft text was discussed at the May 2012 consultation. Following that discussion, a further draft was circulated for public consultation, and the

comments received were collated by the secretariat. This test is intended to measure, under determined and validated conditions, the penetration of an object with a specified shape and size into the product to be examined.

The draft text on the measurement of consistency is based on the text in the *European Pharmacopoeia*, from which permission had been granted to reproduce the text in *The International Pharmacopoeia*.

The Expert Committee adopted the text as proposed.

3.4.7 **General method for the supplementary information section of the Fourth Edition of *The International Pharmacopoeia*: Softening time determination of lipophilic suppositories**

In October 2007 the Expert Committee recommended that a general method text on the determination of softening time of lipophilic suppositories should be included in the supplementary information section of *The International Pharmacopoeia*. A preliminary draft text was discussed at the consultation in May 2012. Following the consultation a revised text was sent out for public consultation and the comments received were collated by the secretariat prior to the meeting of the Expert Committee.

The test is intended to determine, under defined conditions, the time that elapses before a suppository maintained in water softens to the extent that it no longer offers resistance when a defined weight is applied. The proposed text is based on the text in the *European Pharmacopoeia* from which permission had been received to reproduce the text in *The International Pharmacopoeia*.

The Expert Committee adopted the text as proposed.

3.4.8 **Bacterial endotoxin**

The Expert Committee was informed that the establishment of a primary reference standard for endotoxin would be considered by the WHO Expert Committee for Biological Standardization.

4. Quality control – International Reference Materials (International Chemical Reference Substances and Infrared Reference Spectra)

4.1 Update on International Chemical Reference Substances

4.1.1 Overview

International Chemical Reference Substances (ICRS) are reference substances that are used as primary standards in physical and chemical tests that are described in *The International Pharmacopoeia*, and for establishing official secondary standards. The standards are officially adopted by the Expert Committee.

4.1.2 Report on activities of the host organization related to International Chemical Reference Substances

In 2010 the European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe took over responsibility for establishing, preparing, storing and distributing WHO ICRS. The Expert Committee received a report from EDQM regarding this work, as of 31 March 2012. EDQM reported that initial challenges in taking over existing stock of ICRS from Apoteket, which was a former WHO collaborating centre responsible for the distribution of the ICRS, had now been overcome. A good and productive working relationship between EDQM and the staff of *The International Pharmacopoeia* was reported.

In 2011, EDQM distributed a total of 876 ICRS, with 61% of the total number of items being sold within the WHO European Region. Eight studies to establish new ICRS were carried out, and five new ICRS were provisionally adopted or proposed for adoption. One study was performed to establish a new International Infrared Reference Spectrum (IIRS) for proguanil hydrochloride. Monitoring for continued fitness for purpose was carried out on 19 ICRS.

EDQM noted the importance of verifying the feasibility and availability of the envisaged International Chemical Reference Substance as the monograph is being established. Further, it was pointed out that information in terms of chemical composition and structure of the impurities intended to become ICRS should be systematically included in *The International Pharmacopoeia*.

The Expert Committee thanked EDQM for its work and took note of the report.

The secretariat informed the Expert Committee that EDQM announced in 2012 that it could not carry out any production of ICRS involving compounding of different materials into one ICRS. In addition, EDQM stated that it was not in a position to establish ICRS that are not mentioned in *The International Pharmacopoeia*, although they may be mentioned in other WHO quality assurance documents.

EDQM explained that, while it would honour the terms of its contract with WHO, it could not commit to expanding its responsibility to include the development of ICRS not explicitly covered by that agreement.

The Expert Committee expressed concern at the possible lack of compound reference materials. It was suggested that manufacturers and national pharmacopoeias may be able to assist. The Expert Committee requested the secretariat to react to the new situation by approaching national pharmacopoeias to assess what assistance they might provide.

4.1.3 Adoption of established International Chemical Reference Substances

Since the meeting of the Expert Committee in October 2011, EDQM had established several ICRS and one IIRS. Following a decision of the Expert Committee in 2010, the secretariat had already provisionally released some of these ICRS for distribution. These were:

- pyrimethamine ICRS;
- erythromycin ethylsuccinate ICRS;
- niridazole ICRS;
- ciprofloxacin ICRS;
- azobenzene melting-point ICRS.

The decisions to release the substances were taken in consultation with WHO collaborating centres and national control laboratories. The Expert Committee adopted these ICRS as proposed.

Some reference substances had not been provisionally released, namely:

- atenolol ICRS;
- dacarbazine ICRS;
- phenobarbital ICRS;
- spironolactone ICRS.

This was because the establishment reports were received too late to be assessed before the meeting of the Expert Committee. These ICRS were adopted, subject to confirmation by the relevant experts.

In the case of artemisinin the secretariat concluded that it was not possible to assign a single content to the candidate material that would be suitable for both assay methods described in *The International Pharmacopoeia*. The matter was discussed with selected experts and it was decided to revise the monograph on artemisinin.

With regard to pentamidine isetionate, it was found during the revision of the report that the IR spectrum of the candidate material was different from the IR spectra published in the *British Pharmacopoeia* and in the *Indian*

Pharmacopoeia. In agreement with selected experts, the secretariat decided to postpone the provisional release of pentamidine isetionate ICRS 1.

The Expert Committee adopted the ICRS subject to clarification of the differences and to confirmation that the recorded IR spectrum corresponds to pentamidine isetionate.

In addition, EDQM had established the IIRS on proguanil hydrochloride. The Expert Committee took note of this action.

4.1.4 **Supplementary information section of *The International Pharmacopoeia*: 4. Reference substances and reference spectra**

The document on reference substances and reference spectra was initially submitted to the consultation in May 2012. The draft was circulated for comment in June 2012 and the comments were collated in August 2012. The document describes principles to be applied during the establishment and use of ICRS in order to guarantee that the reference substances are suitable for their intended purpose. The document is not applicable to WHO International Biological Reference Preparations. The proposed chapter would be part of the supplementary information section of *The International Pharmacopoeia*, which provides the user with texts for guidance and information, and will not constitute part of the standards.

4.1.5 **New release procedure for International Chemical Reference Substances**

At its forty-fifth meeting, the Expert Committee agreed on a new release procedure for ICRS.¹ On the basis of this procedure, case-reports issued by EDQM after analytical testing of candidate material were reviewed by the secretariat with assistance from collaborating laboratories. If the testing was performed according to the *General guidelines for the establishment, maintenance and distribution of chemical reference substances* and the candidate material was found suitable, the secretariat, in collaboration with the collaborating laboratories, released the ICRS provisionally. In accordance with the rules, the case-reports were subsequently submitted to the Expert Committee at its next meeting for final adoption. After provisional release, EDQM begins the distribution of these ICRS.

This process expedited the release of ICRS and enabled WHO to react more quickly to urgent demands for reference substances. However, the procedure did not clearly allocate the accountability for the release of ICRS to a single person or body. The Expert Committee discussed the issue and agreed on the following amendment to the new procedure:

¹ See Annex 1, WHO Technical Report Series, No. 961, 2011.

After testing of candidate material, the custodian centre for ICRS will submit analytical case-reports to a newly established Expert Committee subgroup on ICRS, which should consist of three experts and a representative of the secretariat. The subgroup will decide on the suitability of the reference substance and adopt the ICRS on behalf of the Expert Committee. During the following meeting of the Expert Committee, the subgroup will report on the newly released ICRS.

A revised procedure appears as Annex 1 to this report.

The Expert Committee approved the nomination of Professor Dekker, Professor Hoogmartens and Professor Jin as members of the subgroup on ICRS. Each subgroup member should nominate one other expert from their respective collaborating centres as a back-up.

4.1.6 Policy on naming International Chemical Reference Substances in *The International Pharmacopoeia*

Following a discussion on the policy for naming ICRS in *The International Pharmacopoeia*, the Expert Committee adopted a proposal to use the following nomenclature for reference standards in new monographs:

- for standards on active pharmaceutical ingredients: [INN name] RS;
- for standards on impurities: [INN name of respective API] impurity [A, B, C or ...] RS;
- for standards or mixture of standards used for system suitability tests or peak identification, as intended: [INN name] for system suitability RS;
- [INN name] for peak identification RS;
- for substances used to calibrate melting-point instruments: [INN name] Melting Point RS.

The Expert Committee adopted the new proposal as a step towards a systematic way of expressing the names for ICRS in future and recognized that the certificate of analysis accompanying the ICRS would include further information on the precise nature of the substance.

4.1.7 Proposal to reduce analytical testing of high-purity candidate material

The Expert Committee reviewed a proposal to reduce collaborative testing of high-purity candidate material for ICRS used for assay and established using the mass-balance approach. Assays of ICRS established by mass balance are usually

established in collaborative trials, where not only EDQM, but also several other collaborating laboratories, analyse the proposed substance following a common protocol that describes the procedures to be employed. The results obtained are used to assign a content value to the reference standards.

To conserve resources in the participating laboratories, it was proposed not to run collaborative trials for candidate material of high purity (at least 99.5%) and to use solely analytical data obtained in a single laboratory to characterize the ICRS. It was noted that the proposal did not apply to reference materials established with approaches other than mass balance (i.e. melting-point standards), where a collaborative study would be carried out in any case.

The Expert Committee adopted the proposal.

5. Quality control – national laboratories

5.1 External Quality Assurance Assessment Scheme

5.1.1 Overview

The External Quality Assurance Assessment Scheme (EQAAS) is a programme for the external evaluation of quality control management systems in chemical control laboratories. It uses interlaboratory comparisons to determine the performance of participating laboratories in carrying out specific tests or measurements. The scheme supplements laboratories' internal quality assurance procedures by providing an external measure for their testing capabilities.

The current Phase 5 of the EQAAS will end in March 2013. The subsequent Phase 6 will be scheduled from 1 April 2013 to 30 March 2016. The Expert Committee noted that funding was being sought for the continuation of this service.

5.1.2 Final report of Procedure 4

Procedure 4 of Phase 5 of the EQAAS was related to pH and weight per millilitre. Forty-two of 53 laboratories (79%) from all six WHO regions reported satisfactory results for the two determinations requested.

The Expert Committee noted the report and endorsed follow-up action by the secretariat with the laboratories.

5.1.3 Preliminary report of Procedure 5 and additional information with regard to possible sources of error

Procedure 5 of Phase 5 of the EQAAS is concerned with assay by liquid chromatography. Forty-seven participant laboratories submitted their results for this study. The raw data from the study were reported to the Expert Committee. Again some 80% of the laboratories reported satisfactory results.

Two further tests remain to be completed in Phase 5.

The Expert Committee noted the report and endorsed follow-up action by the secretariat with the laboratories, for the investigation of the results that were unsatisfactory and on corrective measures for the future.

5.1.4 Proposal for Phase 6

During Phase 6 of the EQAAS, it was proposed to perform proficiency tests on the following samples using the indicated techniques:

- assay by titration;
- determination of specific optical rotation;
- assay by HPLC;

- dissolution test (paddle apparatus, UV-Vis absorption spectrophotometry);
- water determination by Karl Fischer titration;
- related substances by HPLC.

The Expert Committee reviewed the proposal and adopted the test techniques for Phase 6.

There was also a discussion on the possibility of using the opportunity of testing for monitoring quality of the products on the respective national markets in cases where the laboratories met the required standards of performance. This, however, would be outside the scope of the EQAAS.

6. Quality assurance – good manufacturing practices

6.1 Updates of WHO GMP texts

In 2011 the Expert Committee approved updates to three GMP texts. The secretariat reported that no proposals for updating of GMP materials had been received since then. It was noted, however, that a number of European Union (EU) and United States Food and Drug Administration (US-FDA) GMP guidelines had been recently updated.

The Expert Committee requested the secretariat to make a proposal on how to revise the WHO guidelines in light of these trends in other new guidelines.

6.2 Training materials

The process for the revision of the WHO training modules was approved by the Expert Committee in October 2011 to bring them in line with the updated guidelines. Each slide of the modules was therefore checked for correctness in relation to the various revised GMP texts. All basic training modules had been revised and updated and were being reviewed. Major changes were made to the GMP training modules, e.g. for the module on quality management, to include risk assessment and other new factors. The Expert Committee was informed that there was currently no training material on microbiology laboratories and hazardous materials as these GMP texts had only been developed in recent years. A number of other training modules were still under revision. It was noted that all WHO GMP guidelines are to be provided on a CD-ROM.

The Expert Committee expressed its gratitude for the update.

7. Quality assurance – new approaches

7.1 Quality risk management

The first draft points for guidelines on this topic were initially prepared in 2010 and widely circulated for comments. The Expert Committee commented on the drafts in 2010 and 2011. Numerous comments were received during the global consultation phases. During the informal consultation on WHO quality risk management and quality guidelines held on 28–30 June 2011, it was suggested that the principles included in these guidelines could be more concise to enable a timely initial implementation. Full implementation of the quality risk management (QRM) system and the application of the related tools would necessitate a longer time frame. The QRM approach was considered by all experts to be a crucial element of quality assurance in the future.

Subsequent to the meeting of the Expert Committee in October 2011, the document on QRM was completely restructured on the basis of the numerous comments made and advice received before and during the consultation. The aim of the guidelines is to assist the development and implementation of effective QRM, covering activities such as research and development, sourcing of materials, manufacturing, packaging, testing, storage and distribution.

The Expert Committee reviewed the document and the most recent proposals for revisions based on feedback and comments received in response to a further round of global consultation. Members of the Committee made proposals for a number of amendments. The Expert Committee adopted the revision of the guidelines, subject to implementation of the changes approved (Annex 2).

7.2 Pharmacopoeial harmonization

At the International meeting of world pharmacopoeias held on 28 February to 1 March 2012, the 23 pharmacopoeias present committed to further efforts towards pharmacopoeias harmonization. The participants acknowledged that the harmonization of standards would be essential to global public health in the future. Pharmacopoeial harmonization was also a plenary topic at the two-day public conference organized by the International Pharmaceutical Federation (FIP) and WHO in Amsterdam in October 2012.

International meeting of world pharmacopoeias

WHO maintains an *Index of pharmacopoeias* and had organized a meeting inviting all world pharmacopoeias included therein, from 28 February to 2 March 2012. Twenty-three pharmacopoeias attended the meeting to discuss challenges and issues. They committed to working further towards harmonization and to

strengthening WHO's role when developing global standards for the production and testing of medicines. It was recognized that the harmonization of standards has become increasingly important for public health for a number of reasons, one of the most important being to combat falsified and substandard medicines.

The meeting had called for greater collaborative work and sharing of information between world pharmacopoeias. An important recommendation was to develop good pharmacopoeial practices, and a drafting group was established to take this project forward. The role of *The International Pharmacopoeia* was appreciated. Furthermore, it was agreed to hold a public conference of pharmacopoeias in October 2012 in connection with the FIP Centennial Congress, inviting all stakeholders and users to discuss future approaches.

WHO–International Pharmaceutical Federation Conference

The two-day public conference on “International world of pharmacopoeias. Now and in future”, jointly organized by WHO and FIP was held in Amsterdam on 7–8 October 2012. The conference addressed pharmacopoeial harmonization opportunities for collaboration and good pharmacopoeial practice, as well as the way forward for pharmacopoeias in a changing environment. Workshops were held on impurities, residues and on challenges in developing herbal medicines monographs and applying them in practice.

Discussion

The Expert Committee expressed its appreciation for this joint effort between WHO and FIP, and thanked FIP for its continued collaboration.

The Expert Committee urged more frequent communication between the pharmacopoeias and stressed the need to produce a high-level document reflecting those principles and elements considered by pharmacopoeias to be important. It was noted that harmonization of approaches would help to expand access to medicines in developing countries and that consistency between pharmacopoeias would be a help to the pharmaceutical industry. When each country had its own specifications for medicines, this made it very expensive for manufacturers to tailor their exports to comply with each country's requirements.

The Expert Committee agreed to WHO's coordination of pharmacopoeial harmonization activities, and supported further work with the global pharmacopoeias to develop good pharmacopoeial practices as a basis for future harmonization and collaboration. This would be coordinated by the secretariat which would contact the pharmacopoeias for proposals regarding the scope and important elements to be included in the future good pharmacopoeial practices. As this good practice developed, it would be communicated according to the usual consultation process.

7.3 Screening technologies

The Expert Committee was briefed on new developments regarding analytical screening technologies. It was reported that some falsified medicines would produce wrong results, as they may have been deliberately prepared to produce false-positive results. In addition, WHO increasingly receives requests from countries for assistance in dealing with cases of suspect medicines causing serious health problems to patients.

The Expert Committee expressed concern at this growing issue. Members discussed possible causes and solutions, although they recognized that the most effective analytical and forensic solutions were likely to be expensive. In particular, it was stressed that WHO could not effectively find a solution without collaboration with stakeholders, such as manufacturers and regulatory authorities. The secretariat was requested to review the trends of new laboratory technologies and to report back to the Expert Committee.

7.4 Survey on laboratories report

A survey was initiated among WHO collaborating centres and those participating in the EQAAS, being mainly national quality control laboratories (QCLs), to determine the number of QCLs that were involved in testing suspect samples and how they deal with such samples. The data are still being analysed but will be provided to the Expert Committee when they become available.

The Expert Committee welcomed this initiative and noted the report.

8. Quality assurance – distribution and trade of pharmaceuticals

8.1 Revision of model quality assurance system for procurement agencies

The model quality assurance system (MQAS) for procurement agencies was adopted by the Expert Committee in October 2005, since when it has been used by many organizations. At a GFATM–WHO joint stakeholders meeting in August 2011, WHO and GFATM identified the need for revision of the MQAS and the need for an assessment tool for procurement agencies. The MQAS was reviewed and a proposal for revision initiated; and an assessment tool was developed with major procurement organizations and agencies. Both activities followed a consultative process. During this process, it was noted that not all the procurement organizations used the system.

Two informal meetings were organized by GFATM in 2012 to review progress in both the MQAS and the proposed new assessment tool. The revised MQAS and the proposed assessment tool were then circulated for comment in August 2012 by WHO following the usual Expert Committee consultation process. Comments were collated and the draft revised MQAS and the comments were presented to the Expert Committee for consideration.

The Expert Committee considered the comments and proposed a number of amendments to the draft. The Expert Committee endorsed the proposal for a revision of the MQAS, and noted progress made to date.

8.2 Assessment tool based on the model quality assurance system

In August 2011, WHO and GFATM identified the need for a new assessment tool for procurement agencies in conjunction with the revision of the MQAS. The proposed assessment tool was based on the MQAS. A draft of the proposed tool was prepared during 2012 and was circulated for comment. The draft was being tested in a pilot process from August to December 2012, after which it would be further reviewed and revised according to the experience gained.

The Expert Committee endorsed the proposal to develop a new assessment tool based on the MQAS, thanked the GFATM for financing the initiative, and noted progress made to date. It was requested that the assessment tool should be published as an appendix to the MQAS.

8.3 Monitoring and surveillance of national supply chain

WHO has recently initiated a project focusing specifically on building global capacity for surveillance and monitoring of SSFFC medicines; the project

responds to the fact that the problem of SSFFC medicines has continued to grow in complexity, scale and geographical extent.

The project's long-term objective is to significantly improve the quantity, quality and analysis of data on the incidence of SSFFC medicines – through building on existing systems and by creation of a global surveillance and monitoring system – to provide stakeholders with a sound basis on which to build and collaborate on strategies for radically reducing the incidence of SSFFC medicines and protecting supply chains.

Moreover, the increased quality of data and detailed information will enable more efficient information exchange between countries and facilitate regulatory action to protect patients and consumers.

The project aims to create a sustainable surveillance and monitoring system for collecting, disseminating and analysing information on SSFFC medicines, based upon analysis of experience with existing systems such as the rapid alert system (RAS) in the WHO Western Pacific Region, and reflecting at least the requirements of the project participants, but ideally the requirements of all stakeholders. It will collect best practices for reporting of cases of SSFFC medicines, and will facilitate common understanding and unification of the minimum standards needed for individual case-reports. In addition it is intended to help national medicines regulatory authorities (NMRAs) to identify SSFFC medicines that have entered or that threaten to enter their country's supply chain. Data and case-reports relating to SSFFC medicines will be collected from NMRAs, to generate sound and reliable evidence of where incidence of such medicines is most serious. The aim is to promote sharing of information and expertise between NMRAs, in order to stimulate action (including alerts and regulatory action to protect patients and consumers), and closer collaboration, to minimize the negative impact of SSFFC medicines.

The project is currently in the pilot phase testing a new information technology (IT) platform and reporting processes developed over the past two years. At present 10 countries are participating actively in the pilot study. Once the system is up and running other countries will be able to join.

The Expert Committee valued the new project on market surveillance and noted the report.

8.4 **Proposal for revision of good trade and distribution practices**

The WHO guide on *Good trade and distribution practices for pharmaceutical starting materials* was published in 2003. In 2006, the International Pharmaceutical Excipients Council (IPEC) – an industry association comprising excipient manufacturers, excipient distributors and their pharmaceutical customers – published its *GDP Guide for pharmaceutical excipients*, which was fully aligned with the WHO document. Since the publication of these guidelines, a number of

new developments and concepts, including, for example, risk management, have influenced good distribution practices (GDP) principles and processes. It was noted that a number of recent incidents have created awareness of the need for further improvement of the present guidelines.

The IPEC Federation presented an update on its activities concerning good trade and distribution practices. The IPEC Federation proposed a revision and update of the WHO good trade and distribution practices (GTDP) guide and offered its support in providing a proposal. This could be developed by the IPEC Federation member groups by the end of 2012. It was noted that any draft of the WHO GTDP guide would be circulated for review using WHO's wide global consultation process and would be submitted to the WHO Expert Committee for consideration for adoption. Following adoption, the IPEC Federation would then update its own guide in line with that of WHO.

The Expert Committee discussed the need for revising and updating the WHO GTDP guide and endorsed the proposal.

9. Prequalification of priority essential medicines including active pharmaceutical ingredients

9.1 Update on the Prequalification of Medicines Programme managed by WHO

PQP was launched in 2001 at WHO headquarters in partnership with the Joint United Nations Programme on HIV/AIDS (UNAIDS), UNICEF and the United Nations Population Fund (UNFPA), and with support from the World Bank. PQP is thus a United Nations Programme administered by WHO. The Programme's focus was originally the evaluation of medicines for treating HIV/AIDS, malaria and tuberculosis, but products in other therapeutic categories are now also evaluated. Since October 2010 PQP has started to prequalify APIs.

Most prequalified finished pharmaceutical products are generics, but are not exclusively so. The prequalification procedure begins with an invitation for expressions of interest. It was noted that there have been fewer submissions in the area of tuberculosis than for other diseases covered by this Programme. Thirty-five products (34 of them generic) were prequalified during 2011. Sixty-eight dossiers were received and 46 were accepted for evaluation. Nearly 1000 assessment reports were produced and more than 500 variations to prequalified products were assessed.

It was noted that the norms and standards developed and approved through the Expert Committee underpin all of PQP's activities. The Expert Committee expressed its gratitude for the report and for the work of PQP.

10. Prequalification of active pharmaceutical ingredients

10.1 Update on the prequalification of active pharmaceutical ingredients

The prequalification of APIs began in October 2010 as a pilot project intended to identify APIs that are of good quality and are manufactured in compliance with GMP. In 2011 PQP prequalified its first APIs (six for antimalarials and two for antituberculosis medicines). Manufacturers are invited to apply on the basis of their products. The list of prequalified APIs is published on the WHO web site and a document confirming prequalification of the API is supplied to the manufacturer. NMRAs may also request further information on a particular API. As of October 2012, 62 applications for the prequalification of APIs had been received and 23 had been prequalified and published on the web site.

The Expert Committee expressed appreciation for the report.

11. Prequalification of quality control laboratories

11.1 Update on the prequalification of quality control laboratories

The prequalification procedure for quality control laboratories (QCLs) was originally established in 2004 for Africa only and has since expanded globally. Any QCL (whether public or private) may now participate in the programme. Participation is voluntary and 55 laboratories have asked to participate since 2004 (73% being national QCLs). The Expert Committee heard that 24 laboratories are currently prequalified, with at least one in each WHO region. The programme also includes capacity-building, with training and technical assistance provided for national QCLs in developing countries.

An informal network of QCLs, which have been prequalified, have submitted an application for prequalification or have actively participated in prequalification testing projects or other activities, is currently being set up in cooperation with a WHO collaborating centre in South Africa. The objectives are to support the quality of laboratory testing within the network, to facilitate reliable testing of medicines procured by United Nations agencies, and to facilitate information exchange, networking and work-sharing.

The benefits to QCLs of prequalification include the possibility to provide testing services to United Nations agencies and other organizations, the recognition that comes of being listed as a WHO-prequalified laboratory, the learning process of improving laboratory standards, and the possibility of being assisted by WHO expert consultants and of participating in WHO-organized training. The Expert Committee heard that countries appreciate having prequalified laboratories in their own region for the convenience and speed of service that these laboratories provide.

The Expert Committee expressed its appreciation for the report.

11.2 Update on WHO quality monitoring projects

PQP organizes quality monitoring of medicines projects to monitor the quality of prequalified products and of medicines procured by United Nations agencies. It was noted that this contributes to the quality control of medicines in Member States and to capacity-building through cooperation with NMRAs. The Expert Committee heard that, in response to a complaint of poor quality, a survey of the quality of antimalarials supplied within phase 1 of the Affordable Medicines Facility malaria project (AMFm), which is managed by GFATM, is being conducted. The evaluation will cover both the product itself and the storage conditions.

The Expert Committee expressed its appreciation for the report.

12. Regulatory guidance

12.1 Extemporaneous dispensing and administration of medicines to children

In October 2011 the Expert Committee adopted a document on points to consider in the pharmaceutical formulations for paediatric medicines. A revised version of the document was prepared and circulated for public consultation in August 2012. The comments received were subsequently collated by the secretariat. In connection with this new guidance document, a second one on *Provision by health-care professionals of patient-specific preparations for children that are not available as authorized products – points to consider*, was discussed.

This guidance document had been previously discussed during the meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines which took place in Accra, Ghana on 21–25 March 2011.

Both Committees had, despite certain reservations regarding the risks of inappropriate preparations and the risks of diverting efforts aimed at the development of age-appropriate dosage forms for children, recommended further developing such guidance after a careful review and wide consultation in order to meet the current need for advice. The project continued, with the assistance from specialists, as a joint WHO–FIP endeavour.

In the course of further development and consultation on this document, the working group suggested taking a more general approach; offering advice to more than just one group, i.e. those concerned with paediatric patients, and tackling special populations, including, for example, paediatric patients together with geriatric patients in one document. The updated version of the working document was newly entitled *FIP–WHO technical guidelines: considerations on the provision by health-care professionals of patient-specific enteral compounding for special populations (for example, paediatric and geriatric patients) when no suitable authorized products are available*, and the content was adjusted accordingly.

The Expert Committee expressed concern at the effort to address both paediatric and geriatric formulations in one document. In attempting to include formulations for the two patient groups, it was felt that the document had become more technical and had lost some of its initial focus on access to medicines for children, when no registered finished product for children exists on the market.

The Expert Committee requested that the document should be refocused on compounding of paediatric formulations, and should then be circulated in its revised form for public consultation prior to being considered at the next meeting of the Expert Committee.

The secretariat was requested to liaise with the authors to review the documents and to consider all comments made by the Expert Committee over the course of the preparation of this document, and to post the draft on the WHO web site for public review.

12.2 Guidance on variations to a prequalified product

In October 2011, the Expert Committee adopted new generic quality guidelines, published as Annex 4 of WHO Technical Report Series, No. 970, under the title *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*. The Expert Committee at that time also proposed that subsequently a new general document on variations guidelines should be considered, which would be in line with these newly adopted guidelines. The new document was mailed out for public consultation in May 2012 and the comments received were subsequently collated by the secretariat. A revised version was then mailed out for further comment in August 2012.

The revised document *Guidance on variations to a prequalified product* retains the basic structure and function of the previous variations guidelines but has been completely updated and expanded to bring it in line with the principles of the new generic quality guidelines.

The Expert Committee adopted the document (Annex 3). It was noted, however, that the adopted document was intended for use specifically in regard to PQP and the development of a similar general guidance document on variations was recommended.

12.3 Collaborative procedure between the WHO Prequalification of Medicines Programme and national medicine regulatory authorities in the assessment and accelerated registration of national WHO-prequalified pharmaceutical products

The Expert Committee reviewed the draft of a collaborative procedure between the PQP and NMRAs for the assessment and accelerated national registration of WHO-prequalified pharmaceutical products. PQP had been approached by a number of NMRAs seeking assistance with national registration of prequalified products, which in some cases took a long time, delaying the availability of medicines to patients.

The aim of the proposed procedure was to accelerate national registration (marketing authorization) of WHO-prequalified medicines in countries with participating NMRAs, and to assist NMRAs to focus their regulatory resources on the country-specific aspects of national registration decision-making.

Given scarce regulatory resources in countries which are recipients of WHO-prequalified medicines, it was felt that NMRAs in these countries may benefit from information on the outcomes of assessments and inspections already organized when they assess prequalified medicinal products. With the agreement of prequalification holders, PQP would be prepared – under conditions described in the collaborative procedure – to share full assessment and inspection reports

with interested NMRAs. NMRAs would retain their prerogative to make sovereign decisions on registration, and the collaborative procedure would not interfere with national legislation, decision-making processes or regulatory fees.

The principles for the procedure had initially been discussed and agreed at a meeting of the heads of medicines regulatory authorities of East Africa in February 2009. A document describing the procedure had subsequently been discussed at a series of meetings with regulators, manufacturers and experts before being discussed at the consultation in May 2012. The document had also been reviewed by the WHO Legal Counsel.

The Expert Committee discussed the draft document describing the collaborative procedure and made a number of proposals for amendments. The document was adopted subject to the amendments proposed (Annex 4).

12.4 **Proposal for a procedure on sampling and market surveillance survey**

Following the recommendation made by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its forty-sixth meeting in October 2011, to continue the development of sampling procedures based on the numerous examples obtained from many countries as feedback to the secretariat's communications, internal discussions took place to propose new guidance on sampling and market surveillance surveys. A proposal for a procedure on sampling and market surveillance was subsequently drafted and sent out for comment in September 2012 and the comments received prior to the meeting of the Expert Committee in October 2012 were collated by the secretariat.

The proposal was based on an existing survey protocol developed by the WHO Prequalification Laboratory Programme, which had been extensively involved in the establishment of survey protocols for major studies for antimalarial and antituberculosis medicines. The proposal included an annotated survey protocol, survey forms, a testing protocol and listed the content of a typical analytical test report.

The Expert Committee noted that the document would be of particular importance in monitoring and post-marketing surveillance, and agreed that it should be further developed as a general document providing advice on sampling for various groups of medicines. The Expert Committee also noted the need for separate, specific guidance in relation to spurious/falsely-labelled/falsified/counterfeit (SFFC) medical products.

12.5 **Comparator products**

A comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. In 1999 the Expert Committee adopted a document on comparator products. This contained a list

of international comparator pharmaceutical products for the equivalence testing and assessment of interchangeable multisource (generic) products and included a decision-tree for use in identifying comparator pharmaceutical products. The list was intended to serve as an information tool for medicines regulatory authorities and manufacturers of pharmaceuticals, although it was not intended to be binding on those responsible for choosing a reference product. At that time the Expert Committee noted that the list and the guidance provided would need to be updated periodically.

A revision of the comparator list is in progress. The aim is to have a list of suitable comparators of acceptable quality that is harmonized with the PQP list and which contains products that are easily accessible.

The Expert Committee expressed its thanks for the continuing work on comparator products,

12.6 Biowaiver

The term “biowaiver” is applied to a regulatory medicines approval process when the dossier is approved on the basis of evidence of equivalence other than through in vivo equivalence testing. A series of monographs have been published that contain essentially literature reviews, gathering and organizing relevant data that should be taken into consideration in deciding whether a biowaiver could be recommended for a new formulation of a specific API. Further work on these biowaiver reviews has been done by FIP. Some 40–50 reviews of APIs have been published. These scientific reviews provide the basis upon which to update the related annex (WHO Technical Report Series, No. 937, 2006, Annex 8), published together with the *Multisource (generic) pharmaceuticals: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, 2006, Annex 7).

The Expert Committee noted the situation and thanked FIP for its work in this area. The Committee encouraged continuing efforts to update this annex in collaboration with the WHO collaborating centre, to circulate the draft for comments and to present the draft revision to the next meeting of the Expert Committee.

13. Nomenclature, terminology and databases

13.1 Quality assurance terminology

The WHO web site provides access to a database of terms and definitions, which also indicates the WHO guidelines in which these terms and definitions appear. In October 2011 the Expert Committee created a subgroup to review the list of terms and definitions to ensure its standardization and potentially to reduce the number of definitions for each term. Work in this area is ongoing.

13.2 International Nonproprietary Names for pharmaceutical substances

The Expert Committee received an update on the WHO Programme for International Nonproprietary Names (INN) for pharmaceutical substances and received the strategic plan of the INN Programme for 2011–2016.

It was noted that the number of INN had increased significantly in the past two years. The latest cumulative list of INN (Cumulative List 14), containing some 8500 INN, was published by WHO in January 2012. A review of the length of time required for acceptance of an INN showed that the average is 11.9 months, with 86% of INN being accepted after one or two rounds of discussion. New stems and pre-stems have also been published.

A notable increase has been seen in the number of biological INN and this trend is expected to continue. The Expert Committee also noted that the possible need for a nomenclature scheme for cell therapies is under discussion.

In response to a number of requests to use the INN in databases also for commercial products, the Programme has developed a web service – named INN Global Data Hub – to offer INN data access to INN stakeholders. The INN Global Data Hub is a software system designed to support machine-to-machine interaction over the network. The MedNet web site was demonstrated, showing the number of users worldwide.

The Expert Committee noted the report on the work of the INN Programme.

14. Miscellaneous

14.1 Quality assurance of pharmaceuticals: a compendium of guidelines and related materials

The Expert Committee was informed that a CD-ROM had been produced containing a compendium of all current WHO guidelines and related materials on quality assurance.

14.2 Strategy

All areas of WHO had been requested to prepare strategies that would guide their future activities. Members of the Expert Committee were invited to propose elements that could be included in the future strategy of QSM.

Topics raised included:

- biosimilars, which relate both to biologicals and pharmaceutical preparations, through increased liaison and collaboration with the Expert Committee on Biological Standardization;
- increased collaboration between pharmacopoeias and harmonization;
- increased availability of international expertise to national laboratories (in particular in view of the increased need to identify SFFC drugs);
- facilitation of training for NMRAs;
- prioritization, especially to retain and maintain the current core activities in this area.

15. Summary and recommendations

The WHO Expert Committee on Specifications for Pharmaceutical Preparations advises the Director-General of WHO in the area of quality assurance of medicines. The Expert Committee provides recommendations and guidance for the purpose of assuring the quality of medicines throughout their entire life-cycle, i.e. from their initial development through to their final distribution to patients.

Since its creation in 1947, this Expert Committee has given independent expert advice in the form of practical recommendations, clearly defined standards, and international guidelines for quality medicines. The recommendations, standards and guidelines adopted by the Committee are developed through a broad international consensus-building process.

At its forty-seventh meeting from 9 to 12 October 2012, the Expert Committee addressed a range of issues. These included the United Nations Prequalification Programme which is managed by WHO, the prequalification of quality control laboratories, WHO's External Quality Assurance Assessment Scheme, a revision of the Organization's model quality assurance system, guidance on making paediatric formulations available and a revision of WHO's guidance on good trade and distribution practices.

The Expert Committee reviewed specifications and tests for a number of antiretroviral, antimalarial, anti-infective and other medicines, adopting those that it judged to be suitable for inclusion as monographs in *The International Pharmacopoeia*. General texts and supplementary information sections of *The International Pharmacopoeia* were also reviewed and were adopted where appropriate. In addition, arrangements for the quality control of international reference materials were discussed and a number of ICRS and one IIRS were adopted.

The work of this Committee in furthering access to high-quality medicines relates to a number of other WHO committees and United Nations bodies, as well as to national and regional authorities and procurement agencies and to the pharmaceutical industry. Thus, the Committee's discussion included issues that are being addressed by the WHO Expert Committee on Biological Standardization, and the Expert Committee on the Selection and Use of Essential Medicines and its subcommittee on Medicines for Children. Committee members considered reports from the Global Fund to Fight AIDS, Tuberculosis and Malaria and from the United Nations Children's Fund, as well as discussing a variety of elements of regulatory guidance and a proposed revision to WHO's advice on GMP. Training on GMP was discussed and advice was given on quality risk management.

The Expert Committee noted considerable collaboration with other bodies – particularly the FIP, with which WHO had jointly organized recent conferences, and the International Conference of Drug Regulatory Authorities. In addition, following WHO's convening of a meeting of pharmacopoeias in

early 2012, the Committee encouraged further collaboration between the world's pharmacopoeias leading to harmonization of their work.

A full list of the decisions and recommendations made by the Expert Committee at its forty-seventh meeting is given below.

The following new guidelines were adopted and recommended for use:

- Release procedure for International Chemical Reference Substances (Annex 1)
- WHO guidelines on quality risk management (Annex 2)
- WHO guidelines on variations to a prequalified product (Annex 3)
- Collaborative procedure between the World Health Organization Prequalification of Medicines Programme and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products (Annex 4)

For inclusion in *The International Pharmacopoeia*

The following monographs were adopted:

- *for antiretroviral medicines*
 - abacavir sulfate
 - abacavir oral solution
 - nevirapine
 - nevirapine oral suspension
 - nevirapine tablets
 - tenofovir disoproxil fumarate
- *for antimalarial medicines*
 - artesunate
 - artesunate tablets
 - artesunate for injection
 - artemisinin
 - mefloquine hydrochloride
- *for antituberculosis medicines*
 - cycloserine
 - cycloserine capsules

- *for anti-infectives*
 - cloxacillin sodium
 - pyrantel oral suspension
- *for other medicines*
 - levonorgestrel and ethinylestradiol tablets
 - zinc acetate
 - zinc gluconate
- *suppression of monographs*
 - artemisinin tablets
 - artemisinin capsules
- *for harmonized general texts*
 - dissolution test for solid oral dosage forms (based on PDG text)
- *general policy topics and general revision issues for:*
 - capsules
 - parenteral preparations
 - uniformity of content for single-dose preparations
 - high-performance liquid chromatography
- *supplementary information section:*
 - resistance to crushing of tablets
 - measurement of consistency by penetrometry
 - softening time determination of lipophilic suppositories.
- *The Committee adopted the following new ICRS:*
 - atenolol ICRS;
 - azobenzene melting point ICRS;
 - ciprofloxacin ICRS;
 - dacarbazine ICRS;
 - erythromycin ethylsuccinate ICRS;
 - niridazole ICRS;
 - phenobarbital ICRS;

- pyrimethamine ICRS;
- spironolactone ICRS;
- *the following International Infrared Reference Spectrum (IIRS) for:*
 - proguanil hydrochloride IIRS;
- *and new policies on ICRS for:*
 - naming ICRS in *The International Pharmacopoeia*;
 - analytical testing of high purity candidate material.

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

Collaboration with and among pharmacopoeias

- The Expert Committee expressed recognition and support for WHO's initiative to work closely with other pharmacopoeias.
- It endorsed the development of good pharmacopoeial practices under the aegis of WHO and the Expert Committee on Specifications for Pharmaceutical Preparations in collaboration with the world pharmacopoeias.

The International Pharmacopoeia

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

International Chemical Reference Substances (ICRS)

- Continue promoting the use of International Chemical Reference Substances (ICRS) through various activities, including a promotional offer to national authorities.
- Continue the efforts to further enhance the development of new ICRS.

- In response to the concern expressed by the Expert Committee at the possible lack of candidate material for reference substances it was suggested that manufacturers and national pharmacopoeias may be able to assist. The Expert Committee requested the secretariat to react to the new situation by approaching national pharmacopoeias to assess what assistance could be provided.

External Quality Assurance Assessment Scheme (EQAAS)

- Continue the External Quality Assurance Assessment Scheme (EQAAS) for pharmaceutical quality control laboratories, Phase 5, onwards.
- Continuation of the scheme with Phase 6, as funds allow.

Quality control laboratories

- Continue the survey on quality control laboratories performing analysis of suspect spurious/falsely-labelled/falsified/counterfeit (SFFC) medicines and report back on the outcome.

Good manufacturing practices (GMP) and manufacture

- Continue to follow up on the revision process for GMP for biologicals undertaken under the aegis of the Expert Committee on Biological Standardization.
- Study the need for an update of the GMP general principles to cover new developments globally.
- Continue the review of the revised GMP training modules with a view to making them publicly available as soon as possible.

WHO model quality assurance system for procurement agencies

In close collaboration with the Global Fund:

- Continue the process of revision of the model quality assurance system for procurement agencies.
- Continue the development of an assessment tool for procurement agencies.

Update of good trade and distribution practices (GTDP)

- Continue the process of revision of GTDP in collaboration with partner organizations specialized in this field.

Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product

- Develop a new general document for the quality part based on the specific guidance developed for the WHO Prequalification of Medicines Programme.
- Develop a new general document for the variations based on the specific guidance developed for the WHO Prequalification of Medicines Programme.

Provision by health-care professionals of patient-specific preparations for children that are not available as authorized products: points to consider

- Further develop these “points to consider” jointly with FIP as a practice guidance document for compounding, focusing on paediatrics.

Update on biowaiver and comparator products

- Provide an update of the list of possible biowaivers and comparator products following review by the members of the Expert Committee to replace the version of 2002.

Sampling procedures for monitoring of market situations

- Continue development of sampling procedures based on the numerous examples obtained from many countries as feedback to the secretariat's communications.

Screening technologies procedures for monitoring of market situations

- Review the trends in new technologies for screening suspect samples.

Quality assurance terminology

- Continue the work on the preferred terms included in the current quality assurance terminology database based on the analysis prepared by the secretariat, with a group of experts, for which a consultation had already started.

Index of pharmacopoeias

- Consult with representatives of the individual world pharmacopoeias included in the *Index of pharmacopoeias* in order to complete and validate the information therein.

WHO databases

- Maintain the International Nonproprietary Names (INN) database and continue to make it available on the web site.
- Maintain the Quality Assurance database and continue to make it available on the web site.
- Continue the work of the terminology subgroup to further review the list of terms and definitions covered by this Expert Committee.

Financial situation analysis

In view of the number of important tasks ahead, the Expert Committee emphasized the need for continued funding to the Medicines Quality Assurance Programme and the need to reach out to programmes and organizations that use the international guidelines and standards developed by this Committee, as these were almost exclusively supported by the Prequalification of Medicines Programme. The Expert Committee was concerned that the number of staff working in this area was not sufficient to perform the tasks required.

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Active Pharmaceutical Ingredients Committee, European Chemical Industry Council, Brussels, Belgium; Danish Medicines Agency, Copenhagen, Denmark; European Association of Pharmaceutical Full-line Wholesalers, Groupement International de la Répartition Pharmaceutique, Brussels, Belgium; European Commission, Brussels, Belgium; European Directorate for the Quality of Medicines and HealthCare, Council of Europe, Strasbourg, France; European Federation of Pharmaceutical Industries and Associations, Brussels, Belgium; European Medicines Agency, London, England; The Global Fund to Fight AIDS, Tuberculosis and Malaria, Vernier, Switzerland; Healthcare Distribution Management Association, Arlington, VA, USA; Indian Drug Manufacturers' Association, Mumbai, India; International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland; International Generic Pharmaceutical Alliance, Brussels, Belgium; International Pharmaceutical Excipients Council Europe, Brussels, Belgium; International Pharmaceutical Federation, The Hague, Netherlands; International Society for Pharmaceutical Engineering, Tampa, Florida, USA; Pharmaceutical Inspection Co-operation Scheme, Geneva, Switzerland; Pharmaceutical Research and Manufacturers of America, Washington, DC, USA; Swissmedic, Swiss Agency for Therapeutic Products, Berne, Switzerland; Therapeutic Goods Administration, Woden, ACT, Australia; United Nations Children's Fund, Supply Division, Copenhagen, Denmark; United Nations Children's Fund, New York, USA; United Nations Development Programme, New York, USA; The World Bank, Washington, DC, USA; World Intellectual Property Organization, Geneva, Switzerland; World Self-Medication Industry, Ferney-Voltaire, France.

Laboratoire National de Contrôle des Produits Pharmaceutiques, Chéraga, Alger, Algeria; Instituto Nacional de Medicamentos, Buenos Aires, Argentina; Expert Analytic Laboratory, Centre of Drug and Medical Technology Expertise, Yerevan, Armenia; Laboratoire national de contrôle de qualité des médicaments

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Annex 1

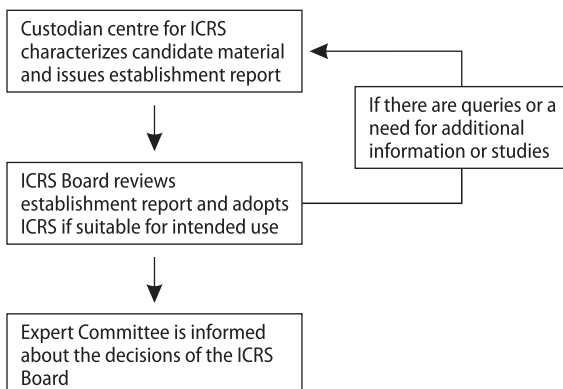
Release procedure for International Chemical Reference Substances

Background

During its forty-fifth meeting in 2010 the Expert Committee on Specifications for Pharmaceutical Preparations agreed on a release procedure for International Chemical Reference Substances (ICRS) (1). Based on this procedure case-reports issued by the custodian centre for ICRS after analytical testing of candidate material were reviewed by the Secretariat with assistance from collaborating laboratories. If the testing was performed according to the *General guidelines for the establishment, maintenance and distribution of chemical reference substances* (2) and the candidate material was found suitable, the Secretariat, in cooperation with the collaborating laboratories, released the ICRS provisionally. In accordance with the rules, the case-reports were subsequently submitted to the Expert Committee on Specifications for Pharmaceutical Preparations during its subsequent meeting, for final adoption. After provisional release the custodian centre for ICRS started the distribution of the ICRS.

This process expedited the release of ICRS and enabled WHO to react more quickly to urgent demands for ICRS. However, the procedure did not clearly allocate the accountability for the release of ICRS to a single time, person or body. Therefore, the Expert Committee members adopted the following new procedure (Figure 1).

Figure 1
New procedure for the adoption of ICRS



New release procedure

After testing of candidate material, the custodian centre for ICRS will submit analytical case-reports to a newly established ICRS Board, which consists of three experts and a representative of the Secretariat. The Board will decide on the suitability of the reference substance on behalf of the Expert Committee and adopt the ICRS, if found to be suitable for the intended use. In case the Board has queries or considers during its in-depth review that there is a need for additional information and/or studies, the Secretariat will contact the custodian centre accordingly. The feedback will in turn be submitted to the Board for its consideration and final decision.

During the subsequent meeting of the Expert Committee its members will be informed about newly adopted ICRS.

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Annex 2

WHO guidelines on quality risk management

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1. Introduction

1.1 Background and scope

In most countries compliance with good manufacturing practices (GMP) (1, 2) (including validation), medicines regulatory activities and inspections, together with supply chain controls throughout the product life-cycle, provide good assurance that risks are largely controlled. However, where control is less effective, patients may be put at risk through the production of medicines of inadequate quality. The assessment of individual risks related to specific products and starting materials and the recognition of hazards at specific stages of production or distribution should permit regulatory authorities to improve control of medicines by increasing the effectiveness of their activities within the limits of the available resources. Quality risk management (QRM) is a process that is relevant to all countries and should provide a rationale to understand risk and mitigate it through appropriate and robust controls.

The aim of these guidelines is to assist the development and implementation of effective QRM, covering activities such as research and development, sourcing of materials, manufacturing, packaging, testing, storage and distribution. In the past, hazard analysis and critical control point (HACCP) methodology, traditionally a food safety management system but subsequently applied to other industries, has been the basis of WHO risk management guidance to the pharmaceutical industry (3).

More recently international guidance has emerged (2, 4–7) that is of specific relevance to the pharmaceutical industry and which addresses the full scope of pharmaceutical industry QRM more effectively than HACCP principles, including how to structure regulatory filings using a risk-based approach. Consequently, these WHO guidelines have been developed as an update on WHO's advice to the pharmaceutical industry, taking account of this new guidance.

To protect patients in terms of quality, safety and efficacy of medicines, international medicines regulatory authorities (MRAs) are recommending pharmaceutical manufacturers to adopt a risk-based approach to the life-cycle of a pharmaceutical product. Some MRAs require the adoption of a risk-based approach for specific areas in the life-cycle of a pharmaceutical product, e.g. environmental monitoring in sterile products manufacture. The level of QRM activity and the density of associated documentation will evolve as the product progresses from early development through to routine production.

QRM is the overall and continuing process of appropriately managing risks to product quality throughout the product's life-cycle in order to optimize its benefit–risk balance. It is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

While the choice of the tools to support the QRM approach is optional and may vary, the tools chosen need to be appropriate for the intended use.

In return for using this approach, there are potential opportunities for both MRAs and pharmaceutical manufacturers (8) as summarized in the following sections.

- Quality risk management (QRM) principles can be applied to both MRAs and pharmaceutical manufacturers:
 - MRAs: systematic and structured planning of reviews and inspections that are risk-based. The submission review and inspection programmes can also operate in a coordinated and synergistic manner.
 - Manufacturers: design, development, manufacture and distribution, i.e. the life-cycle of a pharmaceutical product. QRM should be an integral element of the pharmaceutical quality system (QS).
- Science-based decision-making can be embedded into QRM processes:
 - MRAs: decisions regarding review, inspection or inspection frequency should consider product risk and GMP compliance of the manufacturer. The MRA accepts residual risks through understanding the QRM decisions involved.
 - Manufacturers: quality decisions and filing commitments can be based on a science-based understanding of the process and QRM (when using the quality by design approach, and other approaches where appropriate). Its effective application should offer manufacturers greater freedom to decide how to comply with the principles of GMP and this, therefore, should encourage innovation.

The control strategy for the process focuses on critical quality attributes and critical process parameters.

- Resources can be focused on risks to patients:
 - MRAs: QRM can be used to determine the best allocation of inspection resources, both in terms of product types and for specific areas of focus for a given inspection. This enables the most efficient and effective scrutiny of the most significant health risks. Those manufacturers with poor histories of GMP compliance can also be more closely and frequently evaluated by on-site inspection than those manufacturers with better records.

- Manufacturers: evaluation of quality risk through science-based decisions can be linked ultimately to protection of the patient by ensuring the quality, safety and efficacy of the product. A corporate culture is supported to produce cost-effective medicines, without compromising quality, while maintaining the focus on the patient as a primary stakeholder in all activities.
- Restrictive and unnecessary practices can be avoided:
 - MRAs: regulatory scrutiny should consider the level of risk to patients. Improvement and innovation by manufacturers should be encouraged.
 - Manufacturers: instead of having systems designed to inhibit change and minimize business risk, changes can be managed within a company's quality management system. Innovation and the adoption of the latest scientific advances in manufacturing and technology are supported. Unnecessary testing can be eliminated, for example, with real-time release testing.
- Communication and transparency are facilitated:
 - MRAs: facilitate dialogue with pharmaceutical manufacturers and communicate clearly to the industry and the public how the inspection programme may be adjusted based on the risk to patients. Information-sharing between MRAs will contribute to a better risk management approach globally.
 - Manufacturers: matrix team approach, stakeholders are kept informed through science-based decisions. This builds a culture of trust and a “one-team” mindset with a focus on the product and the patient.

These guidelines will align with the general framework described in other current international guidance on this subject.

1.2 Principles of quality risk management

It is not always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures, e.g. standard operating procedures (SOPs)). The use of an informal risk management process (using empirical tools or internal procedures) can also be considered acceptable.

The two primary principles of QRM are that:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately linked to the protection of the patient.

- The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk.

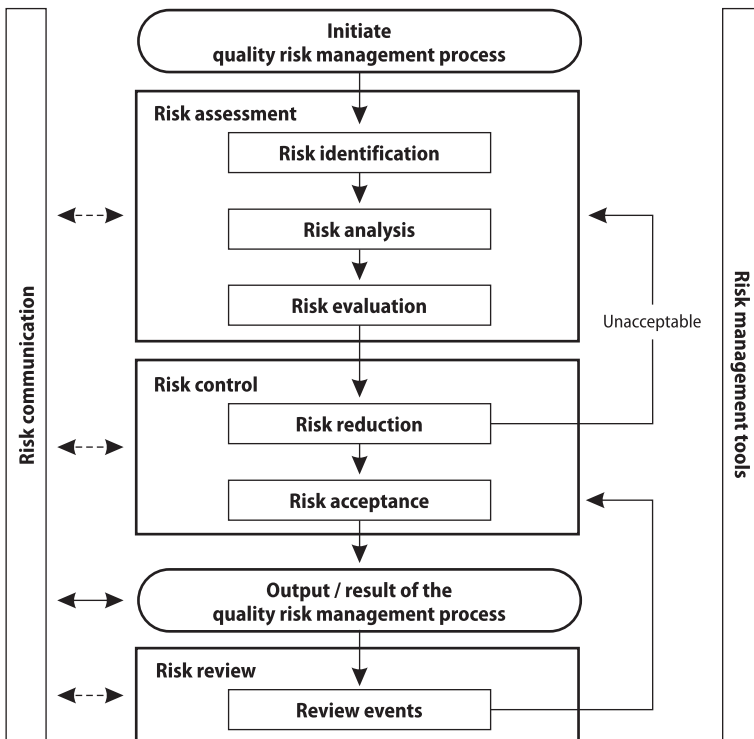
In addition to the two principles above, the following principles are also part of the QRM methodology:

- When applied, processes using QRM methodologies should be dynamic, iterative and responsive to change.
- The capability for continual improvement should be embedded in the QRM process.

This guidance describes the WHO approach to QRM, using the concepts described in ICH Q9 (6) and illustrated in Figure 1. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Figure 1

Overview of a typical quality risk management process



Reproduced from reference 5: ICH Q9: Quality Risk Management.

Decision points are not shown in the diagram above because decisions can occur at any point in the process. The decision might be:

- to return to the previous step and seek further information;
- to adjust the risk models; or even
- to terminate the risk management process based upon information that supports such a decision.

The approach described in these guidelines may be used to:

- systematically analyse products and processes to ensure that the best scientific rationale is in place to improve the probability of success;
- identify important knowledge gaps associated with processes that need to be understood to properly identify risks;
- provide the communication process that will best interface with all relevant parties involved in the QRM activities;
- facilitate the transfer of process knowledge and product development history to ease product progression throughout its life-cycle and to supplement already available knowledge about the product;
- enable the pharmaceutical industry to adopt a risk-based approach to development as described in regulatory guidance (4–6). The QRM outputs will potentially serve as reference documents to support product development and control strategy discussions in regulatory filings.

Early in development, the purpose of the QRM process may be to acquire sufficient product and process knowledge to assess risks associated with formulation development of the finished pharmaceutical product (FPP) according to the quality target product profile (QTPP). In recognizing risks and knowledge gaps, the QRM process plays a significant role in proactively enabling the prioritization and mitigation of risks. The objective is to develop the FPP through maximizing product and process knowledge and risk mitigation.

As FPP development progresses, in addition to supporting that development, the purpose of the QRM process is to determine and manage risks to bioavailability, safety, efficacy and product quality. QRM in development should differentiate process parameters and quality attributes from critical process parameters (CPPs) and critical quality attributes (CQAs), thereby contributing to defining and refining the control strategy.

The long process of product development is inevitably complex and requires the continual exchange of data, decisions and updates both internally

within companies and, where required, with external stakeholders, such as MRAs. A crucial aspect of product development and QRM is the maintenance of an effective and secure knowledge management and documentation system. Such a system must facilitate transparent communication and the highlighting of key issues to stakeholders and must also include a well-structured archive. Clearly, the ability to organize diverse data and information effectively and then retrieve it as required for updating and further evaluation, e.g. for the purposes of process validation, would be hugely beneficial.

Finally, it should be noted that QRM activities are focused on the product/process development and product manufacturing, ultimately to ensure a robust, safe and effective FPP.

2. Glossary

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

control strategy

A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active pharmaceutical ingredients (APIs) and finished pharmaceutical product (FPP) materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

critical quality attribute (CQA)

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

failure mode

Different ways that a process or subprocess can fail to provide the anticipated result.

failure mode, effects and criticality analysis (FMECA)

A systematic method of identifying and preventing product and process problems.

finished pharmaceutical product (FPP)

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

formal experimental design

A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as “design of experiments”.

occurrence

Probability of negative events within a fixed time frame.

pharmaceutical product

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

pharmaceutical product target profile (PPTP)

A definition of the target properties of the FPP, including dosage form and strength(s), route of administration and relevant drug release and pharmacokinetic requirements.

planned risk assessment

An assessment that is conducted in advance of an activity, either before any work is conducted or before further work is conducted. This enables quality to be built into activities and risk to be reduced, e.g. design of high containment facilities for manufacture of cytotoxic products.

process robustness

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

qualification

The action of proving and documenting that any premises, systems and equipment are properly installed and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation.

quality critical process parameter

A process parameter which could have an impact on the critical quality attribute.

quality risk management

A systematic process for the assessment, control communication, and review of risks to the quality of the pharmaceutical product across the product life-cycle.

risk

Combination of the probability of occurrence of harm and severity of the harm.

risk analysis

The estimation of the risk associated with the identified hazards.

risk assessment

A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the evaluation of risk associated with exposure to those hazards.

risk control

The sharing of information about risk and risk management between the decision-maker and other stakeholders.

risk evaluation

The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

risk identification

The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.

risk priority number (RPN)

A numeric assessment of risk assigned to a process, or steps in a process, as part of failure mode effects analysis (FMEA). Each failure mode gets a numeric score that quantifies likelihood of occurrence, likelihood of detection and severity of impact. The product of these three scores is the RPN for that failure mode.
 $RPN = \text{severity rating} \times \text{occurrence rating} \times \text{detection rating}$.

risk review

Review or monitoring of output or results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

stakeholder

Any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Primary stakeholders are the patient, health-care professional, MRAs and the pharmaceutical industry.

unplanned risk assessment

An assessment that is conducted to assess the impact of a situation that has already occurred, e.g. impact of a deviation from normal ways of working.

validation

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

verification

The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with the quality risk management activities.

3. Quality risk management process

3.1 Initiating a QRM process

QRM activities should be performed using systematic processes designed to coordinate, facilitate and improve science-based decision-making with respect to risk. The possible steps to be taken in initiating and planning a QRM process might include the following (5):

- define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;
- assemble background information and/or data on the potential hazard, harm or human health impact relevant to the risk assessment;
- identify a leader and the necessary resources;
- specify a timeline, the deliverables, and an appropriate level of decision-making for the risk management process.

Internal SOPs should define steps, stakeholders, roles and responsibilities (governance and management responsibilities).

3.2 Personnel involved in QRM

The implementing party, i.e. the pharmaceutical manufacturer or regulatory authority, should assure that personnel with appropriate product-specific knowledge and expertise are available to ensure effective planning and completion of QRM activities. This may be best accomplished by assembling a multidisciplinary team according to the guidance provided in section 4.2.

The personnel appointed should be able to:

- conduct a risk analysis;
- identify and analyse potential risks;
- evaluate risks and determine which ones should be controlled and which ones can be accepted;
- recommend and implement adequate risk control measures;
- devise procedures for risk review, monitoring and verification;
- consider the impact of risk findings on related or similar products and/or processes.

QRM activities should be defined and documented.

3.3 Knowledge of the product and process

QRM should be based on knowledge of the product or processes concerned, according to the stage of the product life-cycle.

A flow diagram may be helpful, covering all operations and controls in the process under evaluation. When applying QRM to a given operation, the steps preceding and following that operation should also be considered. A block-type diagram may be sufficiently descriptive. Amendments to the flow diagram may be made where appropriate, and should be documented.

3.4 Risk assessment

When risk assessment is conducted, safety and efficacy need to be considered in addition to the quality concerns.

During the assessment all the risks that may reasonably be expected to occur when conducting the activity under evaluation should be listed. This is usually done when the risk assessment is made for the first time, i.e. initiated, when there is a change or a concern and may also be applied to existing processes. An analysis should be conducted to identify which risks it is essential to eliminate or to reduce to acceptable levels.

A thorough risk assessment is required to ensure effective risk control. Risk assessment should review the materials, operations, equipment, storage, distribution and intended use of the product. Typically a list of the potential risks (biological, chemical and physical) which may be introduced, increased or controlled in each area should be drawn up. In the risk assessment the following basic questions should be addressed:

- What might go wrong?
- What is the nature of possible risks?
- What is the probability of their occurrence and how easy is it to detect them?
- What are the consequences (the severity)?

It should then be decided which of the potential risks should be addressed by the QRM activities and what control measures, if any, should be taken for each risk. If a risk has been identified at a step where control is necessary for safety, and no control measure exists at that step or at any other, the product or process should be modified at that step, or at an earlier or later stage, to include such a control measure. More than one control measure may be required to control a specific risk and more than one risk may be controlled by a specified control measure.

Options for risk assessment methodologies are described in section 5.

Risk assessment can be aided by the use of a decision-tree, which facilitates a logical approach. The way that a decision-tree is used will depend on the operation concerned, e.g. production, packaging, reprocessing, storage or distribution. The best use of QRM tools is discussed further in section 5.

Normally, potential risks in relation to the following should be considered:

- materials and ingredients;
- physical characteristics and composition of the product;
- processing procedures;
- microbial limits, where applicable;
- premises;
- equipment;
- packaging;
- sanitation and hygiene;
- personnel (human error);
- utilities;
- supply chain.

The output of a risk assessment is either a quantitative estimate of risk (numeric probability) or a qualitative description of a range of risk (e.g. high/medium/low) and may be related to a risk matrix (see section 5). The scoring system and trigger points for mitigating action are subjective so the rationale for score categorization should be defined in as much detail as possible. If the score and trigger action are supported by factual evidence it should be more obvious what mitigating action is required – the mitigating action is as important as the score assigned. Professional judgement should be used in interpreting the factual evidence but must be subject to justification.

Records of risk assessments should be maintained.

The expectation of QRM is to assess risks to the product quality and to the patient and then manage these risks so that they are kept at an acceptable level. It is appropriate for companies to assess their control systems so as to implement the appropriate controls to ensure product quality and patient safety. An important principle in QRM is to design risks out of the process or eliminate such risks prospectively, whenever practical and feasible. Risk assessment and mitigation to achieve cost savings, but which could be to the detriment of the well-being of the patient, is an unacceptable practice (9).

3.5 Risk control

Risk control is a decision-making activity designed to reduce and/or accept risks. It usually occurs after risk assessment, and at a fundamental level its purpose is to reduce the risk to an acceptable level.

During risk control activities the following key questions should be asked:

- What can be done to reduce or eliminate risks?
- What is the appropriate balance between benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk control can include:

- not proceeding with the risky activity;
- taking the risk;
- removing the risk source;
- changing the likelihood of the risk;
- changing the consequences of the risk;
- sharing the risk with another party (e.g. contractor);
- retaining the risk by informed decision.

Risk control activities usually involve identifying controls and measures which may reduce or control the risk associated with a failure mode or negative event. Risk control activities can serve to determine critical process parameters for certain controls, how they will be monitored, and the level of qualification and validation, if any, which may be required for such controls.

If risk assessments are conducted and risk controls are employed they should be documented. If the risk assessment is conducted for an ongoing activity it should be subject to periodic review and the frequency of review should be appropriate for the nature of the activity.

Based on the criticality or level of risk, specific corrective actions should be developed to prevent recurrence of instances where there have been deviations from established risk control measures, especially for high risks. These actions should ensure that the risk is brought under control as soon as possible in compliance with the established deviation handling procedures.

Specific corrective actions should be developed in advance for each identified risk, including what is to be done when a deviation occurs and who is responsible for implementing the corrective actions. A record should be kept and maintained of the actions taken.

3.6 Risk review

Appropriate systems should be in place to ensure that the output of the QRM process is periodically monitored and reviewed, as appropriate, to assess new information that may impact on the original QRM decision. Examples of such

changes include changes to control systems, changes to equipment and processes, changes in suppliers or contractors and organizational restructuring.

Monitoring is the scheduled measurement or observation of a specific risk control measure relative to its acceptance limits. Monitoring should be recorded.

All records and documents associated with risk review should be signed and dated by the person(s) carrying out the review and by a responsible official(s) of the quality unit of the company.

3.7 Verification of QRM process and methodologies

Once in production, the QRM documentation can be integrated into the quality system and used to provide input into the product process.

The established QRM process and methodologies need to be verified. Verification and auditing methods, procedures and tests, including random sampling and analysis, can be used to determine whether the QRM process is working appropriately. The frequency of verification should be sufficient to confirm the proper functioning of the QRM process.

Verification activities include:

- review of the QRM process and its records;
- review of deviations and product dispositions (management control);
- confirmation that identified risks are being kept under control.

Initial verification of the planned QRM activities is necessary to determine whether they are scientifically and technically sound, that all risks have been identified and that, if the QRM activities are properly completed, the risks will be effectively controlled.

Information reviewed to verify the QRM process should include:

- expert advice and scientific studies;
- in-plant observations, measurements and evaluations.

Subsequent verifications should be performed and documented by a QRM team or an independent expert, as needed. For example, verifications may be conducted when there is an unexplained system failure, when a significant change in product, process or packaging occurs or new risks are recognized. Where possible, verification should include actions to confirm the efficacy of all elements of the QRM activities.

In addition, a comprehensive review of the QRM process and specific instances of QRM application by an independent third party may be useful. This would include a technical evaluation of the risk analysis and each element of the QRM process and its application as well as an on-site review of all flow

diagrams and appropriate records of the operation of the QRM activity. Such a comprehensive verification is independent of other verification procedures and should be performed to ensure that the QRM process is resulting in the control of the risks. If the results of the comprehensive verification identify deficiencies, the QRM process should be modified as necessary.

Individuals doing verification should have appropriate technical expertise to perform this function.

3.8 Risk communication and documentation

Communication of the QRM process should include key stakeholders. Engaging the key stakeholders in both the data collection process for the risk assessment and the decision-making for risk control will ensure their commitment and support for the QRM. The output of the QRM process and associated risk analysis justifying the approach taken should be documented and endorsed by the organization's quality unit and management. Additionally, this information should be communicated to stakeholders to keep them informed and to ensure their support.

There should be a report for every risk assessment, but the level of effort, formality and documentation necessary will be commensurate with the level of risk (2).

Regarding conclusions of a risk assessment, the mitigation controls should minimize the likelihood of risk to patient safety to an acceptable level of assurance, on the understanding that no risk whatsoever is unlikely in reality. The degree of risk tolerated very much depends on the circumstances, the proximity to the patient and other controls that might follow in response to the process being assessed before the product reaches the patient (2). It is expected that risk mitigation plans will be developed and implemented wherever any risk to patient safety is posed. Companies should take the holistic view and be mindful that critical issues often arise where multiple failures in systems occur together, so mitigation plans should be sufficiently robust to cover this scenario. Inspectors will assess whether risk assessments underrate the likelihood of occurrence and the consequences of overrating detection such that the patient risk is underestimated. The factual evidence behind statements should be robust to challenge by inspectors.

All risk assessments performed by an organization should be documented. The documentation should list and track all key risks as perceived by the organization and summarize how the risks have been mitigated. There should be a clear reference to risk assessments and a list of risk assessments conducted should be maintained. A management process should be in place to review QRM – this may be incorporated into the quality management review process.

4. QRM application for pharmaceuticals

4.1 Training and education

Training of relevant personnel in industry, MRAs and universities in QRM principles and applications is essential for its effective implementation. Industry employees should understand what QRM is, possess the skills necessary to apply it properly, and have access to appropriate resources to enable the effective practice of the QRM principles.

In developing the training programme to support QRM activities, working instructions and procedures should be drawn up which clarify the strategy and define the tasks of all personnel involved in these activities. Specific training should be provided as required to enhance awareness. Staff with the responsibility for managing and reviewing risks should receive formal training in the relevant procedures.

Cooperation between producers, traders and responsible authorities is vital. Opportunities should be provided for the joint training of industrial staff and MRAs to encourage and maintain a continuous dialogue and create a climate of understanding in the practical application of QRM.

The success of QRM depends on the education and training of management and employees to understand the importance of QRM in producing and supplying safe pharmaceuticals.

4.2 Responsibilities

Successful application of QRM is dependent on a clear understanding of responsibilities by all personnel involved in the QRM activities. It is recommended that a cross-functional matrix of assigned responsibilities and accountabilities is drawn up and shared with all relevant personnel.

The pharmaceutical manufacturer should ensure that appropriate knowledge and expertise are available for the effective planning and completion of QRM activities. QRM activities are usually, but not always, undertaken by a matrix of interdisciplinary teams. When teams are formed they should include experts from the appropriate areas (e.g. quality unit, product development, engineering, regulatory affairs, production operations, statistics, clinical, and others, such as sales, marketing or legal, as applicable), in addition to individuals who are knowledgeable about the QRM process.

In this respect it is acceptable for external consultants to participate in the QRM matrix team where they can provide specific expertise or knowledge. Their role should be justifiable and clearly defined and the resultant accountability must be understood. A technical agreement or other equivalent document with the consultant may be appropriate where a GMP responsibility is assumed.

Similarly, contract staff may become involved in leading or participating in risk assessments, e.g. a contract authorized person. The extent of their involvement and responsibility and accountability must be documented in a technical agreement or other equivalent document between the individual concerned and the pharmaceutical company. Regarding the authorized person it is important that a company's internal procedures are clear on where the responsibility lies for final approval of risk acceptance documents.

Effective matrix team leadership is required to take responsibility for coordinating QRM across various functions and departments of the organization and to ensure that the QRM activities are adequately defined, planned, resourced, deployed and reviewed. The leader and team will need to identify critical resources required to implement the QRM activities, and also specify a timeline, deliverables and appropriate levels of decision-making for the QRM process.

4.3 QRM application during product development

The application of QRM procedures evolves through the various stages in the development of a product.

The first QRM exercise should be performed once the QTPP is defined and preformulation work on the candidate medicine is complete. At this stage of a project there may be significant gaps in knowledge. Therefore, it will be important to apply risk tools that are appropriate for such a situation. These might include:

- cause and effect diagrams (also known as Ishikawa or Fishbone diagrams);
- flowcharts (e.g. input-process-output (IPO));
- decision-trees;
- fault-tree analysis;
- relationship matrices.

As the product progresses to later stage of development, a more detailed analysis of the risks associated with both the active pharmaceutical ingredient (API) and the FPP should be considered. Risks would cover concerns associated with stability, bioavailability and patient safety including any challenges to these areas resulting from the manufacturing process (including, for example, API form conversion under certain conditions of processing).

As product knowledge advances, more detailed QRM exercises can be considered, concentrating on areas considered to present higher priority risk. As the product's critical quality attributes (CQAs) become defined, the potential risks arising from each input material (API, excipients, any device or pack components) and each secondary product unit operation can be investigated.

Eventually, for the developed FPP, the increasingly comprehensive risk assessment will support a thorough understanding of the product and will enable all key variables to be identified, understood and controlled.

4.4 QRM application during validation and qualification

In keeping with the principles of QRM, these guidelines recommend that process validation embraces the product life-cycle concept already mentioned. Accordingly, process validation activities should involve the generation and evaluation of data throughout the process, from development to full-scale production, which will provide a science-based assurance of consistent delivery of quality product in the production operation (9–10).

It is important to emphasize that the building of scientific assurance begins early in development. It is obtained through rational design of experiments and robust evaluation of data during product and process development through to the commercial production phase, by which time the API and FPP CQAs are well understood and controlled. In this scenario, validation or (perhaps more appropriately termed) conformance batches serve to reinforce the science- or risk-based decisions that have been made as product development has advanced and should demonstrate good control of all critical sources of variability that have been identified. Any unplanned variations within a batch or between batches should be evaluated employing suitable statistical tools, e.g. trend analysis, to check on process control.

A potential advantage of this approach is that there can be flexibility in the number of validation or conformance batches required for regulatory scrutiny prior to approval. The traditional number of batches required for validation has been three but, with QRM embedded in a product's development process, the number of conformance batches needed depends on the depth of knowledge about the process. For very low-volume products, e.g. orphan drugs, this may preclude the need to manufacture multiple batches. It would be beneficial for decisions of this nature regarding conformance batches to have an effective company–MRA dialogue to agree on requirements for a regulatory submission.

When applicable, the principles of QRM should also be applied for qualification activities.

QRM principles can be used to determine the scope of qualification. They can also be used to determine the optimal schedule for maintenance, monitoring, calibration and requalification.

Manufacturers should have sufficient knowledge of the process and product to ensure that by the time the product is commercialized, processes are optimized and risks are minimized.

4.5 QRM application during commercial manufacturing

In general, implementing QRM should not obviate a manufacturer's obligation to comply with regulatory expectations (e.g. regulatory requirements, regulatory filings and inspection commitments). All QRM activities should be structured in a way that allows responsibility for risk assessment and actions at appropriate levels of the hierarchy within the organization. Special focus can be put on the risk assessment and risk control during the life-cycle of a product, and may include:

- product quality risks;
- adverse impact on patient health resulting from product quality defects;
- interruption of product supply to patients;
- GMP and regulatory compliance risks;
- multisite risks;
- multiproduct risks;
- new facility and changes to existing facility, e.g. start-ups, new commercial manufacturing processes, technology transfers and product discontinuation.

After completion of the risk assessment and risk control activities, the outcomes should be summarized and appropriately communicated. The results may be documented in a new or existing report or they may be included as part of another document approved by appropriate decision-makers (e.g. site or functional management, system owner, or quality unit). A risk review is important if new risks or changes to existing risk levels are identified as a result of planned or unplanned events such as routine operation, changes, complaints, product returns, discrepancies or deviations, data monitoring, trends, inspections or audits, or changes in regulatory environment. Risk review may also include evaluation of, for example:

- effectiveness of risk control activities and actions;
- changes in observed risk levels or existing controls.

In principal, areas of focus when implementing QRM in commercial manufacturing include a system focus, a process focus and a product focus.

4.5.1 QRM integration with key quality system elements

Effective QRM can facilitate the decision on “What to do?” and, therefore, support better and more informed decisions. QRM should be integrated into existing quality system elements and related business processes and documented appropriately.

Accordingly, the use of QRM can be beneficial across a broad spectrum of operations, e.g.:

- integrated quality management:
 - documentation
 - training and education
 - quality defects
 - auditing and inspection
 - change management and change control (includes equipment, facilities, utilities, control and IT systems)
 - continual improvement and corrective and preventive actions (CAPA);
- facilities, equipment and utilities:
 - design
 - qualification
 - maintenance and decommissioning of facility or equipment
 - hygiene aspects
 - cleaning of equipment and environmental control
 - calibration and preventive maintenance
 - computer systems and computer-controlled equipment;
- supplier, materials and contract service management:
 - assessment and evaluation of suppliers and contract manufacturers
 - starting material
 - use of materials
 - storage
 - logistics and distribution conditions;
- technology transfer:
 - from development to manufacturing
 - during commercial manufacturing between sites
 - from commercial manufacturing to product discontinuation.

4.5.2 QRM application in product manufacturing operations

Effective QRM can facilitate the “How to do it?” and, therefore, ensure that the products will meet acceptable standards for safety, quality, and compliance.

Among others, QRM methodology can support the following actions to assess and control quality risks:

- production:
 - manufacturing process risks
 - validation
 - in-process sampling and testing controls
 - production planning
 - deviation and investigation management
 - change management;
- laboratory control and stability studies:
 - out-of-specification results
 - retest period and expiry date
 - method transfers;
- packaging and labelling:
 - design of packages
 - selection of container-closure system
 - label controls;
- storage, transport and distribution:
 - e.g. cold chain.

5. QRM considerations for medicines regulatory authorities

5.1 Introduction

A key principle of these guidelines is that all MRAs, manufacturing sites in developing countries and API manufacturers should demonstrate, wherever appropriate, application of QRM throughout the product life-cycle for development and manufacturing facilities. Inspectors will review this QRM system as part of the quality systems section of the inspection (along with complaints, recalls, deviations, product quality reviews and others).

Equally, it is recommended that QRM be applied by the MRAs (for examples see (2, 8)) themselves (reviewers and inspectorates) as there are clear benefits of a QRM-based review and inspection plan. For example, inspectors can allocate time and resources commensurate with the perceived significance of

risk in any given situation and can be pragmatic regarding the level of scrutiny and degree of formality required.

5.2 QRM application to inspection strategy

5.2.1 Risk management in inspections

The inspection section or unit of an MRA should operate within a written, implemented quality management system (11). SOPs should be followed for activities including (but not limited to) inspection planning, review of corrective and preventive actions after inspections and complaint handling and investigation. Where appropriate, the procedures and activities during inspection should be in line with the principles of QRM.

The unit should have a risk management plan that describes the philosophy, approach, procedures and implementation of risk management. The risk management plan should be reviewed and updated on a continuous basis, or at least annually, and should cover all types of inspections (including GMP, good clinical practices (GCP), good laboratory practices (GLP)) and other activities.

Appropriate risk assessment tools should be used in the process, and the risk assessment for a site to be inspected should be documented on a risk assessment worksheet. Records should be maintained.

A metric system should be used for risk ratings, e.g. on a scale from 1 to 3.

5.2.2 Inspection planning and conduct

The frequency and scope of inspections should be determined based on risk assessment that covers product risk and patient risk.

Risk rating should normally be done only for sites that have been previously inspected. The risk assessment worksheet should be completed after every inspection. Inspection of a site that has not been inspected previously may be waived only in cases where a recognition procedure exists between regulatory inspection units, and where, in addition, appropriate evidence of GXP compliance is available which indicates that there is no risk or an acceptably low risk to products and patients.

Various factors should be considered in the risk assessment exercise, and these factors may be different for the different types of GXP inspections. Risk factors to be considered depend on the type of inspection, and may include:

- outcome of inspection by another regulatory authority;
- outcome of the previous inspection;
- complexity of the site (e.g. buildings, utilities);
- complexity of the product (e.g. sterile, non-sterile);
- type of product (e.g. biological, low-dose);

- complaints and recalls;
- significance of changes (e.g. equipment, key personnel);
- results of product testing;
- risk to the patient;
- complex route of synthesis (API);
- polymorphism (API);
- biopharmaceutical classification of the product;
- innovative or emerging technology.

The number of inspectors and number of days required for the inspection, as well as the scope of the inspection, should be determined based on the risk rating of the site inspection.

Inspection reports should contain findings and observations. Departures from GXP should be classified where appropriate, as “critical”, “major” or “minor”.

The unit should have an SOP that describes the classification process. Classification should be based on risk assessment. The level of risk assigned should be in accordance with the nature of the observation as well as the number of occurrences.

5.2.3 **Corrective action and preventive action review, and scheduling of routine inspections**

CAPA should be requested from a site, following an inspection. The CAPAs should address the observations included in an inspection report. Based on the outcome of the inspection and the acceptability of the CAPA, the risk rating of the site should be reviewed and recorded.

Inspection frequency should be defined based on the risk rating. For example, the frequency can be defined as every 6, 12, 18 or 24 months. (*Note:* The maximum time interval should be no more than every 36 months.)

5.2.4 **Complaint handling and investigation**

Handling and investigation of quality complaints should be done in accordance with a written SOP. The scope and depth of the investigation (including whether a desk review or on-site inspection will be done) should be based on risk assessment.

5.3 **Inspection of QRM at a manufacturing site**

Note: During inspections, inspectors should assess whether a manufacturer has appropriate skills and scientific knowledge, as well as product and process knowledge, for the QRM procedure being inspected. This is also relevant where a company has made use of contracted parties.

The company's QRM procedure should be appropriately detailed and should be integrated into the company's quality management system. It should cover at least the following areas:

- It should specify the general approach to both planned and unplanned risk assessment, including scope, responsibilities, controls, approvals, management systems, applicability and exclusions.
- Personnel should have appropriate qualifications, experience and training. Their responsibilities with regard to QRM should be clearly defined.
- Senior management should be involved in the identification and implementation of QRM principles within the company.
- The risk management procedure(s) for each area of application should be clearly defined.
- Quality assurance principles should be applied to QRM-related documentation, e.g. review, approval, implementation and archiving.

QRM policies and procedures should be clear and the workflow should be systematic and conducted in a logical order.

- The procedure for risk management should be implemented.
- Manufacturers should identify significant risks and consider all the relevant data from reliable sources.
- The level of effort and resources used in risk assessment should be appropriate to the importance of the identified problem.
- Critical issues should be addressed with appropriate urgency and formality.
- There should be a logical selection of tools for risk assessment.
- Risk acceptance criteria should be appropriate.
- Risk assessments should not underrate the severity, nor overrate detection of occurrences resulting in underestimating patient risk.
- The risk acceptance criteria should be appropriate for the specific situation in question.
- Risk controls should be effective.
- The company should have a review programme to measure the effectiveness of the measures taken.
- Risk-based decision(s) should be science-based and concordant with the predefined acceptance criteria.

All documentation related to the QRM activities should be completed within a reasonable period and should be accessible. Risk assessments performed should be reviewed when appropriate, and additional controls implemented when required.

Personnel should be trained and assessed in the principles of QRM. Where appropriate, a team of members of personnel should participate in the QRM processes.

5.4 **QRM applied to dossier review (assessment)**

The assessment processes of national medicines regulatory authorities (NMRAs) rely on QRM principles in the management of resources (time and assessors), as well as in the management of product-related risk factors. Efficient management of resources minimizes the risk that limited resources are not used to their best effect, and ultimately ensures that important products are made available in a timely manner. Key factors to be considered include the prioritization of dossiers, the screening process, identification of the specific risk factors inherent to a given dossier or dosage form, and allocation of resources to the various sections of a dossier for a given product. In addition, product-related risk factors must be managed throughout the life-cycle of the product, for example, through effective communication between assessors and inspectors, and by establishing systems for dealing with the products after approval.

The allocation of priority to dossiers should take into account the therapeutic needs of the regional population (e.g. disease occurrence, the need for paediatric formulations, combination products, or experience with innovative or emerging technology) and the availability of medicines on the market. Prioritization should be a dynamic process to enable it to accommodate emerging issues such as pandemics. Other considerations related to prioritization based on medical need may include fixed-dose combinations versus single-ingredient or co-packaged products, extended release products versus products administered as two or three daily doses, second-line versus first-line products, flexible dosage forms such as dispersible tablets and variable dose products such as oral liquids.

The screening process examines the completeness of a dossier. Screening ensures that only those dossiers that meet minimum standards for completeness can enter into the full assessment process. Insufficient screening processes allow lower quality dossiers to be accepted for review, thus significantly increasing assessment time.

Identification of dossier-related and product-related risk factors allows for the allocation of appropriate resources to specific dossiers. Possible risk factors include: the experience and track record of the manufacturer, narrow therapeutic range products, sterile versus non-sterile APIs and products;

API-related considerations such as use of semi-synthetic and fermentation products, complex routes of synthesis, polymorphism, isomerism and potential genotoxic impurities; and product-related considerations such as the use of novel excipients, the complexity of the formulation, single-ingredient versus fixed-dose combinations, and special delivery systems (e.g. modified release, transdermal products, and inhalation products). Once risk factors have been identified, resources should be allocated to minimize risk. For example, assessors with expertise related to the product-related risk identified should be assigned to assess the dossier whenever possible. When resources allow, the assessors may be organized according to specialization, assigning assessors to various product categories (e.g. generic products, sterile products, solid oral dosage forms, or special delivery systems). This can facilitate the development of expertise in key areas and promote consistency of review, as well as ensuring that products requiring specialized knowledge are identified and assessed by those with the appropriate expertise. Where a high level of risk is identified for a dossier, the more experienced assessors need at least to be available on a consultation basis.

The risk level associated with a dossier may change during the course of assessment. For example, rejection of the bioequivalence study will result in additional time required to conduct and assess additional studies and associated additional quality information. In such a scenario the risk relates both to the use of additional resources and to an increased risk that the overall product quality may be poor.

Allocation of resources to various aspects or sections of the dossier is an important QRM consideration, in order to ensure that the resources used are commensurate with the risk level. An understanding of the relative criticality of dossier sections or aspects is necessary for efficient use of resources. All aspects of the dossier are important to achieve overall quality, safety and efficacy; however some areas are inherently more critical from a risk perspective and warrant more attention in the assessment process. Examples include the clinical reviews, bioavailability reviews, API synthesis, specifications and stability studies, FPP manufacturing details, pharmaceutical development studies including biowaiver justification, process validation, specifications and stability studies. An example applicable to most simple solid oral products is that more time should be allocated to the review of manufacturing steps prior to packaging than to reviewing the packaging process.

During the assessment process there should be a standard procedure for communicating to the inspectors those issues identified which may require consideration during inspection. After approval of a product, QRM principles should be applied to evaluate the impact of proposed variations or changes. Clear guidelines that outline possible post-approval changes and assign an associated risk level are an effective means to achieve this.

6. Risk management tools

A variety of tools can be used for the purposes of QRM, either alone or in combination. It is important to note that no single tool or combination of tools is applicable to every situation in which a QRM procedure is used. Examples of tools are listed in regulatory guidance (6, 8); neither list is exhaustive. The important criterion for acceptability is that the tool or tools are used effectively to support the key attributes of a good risk assessment.

The Product Quality Research Institute (PQRI) Manufacturing Technology Committee (MTC) has produced a summary (9) of common risk management principles and best practices, several working tools to foster consistency in the use of ICH Q9 (5) in day-to-day risk management decision-making, and a series of examples of risk management applications currently in use by major pharmaceutical firms. They have also produced very helpful risk tool training modules for risk ranking and filtering, failure modes effects analysis (FMEA) (12–15), hazard operability analysis (HAZOP) (16) and HACCP (3).

One aspect worth highlighting is the development of a risk matrix to facilitate categorization of risks identified during the risk assessment phase. In order to prioritize a risk, it is essential to agree upon its significance. The risk associated with any situation or event can be represented as the impact of that event multiplied by the probability of its occurrence; in other words: how likely is it to happen? and how severe would it be if it did happen? Impact and probability can each be classified, e.g. into 5 levels (1–5) or with a weighting towards the higher probability and impact ratings (e.g. 1, 3, 5, 7, 10, etc.), so that a grid or matrix can be constructed (Table 1).

Table 1
An example of a probability versus impact matrix

Probability	Impact				
	Negligible	Marginal	Moderate	Critical	Catastrophic
Almost certain	5	10	15	20	25
Likely	4	8	12	16	20
Possible	3	6	9	12	15
Unlikely	2	4	6	8	10
Rare	1	2	3	4	5

The shading in the table represents an example of how the risk values (sometimes called composite risk indices or risk index values) can be assigned a high, medium or low status. The definition for each status should be predetermined in the QRM process after consideration of the specific consequences for the process undergoing risk assessment. These consequences can be split according to the probability and impact scores, as exemplified in Table 2.

Table 2
Example of a consequences table for probability and impact

Score	Probability	Example	Score	Impact	Consequence
1	Rare	• Seen every 10–30 years	1	Negligible	• No regulatory issue • No effect on and not noticeable by patient
2	Unlikely	• Seen every 5–10 years	2	Marginal	• May require MRA notification • Decision to release product not compromised
3	Possible	• Seen every 1–5 years	3	Moderate	• MRA inspection may identify a major concern but deficiency quite easily resolved • Limited product recall possible
4	Likely	• Seen to occur more than once a year	4	Critical	• MRA inspection may conclude serious non-compliance • Likely product recall from one or more markets
5	Almost certain	• Seen several times a year	5	Catastrophic	• Enforcement action by MRA such as consent decree, product seizure • Global product recall

MRA, Medicines regulatory authority.

Source: Based on reference 9. This table has been amended, but was originally produced within the context of the Product Quality Research Institute (PQRI), 2107 Wilson Blvd, Suite 700, Arlington, Virginia 22201-3042, USA; web site: <http://www.pqri.org/index.asp>. PQRI has kindly agreed to the use of its material.

This table is a very basic example and would need to be customized for the specific process in question to enable a better and more practical definition of the consequence categories. It should be cautioned that the value of a risk matrix relies very heavily upon input information and should only be used by staff with a good understanding of the embedded judgements and, as such, the resolution of the low, medium or high categorization.

As a summary of the common, well-recognized QRM tool options available for the purposes of these guidelines, Table 3 has been based on the one from the Product Quality Research Institute Manufacturing Technology Committee (PQRI-MTC) report (9). The list is not comprehensive but it does include some of the more frequently used approaches.

Table 3
Examples of common risk management tools

Risk management tool	Description, attributes	Potential applications
Tools		
Diagram analysis <ul style="list-style-type: none"> • Flowcharts • Check sheets • Process mapping • Cause/effect diagrams 	<ul style="list-style-type: none"> • Simple techniques that are commonly used to gather and organize data, structure risk management processes and facilitate decision-making 	<ul style="list-style-type: none"> • Compilation of observations, trends or other empirical information to support a variety of less complex deviations, complaints, defaults or other circumstances
Risk ranking and filtering	<ul style="list-style-type: none"> • Method to compare and rank risks • Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk, and weighting factors and risk score 	<ul style="list-style-type: none"> • Prioritizing operating areas or sites for audit or assessment • Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool
Fault-tree analysis	<ul style="list-style-type: none"> • Method used to identify all root causes of an assumed failure or problem • Used to evaluate system or subsystem failures one at a time, but can combine multiple causes of failure by identifying causal chains • Relies heavily on full process understanding to identify causal factors 	<ul style="list-style-type: none"> • Investigate product complaints • Evaluate deviations

continues

Table 3 *continued*

Risk management tool	Description, attributes	Potential applications
Tools		
Hazard operability analysis (HAZOP)	<ul style="list-style-type: none"> • Tool assumes that risk events are caused by deviations from the design and operating intentions • Uses a systematic technique to help identify potential deviations from normal use or design intentions 	<ul style="list-style-type: none"> • Access manufacturing processes, suppliers, facilities and equipment • Commonly used to evaluate process safety hazards
Hazard analysis and critical control point (HACCP)	<ul style="list-style-type: none"> • Identify and implement process controls that consistently and effectively prevent hazard conditions from occurring • Bottom-up approach that considers how to prevent hazards from occurring and/or propagating • Emphasizes strength of preventive controls rather than ability to detect 	<ul style="list-style-type: none"> • Better for preventive applications than reactive • Valuable precursor or complement to process validation • Assessment of the efficacy of critical control points and the ability to consistently execute them for any process
Failure modes effects analysis (FMEA)	<ul style="list-style-type: none"> • Assumes comprehensive understanding of the process and that CPPs have been defined prior to initiating the assessment. Tool ensures that CPPs will be met. • Assesses potential failure modes for processes, and the probable effect on outcomes and/or product performance • Once failure modes are known, risk reduction actions can be applied to eliminate, reduce or control potential failures 	<ul style="list-style-type: none"> • Evaluate equipment and facilities; analyse a manufacturing process to identify high risk steps and/or critical parameters

continues

Table 3 *continued*

Risk management tool	Description, attributes	Potential applications
Tools		
Failure modes effects analysis (FMEA)	<ul style="list-style-type: none"> Highly dependent upon strong understanding of product, process and/or facility under evaluation Output is a relative “risk score” for each failure mode 	

Source: Based on reference 9. This table has been amended, but was originally produced within the context of the Product Quality Research Institute (PQRI), 2107 Wilson Blvd, Suite 700, Arlington, Virginia 22201-3042, USA; web site: <http://www.pqri.org/index.asp>. PQRI has kindly agreed to the use of its material.

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Annex 3

WHO guidelines on variations to a prequalified product

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Introduction

The variation guidelines have been completely updated and expanded, bringing them into line with the principles of the new generic quality guidelines, WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

The guidelines¹ retain the basic structure and function of the previous variation guidelines, and have been expanded to include the classification of additional post-approval/post-prequalification changes and to establish the level of risk inherent to each change.² Although the general requirements have not significantly changed, the additional details help the reader to classify changes that may occur related to all the major sections of a quality dossier, to understand the considerations necessary to assess the risk of each change, and to determine the documentation required to support the change.

In some cases, changes that previously were considered major changes by default are now classified minor variations or notifications, and some minor variations have been reclassified as notifications. In addition, for some categories that previously required acceptance of the change prior to implementation, the applicant can now implement the change immediately upon notification.

The change categories are organized according to the structure of the common technical document (CTD). The specific CTD sections associated with individual data requirements have been identified in order to assist in the filing of documentation (reproduced with corresponding numbers in bold). Presentation corresponds to section 1.4 in Annex 4 of WHO Technical Report Series, No. 970.³

Changes are classified as major only in those instances where the level of risk is considered to be high and it is deemed necessary to provide the WHO Prequalification of Medicines Programme (WHO/PQP) with adequate time for an assessment of the supporting documentation. Particular circumstances are identified where lower reporting requirements (annual notification (AN), immediate notification (IN) or minor variation (Vmin)) are possible. In all cases where notification to WHO/PQP or acceptance by WHO/PQP is required prior

¹ Guidance on variations to a prequalified product dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007 (WHO Technical Report Series, No. 943), Annex 6.

² WHO Guidelines on quality risk management. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh report*. Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2.

³ Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report*. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 4.

to implementation, assessment timelines will be published in order to provide predictable and reasonable timeframes.

In addition, the guidelines assist in understanding the possible consequences of the listed changes, and may be useful as a risk management tool to promote or enhance best practices within organizations.

A companion Question and Answer document is in preparation to assist in interpretation of the guidelines. This document will address many of the questions raised during the guidelines circulation process.

1. Background

This guidance document is technically and structurally inspired by the European Union Institutions and Bodies Commission's Guideline on the details of the various categories of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products. It is intended to provide supportive information on how to present an application to implement a change to a product.

This guidance supersedes the guidance published in 2007.⁴

An applicant is responsible for the safety, efficacy and quality of a product throughout its life-cycle. Therefore, the applicant is required to make changes to the details of the product in order to accommodate technical and scientific progress, or to improve or introduce additional safeguards for the prequalified product. Such changes, whether administrative or substantive, are referred to as variations and may be subject to acceptance by WHO/PQP prior to implementation.

Technical requirements for the different types of variations are set out in these guidelines in order to facilitate the submission of appropriate documentation by applicants and their assessment by WHO/PQP and to ensure that variations to the medicinal product do not result in health concerns.

The procedure for submitting variations is not within the scope of these guidelines. Advice on the procedure for submitting a variation and current review timelines are set out on the WHO/PQP web site which may be updated from time to time. Applicants are advised to consult information on the web site whenever they are considering the submission of a variation application.

1.1 Objectives

These guidelines are intended to:

- assist applicants with the classification of changes made to the quality part of a prequalified finished pharmaceutical product (FPP);

⁴ See footnote 1.

- provide guidance on the technical and other general data requirements to support changes to the quality attributes of the active pharmaceutical ingredient (API) or FPP.

1.2 Scope and application

These guidelines apply to applicants intending to make changes to the quality sections of product dossiers for an API or an FPP. This guidance should be read in conjunction with the *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*⁵ as well as other related WHO guidelines.

This guidance document is applicable only to APIs and excipients manufactured by chemical synthesis or semi-synthetic processes and FPPs containing such APIs and excipients. APIs produced by fermentation and APIs of biological, biotechnological or herbal origin are treated as special cases. The applicant is requested to contact WHO/PQP regarding planned variations to such products.

The notification requirements for API-related changes differ depending on the manner in which information on the API was submitted in the FPP application, namely, use of a prequalified API, use of a European Pharmacopoeia Certificate of Suitability (CEP), use of the API master file (APIMF) procedure, or as provided in full within the dossier.

The conditions and documentation stipulated in this guidance for API-related variations focus primarily on those FPPs that relied upon the provision of full API information within the FPP dossier. In general FPPs that rely upon the APIMF procedure have reduced reporting requirements because the API manufacturers themselves have notified the relevant API-related change directly to WHO/PQP. Similarly, when an FPP relies upon a CEP or a prequalified API, FPP applicants are required to notify WHO/PQP only when the associated CEP or Confirmation of API Prequalification document has been revised.

Guidance for API manufacturers on the technical and procedural requirements for changes to prequalified APIs and to APIs supported by the APIMF procedure is available on the Prequalification web site. Regardless of whether the API-related change is notified primarily by the API manufacturer (API prequalification (API-PQ) procedure, APIMF procedure or CEP), or the FPP manufacturer (full API information in dossier) the technical requirements are in principle the same as those stipulated in these guidelines.

Whenever FPPs have been prequalified on the basis of approval by a stringent regulatory authority (SRA) (innovator products or generic products), subsequent applications for variations should be approved by the same SRA and

⁵ See footnote 3.

WHO/PQP should be notified of the approval of the changes. Applicants are advised to refer to the Letter of Prequalification.

When a variation leads to a revision of the summary of product characteristics (SmPC), the patient information leaflet (PIL), labelling and packaging leaflet and updated product information should be submitted as part of the application.

For variations that require generation of stability data on the API or FPP, the stability studies required, including commitment batches, should always be continued to cover the currently accepted retest or shelf-life period. WHO/PQP should be informed immediately if any problems with the stability of APIs or FPPs occur during storage, e.g. if found to be outside specifications or potentially outside specifications.

Applicants should be aware that some variations may require the submission of additional consequential variations, including where the variation states, “no variation is required, such changes are handled as amendments to the APIMF by the APIMF holder”. Therefore, for any given change the applicant should consider whether one or more variations may be required to be submitted.

If changes to the dossier only concern editorial changes, such changes need not be submitted as a separate variation, but can be included as a notification together with a subsequent variation concerning that part of the dossier. In such a case, a declaration should be provided that the contents of the associated sections of the dossier have not been changed by the editorial changes beyond the substance of the variation submitted.

2. Guidance for implementation

2.1 Reporting types

The definitions outlined in the following reporting types are intended to provide guidance with respect to the classification of quality-related changes. Specific examples of changes are provided in these guidelines. However, it should be noted that a change not covered by these guidelines, should be considered as a major change by default. Whenever the applicant is unclear about the classification of a particular change, WHO/PQP should be contacted. It remains the responsibility of the applicant to submit relevant documentation to justify that the change will not have a negative impact on the quality of the product.

Individual changes normally require the submission of separate variations. Grouping of variations is acceptable only under the following circumstances:

- when variations are consequential to each other, e.g. introduction of a new impurity specification that requires a new analytical procedure;

- when the same change affects multiple FPPs, e.g. addition of a new API manufacturing site for multiple FPPs;
- when all the changes are annual notification.

For the purposes of classification, an application involving two or more types of variations will be considered as the highest risk type, e.g. a variation grouping both a minor change and a major change will be classified as a major change.

Applicants are also advised to exercise caution whenever several changes to the same FPP are envisaged. Although each of the individual changes may be classified as a particular reporting type, classification within a higher risk category may be warranted as a result of the composite effect of these changes. In all such cases, applicants are advised to contact WHO/PQP prior to submission of the variation application to obtain guidance on classifying such changes.

2.1.1 Notifications

Notifications are changes that could have minimal or no adverse effects on the overall safety, efficacy and quality of the FPP. Such notifications do not require prior acceptance, but must be notified to WHO/PQP immediately after implementation (immediate notification (IN)), or within 12 months following implementation (annual notification (AN)) of the change.

It should be highlighted that an IN or AN may be rejected in specific circumstances with the consequence that the applicant must cease to apply the already implemented variation.

Annual notification (AN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change. The change should be summarized as part of the notification but the indicated documentation is not required to be submitted. The documentation indicated for ANs should be available on request or at the time of inspection. ANs should be submitted to WHO/PQP within 12 months of implementation of the changes. For convenience applicants may group several AN changes as a single submission.

Immediate notification (IN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application. Such changes can be implemented immediately at the time of submission and they can be considered accepted if an objection is not issued by WHO/PQP within 30 calendar days of the date of acknowledgement of receipt of the application.

2.1.2 Minor variation (Vmin)

Minor variations are changes that may have minor effects on the overall safety, efficacy and quality of the FPP. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application.

Such variations can be implemented if no objection letter has been issued within a time period indicated on the WHO/PQP web site. Should questions arise during the specified period, the change can only be implemented on receipt of a letter of acceptance from WHO/PQP.

2.1.3 Major variation (Vmaj)

Major variations are changes that could have major effects on the overall safety, efficacy and quality of the FPP. The documentation required for the changes included in this reporting type should be submitted. Prior acceptance by WHO/PQP is required before the changes can be implemented. A letter of acceptance will be issued for all major variations if and when the variation is considered acceptable.

2.1.4 New applications and extension applications

Certain changes are so fundamental that they alter the terms of the accepted dossier and consequently cannot be considered as changes. In these cases a new dossier must be submitted. Examples of such changes are listed in Appendix 1.

2.1.5 Labelling information

For any change to labelling information (SmPC, PIL, labels) not covered by the variation categories described in this document, WHO/PQP must be notified and submission of the revised labelling information is expected as per the guidance on the WHO/PQP web site.

2.2 Conditions to be fulfilled

For each variation, attempts have been made to identify particular circumstances where lower reporting requirements (IN, AN or Vmin) are possible. A change that does not meet all of the conditions stipulated for these specific circumstances is considered to be a Vmaj.

In some circumstances Vmaj categories have been specifically stated for a given variation. This has been done to indicate to applicants what documents should be provided. This is for informational purposes only. The list of documentation is not intended to be comprehensive and further documentation may be required. For all changes it remains the responsibility of the applicant to provide all necessary documents to demonstrate that the change does not have a negative effect on the safety, efficacy or quality of the FPP.

2.3 Documentation required

Examples of variations are organized according to the structure of the CTD. For each variation, certain documents have been identified as supporting data and are organized according to CTD structure. Regardless of the documents specified, applicants should ensure that they have provided all relevant information to support the variation.

Where applicable, the following should be included in the application:

- a variation application form (a template can be downloaded from the web site). All sections of this form should be completed and the document signed. Electronic versions of the application form, both as a Word document and a scanned signed PDF, should be provided in addition to the printed version;
- an updated quality information summary (QIS) (if applicable);
- replacement of the relevant sections of the dossier as per CTD format;
- copies of SmPC, PIL and labels, if relevant.

It should be noted that WHO/PQP reserves the right to request further information not explicitly described in these guidelines.

The QIS provides a summary of the key quality information from the product dossier. For FPPs that have an agreed-upon QIS, the QIS should be revised and submitted (in Word format only) with every variation application. Any revised sections within the QIS should be highlighted. If there is no change to the QIS as a result of the variation, a statement should be made in the covering letter to this effect.

Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. It is also important to note that WHO/PQP may request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the safety, efficacy and quality of an FPP.

3. Glossary

The definitions provided below apply to the terms used in this guidance. They may have different meanings in other contexts and documents.

active pharmaceutical ingredient (API)

A substance used in the FPP, intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.

active pharmaceutical ingredient (API) starting material

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

applicant

For the purposes of this document, the term applicant refers to any person or entity who has participated in the procedure for prequalification of FPPs by submission of the required documentation on a product that has been listed after evaluation as prequalified.

biobatch

The batch used to establish bioequivalence or similarity to the comparator product as determined in bioequivalence or biowaiver studies, respectively.

final intermediate

The last reaction intermediate in the synthetic pathway that undergoes synthetic transformation to the API or the crude API. Purification is not considered to be a synthetic transformation.

finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product which has undergone all stages of manufacture including packaging in its final container and labelling.

in-process control

Check performed during manufacture to monitor or to adjust the process in order to ensure that the final product conforms to its specifications.

manufacturer

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

officially recognized pharmacopoeia (or compendium)

Those pharmacopoeias recognized in the WHO/PQP (i.e. *The International Pharmacopoeia* (Ph. Int.), the *European Pharmacopoeia* (Ph. Eur.), the *British Pharmacopoeia* (BP), the *Japanese Pharmacopoeia* (JP) and the *United States Pharmacopoeia* (USP)).

pilot-scale batch

A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth

that of a full production scale or 100 000 tablets or capsules, whichever is the larger, unless otherwise adequately justified.⁶

production batch

A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application.

stringent regulatory authority (SRA)

A stringent regulatory authority is:

- the medicines regulatory authority in a country which is: (a) a member of the International Conference on Harmonisation (ICH) (European Union (EU), Japan and the United States of America); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by SwissMedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time);
- only in relation to good manufacturing practices (GMP) inspections: a medicines regulatory authority that is a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) as specified at <http://www.picscheme.org>

4. Administrative changes

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
1 Change in the name and/or corporate address of the supplier of the FPP.	1	1	IN

Conditions to be fulfilled

1. Confirmation that the supplier of the product remains the same legal entity.

Documentation required

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

continues

⁶ Procedure for prequalification of pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009 (WHO Technical Report Series, No. 953), Annex 3.

Table *continued*

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
2 Change in the name or address of a manufacturer of an API that is not a supplier of a prequalified API or that is not supported by a CEP.	1	1–2	IN

Conditions to be fulfilled

1. No change in the location of the manufacturing site and in the manufacturing operations.

Documentation required

1. A formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned.
2. An updated Letter of Access in case of change in the name of the holder of the APIMF.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
3 Change in the name and/or address of a manufacturer of the FPP.	1	1	IN

Conditions to be fulfilled

1. No change in the location of the manufacturing site and in the manufacturing operations.

Documentation required

1. Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
4 Deletion of a manufacturing site or manufacturer involving:			
4a production of the API starting material	1	1	AN
4b production or testing of the API intermediate or API	1–2	1	IN
4c production, packaging or testing of the intermediate or FPP	1–2	1	IN

continues

Table *continued***Conditions to be fulfilled**

1. At least one other site continues to perform the same function(s) as the site(s) intended to be deleted.
2. The deletion of the site is not a result of critical deficiencies in manufacturing.

Documentation required

1. Clear identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application.

5. Changes to a CEP or to a confirmation of API-prequalification document

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
5	Submission of a new or updated CEP for an API or starting material or intermediate used in the manufacturing process of the API:			
5a.1	from a currently accepted manufacturer	1–5	1–5	AN
5a.2		1–4	1–6	IN
5a.3		1, 3–4	1–6	Vmin
5b.1	from a new manufacturer	1–4	1–6	IN
5b.2		1, 3–4	1–6	Vmin

Conditions to be fulfilled

1. No change in the FPP release and shelf-life specifications.
2. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for any impurities including organic, inorganic and genotoxic impurities and residual solvents, with the exception of residual solvents when the limits stipulated comply with ICH requirements.
3. The manufacturing process of the API, starting material or intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4. For low solubility APIs the polymorph is the same, and whenever particle size is critical (including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.
5. No revision of the FPP manufacturer's API specifications is required.

continues

Table *continued***Documentation required**

1. Copy of the current (updated) CEP, including any annexes and a declaration of access for the CEP to be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the WHO/PQP who refers to the CEP.
2. A written commitment that the applicant will inform WHO/PQP in the event that the CEP is withdrawn and an acknowledgement that withdrawal of the CEP will require additional consideration of the API data requirements to support the product dossier.
3. Replacement of the relevant pages of the dossier with the revised information for the CEP submission option stipulated under section 3.2.S of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.
4. (S.2.5) For sterile APIs, data on the sterilization process of the API, including validation data.
5. (P.8.2) In the case of the submission of a CEP for an API, if the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one batch of the FPP of at least pilot-scale, and to continue the study throughout the currently accepted shelf-life and to immediately report any out-of-specification results to WHO/PQP.
6. (S.4.1) Copy of FPP manufacturer's revised API specifications.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
6	Submission of a new or updated confirmation of API-prequalification document			
6a.1	from a currently accepted manufacturer	1–3	1–3, 5	AN
6a.2		1–2	1–5	Vmin
6b.1	from a new manufacturer	1–3	1–3, 5	IN
6b.2		1–2	1–5	Vmin

Conditions to be fulfilled

1. No change in the FPP release and shelf-life specifications.
2. For low solubility APIs the API polymorph is the same, and whenever particle size is critical (including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.
3. There is no difference in impurity profile of the proposed API to be supplied, including organic, inorganic, genotoxic impurities and residual solvents, compared to that of the API currently supplied. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications.

continues

Table *continued***Documentation required**

1. Copy of the current (updated) confirmation of API-PQ document. The API manufacturer should duly fill out the authorization box with the name of the applicant or FPP manufacturer seeking to use the document.
2. Replacement of the relevant pages of the dossier with the revised information for the API-PQ procedure submission option (*Option 1: confirmation of API Prequalification document*) stipulated under section 3.2.S. of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.
3. (S.2.5) For sterile APIs, data on the sterilization process of the API, including validation.
4. (S.4.1) Copy of FPP manufacturer's revised API specifications.
5. (P.8.2) If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one batch of at least pilot-scale of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out-of-specification results to WHO/PQP.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
7 Submission of a new or updated transmissible spongiform encephalopathy (TSE) CEP for an excipient or API (addition or replacement)	None	1	AN

Conditions to be fulfilled

None

Documentation required

1. Copy of the current (updated) TSE CEP.

6. Quality changes

3.2. S Drug substance (or API)

3.2. S.2 Manufacture

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
8 Replacement or addition of a new manufacturing site or manufacturer of an API involving:			

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
8a.1	API testing only	1, 2, 4	1, 3–4	IN
8a.2		2, 4	1, 3–4	Vmin
8b.1	production of API starting material	3–4	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder.	
8b.2		4–5	1–2, 12	IN
8b.3		None	1,2,5, 7–8,12, 13	Vmaj
8c.1	production of API intermediate	3–4	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder.	
8c.2		4, 6	1–2, 12	IN
8c.3		None	1, 2, 5, 7–8, 12, 13	Vmaj
8d.1	production of API (APIMF procedure)	3, 7–9	1, 2, 6, 8	IN
8d.2		3, 7, 9	1, 2, 6–8	Vmin
8e.1	production of API (full dossier)	1, 9–11	1–2, 4, 8–9	IN
8e.2		None	1, 2, 4, 5, 7–8, 10–11, 13	Vmaj

Conditions to be fulfilled

1. The API is non-sterile.
2. The transfer of analytical methods has been successfully undertaken.
3. The new site is supported by an APIMF that is currently accepted through the APIMF procedure and the FPP manufacturer holds a valid Letter of Access.
4. No change in the FPP manufacturer's API specifications.
5. The impurity profile of the API starting material is essentially the same as other accepted sources. The introduction of the new supplier does not require the revision of the API manufacturer's API starting material specifications. The route of synthesis is verified as identical to that already accepted.
6. Specifications (including in-process, methods of analysis of all materials), method of manufacture and detailed route of synthesis are verified as identical to those already accepted. The introduction of the new supplier does not require the revision of the API manufacturer's API intermediate specifications.

continues

Table *continued***Conditions to be fulfilled**

7. No change in the FPP release and end-of-shelf-life specifications.
8. No difference in impurity profile of the proposed API to be supplied, including organic, inorganic and genotoxic impurities and residual solvents. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications.
9. For low-solubility APIs the API polymorph is the same, and whenever particle size is critical (including low-solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.
10. Specifications (including in-process controls, methods of analysis of all materials), method of manufacture (including batch size) and detailed route of synthesis are verified as identical to those already accepted (such situations are generally limited to additional sites by the same manufacturer or a new contract manufacturing site with evidence of an acceptable and similar quality system to that of the main manufacturer).
11. 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* (www.who.int/biologicals) or EMA's *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* (www.emea.europa.eu/ema) or equivalent guidelines of the ICH region and associated countries.

Documentation required

1. (S.2.1) Name, address, and responsibility of the proposed site or facility involved in manufacture or testing (including block(s) and unit(s)). A valid testing authorization or a certificate of GMP compliance, if applicable.
2. (S.2.2) A side-by-side comparison of the manufacturing flowcharts for production of the API, intermediate, or API starting material (as applicable) at the parent and proposed sites and a tabulated summary of the differences.
3. (S.4.3) Copies or summaries of validation reports or method transfer reports, which demonstrate equivalence of analytical procedures to be used at the proposed testing site.
4. (S.4.4) Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot-scale) batches of the API from the currently accepted and proposed manufacturers and/or sites.
5. Relevant sections of (S) documentation in fulfilment of requirements for full information provided in the dossier under section 3.2.S of the *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.⁷

*continues*⁷ See footnote 3.

Table *continued*

Documentation required

6. The open part of the new APIMF (with a Letter of Access provided in Module 1) and documentation in fulfilment of requirements for the APIMF option under section 3.2.S of the *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.⁸
 7. (P.8.2) If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one production-scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to WHO/PQP.
 8. (S.4.1) A copy of the FPP manufacturer's API specifications.
 9. (S.2) A declaration from the supplier of the prequalified FPP that the route of synthesis, materials, 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 accepted.
 10. A discussion of the impact of the new API on the safety, efficacy and quality of the FPP.
 11. For low solubility APIs where polymorphic form is different or whenever particle size is critical (including low-solubility APIs) where there is a significant difference in particle size distribution compared to the lot used in the biobatch, evidence that the differences do not impact the quality and bioavailability of the FPP.
 12. Certificates of analysis for at least one batch of API starting material or intermediate (as applicable) issued by the new supplier and by the API manufacturer. Comparative batch analysis of final API manufactured using API starting material or intermediate (as applicable) from the new source and from a previously accepted source. For an alternative source of plant-derived starting material, control of pesticide residues must be established. This can either be in the form of an attestation from the starting material supplier that no pesticides are used during the growth of the plant material, or by providing the results of pesticide screening from one batch of the starting material.
 13. An analysis of the impact of the change in supplier with respect to the need for API stability studies and a commitment to conduct such studies if necessary.
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continues

⁸ See footnote 3.

Table continued

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
9a change or addition of a manufacturing block or unit at a currently accepted site of API manufacture	1–5	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder.	
9b	1, 3–5	1–4	IN

Conditions to be fulfilled

1. The API is non-sterile.
2. The API manufacturing block or unit is currently accepted through the APIMF procedure.
3. The same quality system covers currently accepted and proposed units or blocks.
4. For low-solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change to the particle size distribution compared to the API lot used in the preparation of the biobatch.
5. No change in 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). Minor changes in the equipment are acceptable.

Documentation required

1. (S.2) A declaration from the supplier of the 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 accepted.
2. (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and/or testing (including block(s) and unit(s)). A valid manufacturing and/or testing authorization and a certificate of GMP compliance, if available.
3. (S.4.4) Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot-scale) batches of the API from the currently accepted and proposed units or blocks.
4. (S.2.2) A summary of differences between manufacture and control of the API at the currently accepted and proposed units or blocks, if applicable.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
10a change in the manufacturing process of the API	1–3, 9	1–2, 8	AN
10b.1	1–2, 4, 6–9	3–4, 11–12	IN

continues

Table *continued*

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
10b.2 change in the manufacturing process	1–2, 4, 6–8, 10	3–4, 11–12	Vmin
10c of the API	1–2, 4–7	3–4, 11–12	Vmin
10d	None	2–14	Vmaj

Conditions to be fulfilled

1. No change in the physical state (e.g. crystalline, amorphous) of the API.
2. For low solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change in the particle size distribution compared to that of the API lot used in the preparation of the biobatch.
3. The API manufacturing site is currently accepted through the APIMF procedure.
4. Where materials of human or animal origin are used in the process, the manufacturer does not use any new process for which assessment of viral safety data or TSE risk assessment is required.
5. No change in the route of synthesis (i.e. intermediates remain the same) and there are no new reagents, catalysts or solvents used in the process.
6. No change in qualitative and quantitative impurity profile or in physicochemical properties of the API.
7. The change does not affect the sterilization procedures of a sterile API.
8. The change involves only steps before the final intermediate.
9. The change does not require revision of the starting material, intermediate or API specifications.
10. The change does not require revision of the API specifications.

Documentation required

1. A copy of the APIMF amendment acceptance letter.
2. (P.8.2) If the quality characteristics of the API are changed in a way that may impact the stability of the FPP, a commitment to put under stability one production-scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to WHO/PQP.
3. (S.2.2) A side-by-side comparison of the current process and the new process.
4. (S.2.2) A flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).
5. (S.2.3) Information on the quality and controls of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable.

continues

Table *continued***Documentation required**

6. (S.2.3) Either a TSE CEP for any new source of material or, where applicable, documented 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 guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products* (www.who.int/biologicals) or EMA's *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* (www.emea.europa.eu/ema) or equivalent guidelines of the ICH region and associated countries.
7. (S.2.4) Information on controls of critical steps and intermediates, where applicable.
8. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, if applicable.
9. (S.3.1) Evidence for elucidation of structure, where applicable.
10. (S.3.2) Information on impurities.
11. (S.4.1) A copy of currently accepted specifications of API (and starting material and intermediate, if applicable).
12. (S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results, in a comparative tabular format, for at least two batches (minimum pilot-scale) manufactured according to the current and proposed processes.
13. (S.7.1) Results of two batches of at least pilot-scale with a minimum of three months of accelerated (and intermediate as appropriate) and three months of long-term testing of the proposed API.
14. For low-solubility APIs where the polymorphic form has changed or whenever particle size is critical (including low-solubility APIs) where there is dissimilar particle size distribution compared to the lot used in the biobatch, evidence that the differences do not impact the quality and bioavailability of the FPP.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
11	Change in the in-process tests or limits applied during the manufacture of the API:			
11a	any change in the manufacturing process controls	1	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder	
11b	tightening of in-process limits	2–4	1	AN
11c	addition of a new in-process test and limit	2, 5	1–5	AN

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
11d	addition or replacement of an in-process test as a result of a safety or quality issue	None	1–5, 7, 8–10	Vmin
11e.1	deletion of an in-process test	2, 6–7	1–3, 6	AN
11e.2		None	1–3, 7–10	Vmaj
11f	relaxation of the in-process test limits	None	1–3, 5, 7–10	Vmaj

Conditions to be fulfilled

1. API manufacturing site is currently accepted through the APIMF procedure.
2. The change is not necessitated by unexpected events arising during manufacture e.g. a new unqualified impurity or a change in total impurity limits.
3. The change is within the range of currently accepted limits.
4. The analytical procedure remains the same, or changes to the analytical procedure are minor.
5. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The affected parameter is non-significant.
7. The change does not affect the sterilization procedures of a sterile API.

Documentation required

1. A comparison of the currently accepted and the proposed in-process tests.
2. (S.2.2) Flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).
3. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed API.
4. Details of any new non-pharmacopoeial analytical method and validation data where relevant.
5. Justification for the new in-process test and/or limits.
6. Justification and/or risk-assessment showing that the parameter is non-significant.
7. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, where applicable.
8. (S.3.2) Information on impurities, if applicable.
9. (S.4.1) Copy of currently accepted specifications of API (and intermediates, if applicable).
10. (S.4.4) Description of the batches, certificates of analysis or batch analysis report and summary of results, in a comparative tabular format, for at least two batches (minimum pilot-scale) for all specification parameters.

continues

Table *continued*

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
12	Change in batch size of the API or intermediate involving:			
12a	up to 10-fold compared to the currently accepted batch size	1–2, 4, 6	1, 3–4	AN
12b.1	downscaling	1–4	1, 3–4	AN
12b.2		1–3	1–4	IN
12c	any change in scale (APIMF procedure)	5	1–2, 4–5	AN
12d	more than 10-fold increase compared to the currently accepted batch size	1–2, 4, 6	1, 3–4	Vmin

Conditions to be fulfilled

1. No changes to the manufacturing process other than those necessitated by changes in scale (e.g. use of a different size of equipment).
2. The change does not affect the reproducibility of the process.
3. The change is not necessitated by unexpected events arising during manufacture or due to stability concerns.
4. The change does not concern a sterile API.
5. The API manufacturing site and batch size is currently accepted through the APIMF procedure.
6. The proposed batch size increase is relative to either the originally accepted batch size, or the batch size accepted through a subsequent major or minor variation.

Documentation required

1. (S2.2) A brief narrative description of the manufacturing process.
2. (S.2.5) Where applicable, evidence of process validation and/or evaluation studies for sterilization.
3. (S.4.1) Copy of the currently accepted specifications of the API (and of the intermediate, if applicable).
4. (S.4.4) Batch analysis data (in tabular format) issued by the FPP manufacturer for a minimum of two batches each of the currently accepted batch size and the proposed batch size.
5. A copy of the APIMF amendment acceptance letter.

continues

Table *continued*

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
13 Change to the specifications or analytical procedures applied to materials used in the manufacture of the API (e.g. raw materials, starting materials, reaction intermediates, solvents, reagents, catalysts) involving:			
13a any change	1	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder	
13b tightening of the specification limits	2–4	1–3	AN
13c minor change to an analytical procedure	5–7	2–3	AN
13d addition of a new specification parameter and a corresponding analytical procedure where necessary	2, 7–9	1–3	AN
13e deletion of a specification parameter or deletion of an analytical procedure	2, 10	1–4	AN
13f addition or replacement of a specification parameter as a result of a safety or quality issue	None	1–3, 5	Vmin
13g relaxation of the currently accepted specification limits for solvents, reagents, catalysts and raw materials	4, 7, 9–10	1, 3–4	IN
13h relaxation of the currently accepted specification limits for API starting materials and intermediates	None	1–3, 5	Vmaj

continues

Table *continued***Conditions to be fulfilled**

1. API manufacturing site is currently accepted through the APIMF procedure.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any change is within the range of currently accepted limits.
4. The analytical procedure remains the same.
5. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments, to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method).
6. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former analytical procedure.
7. No change to the total impurity limits; no new impurities are detected.
8. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
9. The change does not concern a genotoxic impurity.
10. The affected parameter is non-significant or the alternative analytical procedure has been previously accepted.

Documentation required

1. Comparative table of currently accepted and proposed specifications.
2. (S.2.3) Information on the quality and controls of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable.
3. (S.2.4) Information on intermediates, where applicable.
4. Justification and/or risk assessment showing that the parameter is non-significant.
5. (S.3.2) Information on impurities, where applicable.

3.2. S.4 Control of the API by the API manufacturer

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
14	Changes to the test parameters, acceptance criteria, or analytical procedures of the API manufacturer that do not require a change to the FPP manufacturer's API specifications involving:		
14a	a. API supported through the APIMF procedure.	1–2	No variation is required; such changes are handled as amendments to the associated APIMF

continues

Table *continued*

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
14b b. API not supported through the APIMF procedure.	2	1–4	IN

Conditions to be fulfilled

1. The revised test parameters, acceptance criteria, or analytical procedures have been submitted as amendments to the associated APIMF and accepted.
2. The API manufacturer has provided the relevant documentation to the FPP manufacturer. The FPP manufacturer has considered the API manufacturer's revisions and determined that no consequential revisions to the FPP manufacturer's API test parameters, acceptance criteria, or analytical procedures are required to ensure that adequate control of the API is maintained.

Documentation required

1. (S.4.1) Copy of the current and proposed API specifications dated and signed by the API manufacturer.
2. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (S.4.3) Copies or summaries of validation reports for new or revised analytical procedures, if applicable.
4. Justification as to why the change does not affect the FPP manufacturer's specifications.

3.2. S.4 Control of the API by the FPP manufacturer

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
15 Change to the test parameters or acceptance criteria of the API specifications of the FPP manufacturer involving:			
15a updating a test parameter or acceptance criterion controlled in compliance with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the API is controlled.	11	1–5	AN

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
15b.1	deletion of a test parameter	1–2	1, 6	AN
15b.2		10	1, 6, 8	IN
15b.3		None	1, 6	Vmaj
15c.1	addition of a test parameter	1, 4–8	1–6	AN
15c.2		1, 5–6, 10	1–6, 8	IN
15c.3		1, 5–6	1–6	Vmin
15c.4		None	1–7	Vmaj
15d.1	replacement of a test parameter	1, 5–8	1–6	IN
15d.2		5, 7, 10	1–6, 8	Vmin
15d.3		None	1–7	Vmaj
15e.1	tightening of an acceptance criterion	1, 3, 9	1, 6	AN
15f.1	relaxation of an acceptance criterion	1, 5–9	1, 6	IN
15f.2		5, 7, 10	1, 6, 8	Vmin
15f.3		None	1, 6–7	Vmaj

Conditions to be fulfilled

1. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
2. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
3. The change is within the range of currently accepted acceptance criteria.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. For insoluble APIs there is no change in the polymorphic form and whenever particle size is critical (including low-solubility APIs) there is no change in particle size distribution acceptance criteria.
6. No additional impurity found over the ICH identification threshold.
7. The change does not concern sterility testing.
8. The change does not involve the control of a genotoxic impurity.
9. The associated analytical procedure remains the same.
10. The change has resulted from a revision of the API manufacturer's specifications and is accepted as part of an APIMF amendment.
11. No change is required in FPP release and shelf-life specifications.

continues

Table *continued***Documentation required**

1. (S.4.1) A copy of the proposed API specifications (of the FPP manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications. In addition, if the change has resulted from a revision to the API manufacturer's specifications, a copy of the API specifications (of the API manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (S.4.3) Copies or summaries of validation or verification reports issued by the FPP manufacturer, if new analytical procedures are used.
4. (S.4.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
5. (S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results in tabular format, for at least one batch if new tests and/or analytical methods are implemented.
6. (S.4.5) Justification of the proposed API specifications (e.g. test parameters, acceptance criteria, or analytical procedures).
7. (P.2) Where changes have occurred to the particle size criteria of an insoluble API or wherever particle size is critical, evidence is provided that the changes do not affect the in vitro release properties and bioavailability of the FPP. In general, it is sufficient to provide multipoint comparative dissolution profiles (in three media covering the physiological range (pH 1.2 or (0.1N HCl), 4.5 and 6.8) without surfactant) for one batch of FPP manufactured using API that meets the proposed criteria; one batch of FPP manufactured using API that meets the currently accepted criteria; and data on the FPP batch used in the registration bioequivalence study. However, if the routine dissolution medium contains a surfactant, the applicant should contact WHO/PQP for advice. For changes to the polymorph of an insoluble API the applicant should contact WHO/PQP for advice before embarking upon any investigation.
8. Copy of the APIMF amendment acceptance letter.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
16	Change to the analytical procedures used to control the API by the FPP manufacturer involving:		
16a	None	1–3	AN
	change in an analytical procedure as a result of a revision to the officially recognized pharmacopoeial monograph to which the API is controlled.		

continues

Table *continued*

16b	change from a currently accepted in-house analytical procedure to an analytical procedure in an officially recognized pharmacopoeia or from the analytical procedure in one officially recognized pharmacopoeia to an analytical procedure in another official recognized pharmacopoeia	None	1–4	IN
16c.1	addition of an analytical procedure	1–3	1–3	AN
16c.2		3, 8	1–3, 5	AN
16c.3		8	1–3, 5	Vmin
16c.4		None	1–3	Vmaj
16d.1		1–6	1–4	AN
16d.2	modification or replacement of an analytical procedure	2–3, 5–6, 8	1–5	AN
16d.3		1–3, 5–6	1–4	Vmin
16d.4		5–6, 8	1–5	Vmin
16d.5		None	1–4	Vmaj
16e.1		deletion of an analytical procedure	6–7	1, 6
16e.2	6, 8		1, 5, 6	IN
16e.3	None		1, 6	Vmaj

Conditions to be fulfilled

1. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. No new impurities have been detected as a result of the use of the new analytical method.
4. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected.

continues

Table *continued***Conditions to be fulfilled**

5. Comparative studies are available demonstrating that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure.
6. The change does not concern sterility testing.
7. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method.
8. The new or modified analytical method is identical to that used by the API manufacturer and has been accepted as part of an amendment to the associated APIMF.

Documentation required

1. (S.4.1) Copy of the proposed API specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (S.4.2) Copies or summaries of analytical procedures if new or significantly modified analytical procedures are used.
3. (S.4.3) Copies or summaries of validation or verification reports issued by the FPP manufacturer if new or significantly modified analytical procedures are used.
4. (S.4.4) Comparative analytical results demonstrating that the proposed analytical procedures are at least equivalent to the accepted analytical procedures.
5. A copy of the APIMF acceptance letter.
6. (S.4.5) Justification for the deletion of the analytical procedure, with supporting data.

3.2. S.6 Container-closure system

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
17a	Change in the immediate packaging (primary and functional secondary components) for the storage and shipment of the API	3, 4	1–2, 4	AN
17b		1–2, 4	2–3	IN
17c		4	1–3	Vmin

Conditions to be fulfilled

1. Results demonstrate that the proposed primary packaging type is at least equivalent to the currently accepted primary packaging type with respect to its relevant properties (e.g. including results of transportation or interaction studies, and moisture permeability among others).
2. The change does not concern a sterile API.
3. The change has previously been accepted through the APIMF procedure.
4. The change is not the result of stability issues.

continues

Table *continued***Documentation required**

1. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization if different from the current process.
2. (S.6) Information on the proposed primary packaging (e.g. description and specifications) and data in fulfillment of condition 1.
3. (S.7.1) Results of (or a commitment to study in the case of demonstrated equivalent or more protective packaging) a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing of the API in the proposed primary packaging type.
4. A copy of the APIMF amendment acceptance letter.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
18	Change in the specifications of the immediate packaging for the storage and shipment of the API involving:			
18a	tightening of specification limits	1–2	1	AN
18b	addition of a test parameter	2–3	1–3	AN
18c	deletion of a non-critical parameter	2	1, 4	AN
18d	any change (APIMF procedure)	4	No variation is required; such changes are handled as amendments to the associated APIMF	

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. The change has previously been accepted through the APIMF procedure.

Documentation required

1. (S.4.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.
2. (S.4.2) Details of method and summary of validation of new analytical procedure.
3. (S.6) Certificate of analysis for one batch.
4. Justification to demonstrate that the parameter is not critical.

continues

Table *continued*

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
19	Change to an analytical procedure on the immediate packaging of the API involving:			
19a	minor change to an analytical procedure	1–3	1	AN
19b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2–4	1	AN
19c	deletion of an analytical procedure	5	2	AN
19d	any change (APIMF procedure)	6	No variation is required; such changes are handled as amendments to the associated APIMF	

Conditions to be fulfilled

1. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method).
2. Appropriate (re)validation studies have been performed in accordance with the relevant guidelines.
3. Comparative studies indicate the new analytical procedure to be at least equivalent to the currently accepted procedure.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method.
6. The change has previously been accepted through the APIMF procedure.

Documentation required

1. (S.6) Comparative validation results demonstrating that the currently accepted and proposed procedures are at least equivalent.
2. Justification for deletion of the analytical procedure.

3.2. S.7 Stability

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
20	Change in the retest period or shelf-life of the API involving:			
20a	any change (APIMF procedure)	4	4	IN
20b	reduction	3	1–2	IN
20c	extension	1–2	1–3	Vmin

Conditions to be fulfilled

1. No change to the primary packaging in direct contact with the API or to the recommended condition of storage.
2. Stability data were generated in accordance with the currently accepted stability protocol.
3. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
4. The revised retest period has previously been accepted through the APIMF procedure.

Documentation required

1. (S.7.1) Proposed retest period or shelf-life, summary of stability testing according to currently accepted protocol and test results.
2. (S.7.2) Updated post-acceptance stability protocol and stability commitment and justification of change, when applicable.
3. (S.7.3) Stability data to support the change.
4. A copy of the APIMF acceptance letter.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
21	Change in the labelled storage conditions of the API involving:			
21a	any change in storage conditions (APIMF procedure)	1	1	IN
21b	any change in storage conditions	2	2	Vmin

Conditions to be fulfilled

1. The revised storage conditions have previously been accepted through the APIMF procedure.

continues

Table *continued***Conditions to be fulfilled**

2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

Documentation required

1. A copy of the APIMF acceptance letter.
2. (S.7.1) Stability and/or compatibility test results to support the change to the storage conditions.

3.2. P Drug product (or FPP)**3.2. P.1 Description and composition of the FPP**

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
22a Change in the composition of a solution dosage form	1–6	2, 4, 7, 9–10	IN
22b	None	1–10	Vmaj

Conditions to be fulfilled

1. The affected excipient(s) does/do not function to affect the solubility and/or the absorption of the API.
2. The affected excipient(s) does/do not function as a preservative or preservative enhancer.
3. No change in the specifications of the affected excipient(s) or the FPP.
4. No change in the physical characteristics of the FPP (e.g. viscosity, osmolality, pH).
5. The change does not concern a sterile FPP.
6. The excipients are qualitatively the same. The change in the amount (or concentration) of each excipient is within $\pm 10\%$ of the amount (or concentration) of each excipient in the originally prequalified product.

Documentation required

1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.
2. (P.1) Description and composition of the FPP.
3. (P.2) Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients, suitability studies on the packaging system for the changed product).
4. (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.

continues

Table *continued*

5. (P.4) Control of excipients, if new excipients are proposed.
6. (P.4.5) If applicable, either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines 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 derived, country of origin of the source animals, and use of the material.
7. (P.5) Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
8. (P.8.1) Results of stability testing generated on at least two pilot- or production-scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
9. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
10. (R.1) Copies of relevant pages of blank master production documents with changes highlighted, as well as relevant pages of the executed production document for one batch and confirmation that there are no changes to the production documents other than those highlighted.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
23	Change in the colouring system or the flavouring system currently used in the FPP involving:			
23a	reduction or increase of one or more components of the colouring or the flavouring system	1–3, 6	1, 4, 6–7	AN
23b	deletion, addition or replacement of one or more components of the colouring or the flavouring system	1–6	1–7	IN

Conditions to be fulfilled

1. No change in the functional characteristics of the pharmaceutical form e.g. disintegration time or dissolution profile.

continues

Table *continued***Conditions to be fulfilled**

2. Any minor adjustment to the formulation to maintain the total weight is made using an excipient which currently makes up a major part of the FPP formulation.
3. Specifications for the FPP are updated only with respect to appearance, odour and/or taste or if relevant, deletion or addition of a test for identification.
4. Any new component must comply with section 3.2.P.4 of the *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.⁹
5. Any new component does not include the use of materials of human or animal origin for which assessment of viral safety data is required, or is in compliance with the current *WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products* (www.who.int/biologicals) or EMA's *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* (www.emea.europa.eu/ema) or an equivalent guide from the ICH region and associated countries.
6. Where applicable, the change does not affect the differentiation between strengths and for paediatric formulations it does not require submission of results of taste acceptability studies.

Documentation required

1. Sample of the FPP.
2. (P.2) Discussion on the components of the FPP (e.g. compatibility of API and qualitative composition of the colouring or flavouring system if purchased as a mixture, with specifications, if relevant).
3. (P.4.5) Either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines 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 derived, country of origin of the source animals, and use of the material.
4. (P.5) Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches.
5. (P.5.3) If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
6. (P.8.1) Results of stability testing generated on at least two pilot- or production-scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
7. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch and confirmation that there are no changes to the production documents other than those highlighted.

*continues*⁹ See footnote 3.

Table continued

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
24	Change in weight of tablet coatings or capsule shells involving:			
24a	immediate-release oral FPPs	1–3	2–5	AN
24b	gastro-resistant, modified or prolonged release FPPs	None	1–5	Vmaj

Conditions to be fulfilled

1. Multipoint in vitro dissolution profiles of the proposed version of the product (determined in the routine release medium on at least two batches of pilot- or production-scale), are similar to the dissolution profiles of the biobatch.
2. Coating is not a critical factor for the release mechanism.
3. Specifications for the FPP are updated only with respect to weight and dimensions, if applicable.

Documentation required

1. Justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence (*Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms*, WHO Technical Report Series, No. 937, 2006, Annex 8).
2. (P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium (or media), on at least two batches of pilot- or production-scale of the proposed product versus the biobatch.
3. (P.5) Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of one pilot- or production-scale batch.
4. (P.8.1) Results of stability testing generated on at least one pilot- or production-scale batch with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
5. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch and confirmation that there are no changes to the production documents other than those highlighted.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
25	Change in the composition of an immediate-release solid oral dosage form including:			
25a.1	replacement of a single excipient with a comparable excipient at a similar concentration	1–5	1–10	Vmin
25a.2	replacement of a single excipient with a comparable excipient at a similar concentration	None	1–10	Vmaj

continues

Table *continued*

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
25b.1 quantitative changes in excipients	1–4	1–4, 7–10	Vmin
25b.2	None	1–4, 7–10	Vmaj

Conditions to be fulfilled

1. No change in functional characteristics of the pharmaceutical form.
2. Only minor adjustments (see Appendix 2) are made to the quantitative composition of the FPP; any minor adjustment to the formulation to maintain the total weight is made using an excipient which currently makes up a major part of the FPP formulation.
3. Stability studies have been started under conditions according to WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*¹⁰ (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot- or production-scale batches, satisfactory stability data covering at least 3 months are at the disposal of the applicant, and the stability profile is similar to that of the currently accepted product.
4. The dissolution profile of the proposed product determined on a minimum of two pilot-scale batches is similar to the dissolution profile of the biobatch.
5. The change is not the result of stability issues and/or does not result in potential safety concerns, i.e. differentiation between strengths.

Documentation required

1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.
2. (P.1) Description and composition of the FPP.
3. (P.2) Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients), comparative multipoint in vitro dissolution profiles obtained on at least two batches of pilot- or production-scale of the proposed product and the biobatch (depending on the solubility and permeability of the drug, dissolution in the routine release medium or in multiple media covering the physiological pH range).
4. (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
5. (P.4) Control of excipients, if new excipients are proposed.

*continues*¹⁰ See footnote 3.

Table *continued***Documentation required**

6. (P.4.5) If applicable, either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines 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 derived, country of origin of the source animals and its use.
7. (P.5) Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
8. (P.8.1) Results of stability testing generated on at least two pilot- or production-scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
9. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
10. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch, and confirmation that there are no changes to the production documents other than those highlighted.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
26	Change or addition of imprints, embossing or other markings, including replacement or addition of inks used for product markings and change in scoring configuration involving:			
26a	changes in imprints, embossing or other markings	1–3	1–2, 5–6	IN
26b	deletion of a scoreline	2–5	1, 5–6	IN
26c.1	addition of a scoreline	2–4	1, 3, 5–6	Vmin
26c.2		None	1, 3–6	Vmaj

continues

Table *continued***Conditions to be fulfilled**

1. Any ink complies with section 3.2.P4 of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.¹¹
2. The change does not affect the stability or performance characteristics (e.g. release rate) of the FPP.
3. Changes to the FPP specifications are those necessitated only by the change to the appearance or to the scoring.
4. Addition or deletion of a score line from a generic product is consistent with a similar change in the comparator product or was requested by WHO/PQP.
5. The scoring is not intended to divide the FPP into equal doses.

Documentation required

1. Sample of the FPP.
2. (P.1.) Qualitative composition of the ink, if purchased as a mixture.
3. (P.2) Demonstration of the uniformity of the dosage units of the tablet portions, where the scoring is intended to divide the FPP into equal doses.
4. (P.2) Demonstration of the similarity of the release rate of the tablet portions for gastro-resistant, modified or prolonged release products.
5. (P.5) Copies of revised FPP release and shelf-life specifications.
6. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documentation for one batch and confirmation that there are no changes to the production documents other than those highlighted.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
27	Change in dimensions without change in qualitative or quantitative composition and mean mass of:		
27a	tablets, capsules, suppositories and pessaries other than those stated in change no. 27b	1–2	2–6 IN
27b	gastro-resistant, modified or prolonged-release FPPs and scored tablets	1–2	1–6 Vmin

*continues*¹¹ See footnote 3.

Table *continued***Conditions to be fulfilled**

1. Specifications for the FPP are updated only with respect to dimensions of the FPP.
2. Multipoint in vitro dissolution profiles of the current and proposed versions of the product (determined in the routine release medium, on at least one batch of pilot- or production-scale), are comparable.

Documentation required

1. For gastro-resistant, modified or prolonged release FPPs, justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence. For scored tablets where the scoring is intended to divide the FPP into equal doses, demonstration of the uniformity of the tablet portions.
2. Sample of the FPP.
3. (P.2) Discussion on the differences in manufacturing process(es) between the currently accepted and proposed products and the potential impact on product performance.
4. (P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium, on at least one batch of pilot- or production-scale of the current and proposed products.
5. (P.5) Copies of revised FPP release and shelf-life specifications.
6. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of executed production documentation for one batch and confirmation that there are no changes to the production documents other than those highlighted.

3.2. P.3 Manufacture

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
28	Addition or replacement of a manufacturing site for part or all of the manufacturing process for an FPP involving:			
28a	secondary packaging of all types of FPPs	2–3	1	IN
28b	primary packaging site of:			
28b.1	solid FPPs (e.g. tablets, capsules), semi-solid FPPs (e.g. ointments, creams) and solution liquid FPPs	2–4	1, 8	IN
28b.2	other liquid FPPs (suspensions, emulsions)	2–5	1, 5, 8	IN

continues

Table *continued*

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
28c	all other manufacturing operations except batch control and/or release testing	1–3, 5	1–9	Vmin

Conditions to be fulfilled

1. No change in the batch formula, description of manufacturing process and process controls, equipment class and process controls, controls of critical steps and intermediates, or FPP specifications.
2. Satisfactory inspection in the last three years either by WHO or an SRA.
3. Site appropriately authorized by an NMRA (to manufacture the pharmaceutical form and the product concerned).
4. The change does not concern a sterile FPP.
5. Validation protocol is available or validation of the manufacturing process at the new site has been successfully carried out on at least three production-scale batches in accordance with the current protocol.

Documentation required

1. Evidence that the proposed site has been appropriately authorized in the last three years, for the pharmaceutical form and the product concerned:
 - a copy of the current manufacturing authorization, a GMP certificate or equivalent document issued by the NMRA;
 - a GMP statement or equivalent issued by WHO or an SRA;
 - date of the last satisfactory inspection concerning the packaging facilities by WHO or an SRA in the last three years.
2. Date and scope (with indication as to whether scope was e.g. product-specific or related to a specific pharmaceutical form) of the last satisfactory inspection.
3. (P.2) Where applicable, for semisolid and liquid formulations in which the API is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.
4. (P.2) For solid dosage forms, data on comparative dissolution tests in the routine release medium, with demonstration of similarity of dissolution profiles with those of the biobatch, performed on one production-scale batch each from current and proposed manufacturing sites and comparison with the biobatch results, with commitment to generate dissolution profiles on two more production-scale batches.
5. (P.3.5) Process validation reports or validation protocol (scheme) for three batches of the proposed batch size, which includes comparative dissolution against the biobatch results with f2 calculation as necessary.
6. (P.5.1) Copies of release and shelf-life specifications.
7. (P.5.4) Batch analysis data on one production-scale batch from the proposed site and comparative data on the last three batches from the previous site.

continues

Table *continued***Documentation required**

8. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the FPP produced at the new site into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
9. (R.1) Executed production documents for one batch of the FPP manufactured at the new site.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
29 Replacement or addition of a site involving batch control testing	1–2	1–3	AN

Conditions to be fulfilled

1. Site is appropriately authorized by the NMRA and satisfactorily inspected either by WHO or an SRA.
2. Transfer of methods from the current testing site to the proposed testing site has been successfully completed.

Documentation required

1. Clear identification of the currently accepted and proposed quality control sites on the letter accompanying the application.
2. Documented evidence that the site is appropriately authorized by the NMRA and satisfactorily inspected either by WHO or an SRA.
3. (P.5.3) Documented evidence of successful transfer of analytical procedures from the current to the proposed site.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
30 Change in the batch size of the FPP involving:			
30a up to and including a factor of 10 compared to the biobatch	1–7	2, 5–6	IN
30b downscaling	1–5	2, 6	AN
30c other situations	1–7	1–7	Vmin

Conditions to be fulfilled

1. The change does not affect the reproducibility and/or consistency of the product.

continues

Table *continued*

Conditions to be fulfilled

2. The change pertains only to immediate-release oral pharmaceutical forms and to non-sterile liquid forms.
 3. 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 of three production-scale batches has been successfully undertaken in accordance with the current validation protocol.
 5. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
 6. The change does not require supporting in vivo data.
 7. The biobatch size was at least 100 000 units in the case of solid oral dosage forms.
-

Documentation required

1. (P.2) For solid dosage forms: dissolution profile data, in the routine release medium, on a minimum of one representative production-scale batch and comparison of the data with the biobatch results and one production-scale batch of the previous batch size. Data on the next two full production-scale batches should be available on request and should be reported if they do not meet dissolution profile similarity (f2) requirements. For semi-solid dosage forms (e.g. lotions, gels, creams and ointments), containing the API in the dissolved or non-dissolved form, comparative in vitro data on membrane diffusion (membrane release testing) should be submitted or be available on request.
 2. (P.3.5) Process validation reports for three batches of the proposed batch size or validation protocol (scheme).
 3. (P.5.1) Copies of release and shelf-life specifications.
 4. (P.5.4) Batch analysis data (in a comparative tabular format) on a minimum of one production-scale batch manufactured to both the currently accepted and the proposed batch sizes. Batch data on the next two full production-scale batches should be available on request and should be reported immediately by the supplier of the product, if outside specifications (with proposed remedial action).
 5. (P.8.2) Updated post-acceptance stability protocol (approved by authorized personnel) and stability commitment to place the first production-scale batch of each strength at the proposed scale into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
 6. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documentation for one batch (if manufactured as required by documentation 4) (above) and confirmation that there are no changes to the production documents other than those highlighted.
 7. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.
-

continues

Table *continued*

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
31a	1–9	1–4, 6–7	AN
31b	1–3, 5–9	1–7	Vmin

Conditions to be fulfilled

1. The change does not require supporting in vivo data.
2. No change in qualitative and quantitative impurity profile or in physicochemical properties; dissolution profiles are similar to those of the biobatch.
3. The manufacturing processes for the currently accepted and proposed products use the same principles (e.g. a change from wet to dry granulation, from direct compression to wet or dry granulation or vice versa would be considered a change in manufacturing principle), the same processing intermediates and there are no changes to any manufacturing solvent used in the process.
4. The same classes of equipment, operating procedures, in-process controls (with no widening or deleting of limits) are used for the currently accepted and proposed products; no change in critical process parameters.
5. No change in the specifications of the intermediates or the FPP.
6. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
7. The change does not involve packaging or labelling where the primary packaging provides a metering and/or delivery function.
8. The change does not concern a gastro-resistant, modified or prolonged-release FPP.
9. The change does not affect the sterilization parameters of a sterile FPP.

Documentation required

1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.
2. (P.2) Discussion on the development of the manufacturing process; where applicable:
 - comparative in vitro testing, e.g. multipoint dissolution profiles in the routine release medium for solid dosage units (one production batch and comparative data on one batch from the previous process and the biobatch results; data on the next two production batches should be available on request or reported if outside specification);
 - comparative in vitro membrane diffusion (membrane release testing) for non-sterile semisolid dosage forms containing the API in the dissolved or non-dissolved form (one production batch and comparative data on one batch from the previous process and the biobatch results; data on the next two production batches should be submitted or be available on request);

continues

Table *continued***Documentation required**

- microscopic imaging of particles to check for visible changes in morphology and comparative size distribution data for liquid products in which the API is present in non-dissolved form.
3. (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
 4. (P.5) Specification(s) and certificate of analysis for one production-scale batch manufactured according to the currently accepted process and for a batch manufactured according to the proposed process.
 5. (P.8.1) Results of stability testing generated on at least two pilot batches (for uncomplicated products, one pilot batch; the other one can be smaller) with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
 6. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme.
 7. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as executed production documentation for one batch and confirmation that there are no changes to the currently accepted production documents other than those highlighted.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
32	Change to in-process tests or limits applied during the manufacture of the FPP or intermediate involving:			
32a	tightening of in-process limits	1–2, 5	1	AN
32b	deletion of a test	2, 4	1, 6	AN
32c	addition of new tests and limits	2–3	1–6	AN
32d	revision or replacement of a test	2–3	1–6	IN

Conditions to be fulfilled

1. The change is within the range of acceptance limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

continues

Table *continued***Conditions to be fulfilled**

3. Any new test does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. The deleted test has been demonstrated to be redundant with respect to the remaining analytical procedures (e.g. colour) and does not affect the critical quality attributes of the product (e.g. blend uniformity, weight variation).
5. No change in the analytical procedure.

Documentation required

1. (P.5.1) Copy of the proposed in-process specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
4. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
5. (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using current and proposed methods, if new analytical procedures are implemented.
6. (P.5.6) Justification for the addition or deletion of the tests and limits.

3.2. P.4 Control of excipients

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
33	Change in source of an excipient from a TSE risk to a material of vegetable or synthetic origin.	1	1	AN

Conditions to be fulfilled

1. No change in the excipient and FPP release and shelf-life specifications.

Documentation required

1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin.

continues

Table *continued*

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
34	Change in the specifications or analytical procedures for an excipient involving:			
34a	deletion of a non-significant in-house parameter	2	1-3	AN
34b	addition of a new test parameter or analytical procedure	2-3	1-2	AN
34c	tightening of specification limits	1-2, 4	1-2	AN
34d	change or replacement of an analytical procedure	2-3	1-2	Vmin

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. No change in the analytical procedure.

Documentation required

1. Justification for the change.
2. (P.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications and details of procedure and summary of validation of any new analytical procedure (if applicable).
3. Justification to demonstrate that the parameter is not critical.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
35	Change in specifications of an excipient to comply with an officially recognized pharmacopoeia	1	1	AN

Conditions to be fulfilled

1. No change to the specifications other than those required to comply with the pharmacopoeia (e.g. no change in particle size distribution).

Documentation required

1. Comparative table of currently accepted and proposed specifications for the excipient.

3.2. P.5 Control of FPP

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
36a	Change in the standard claimed for the FPP from an in-house to an officially recognized pharmacopoeial standard	1–3	1–5	AN
36b	Update to the specifications to comply with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the FPP is controlled	None	1, 3, 5	AN

Conditions to be fulfilled

1. The change is made exclusively to comply with the officially recognized pharmacopoeia.
2. No change to the specifications that results in a potential impact on the performance of the FPP (e.g. dissolution test).
3. No deletion of or relaxation of any of the tests, analytical procedures or acceptance criteria of the specifications. Any deletion or relaxation of the tests should meet the conditions of 37a or 37d and should follow the corresponding reporting types.

Documentation required

1. (P.5.1) Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
3. (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using current and proposed procedures, if new analytical procedures are implemented.
4. (P.5.6) Justification for the proposed FPP specifications.
5. (P.5.3) Demonstration of the suitability of the monograph to control the FPP.

continues

Table *continued*

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
37	Change in the specifications of the FPP involving test parameters and acceptance criteria:			
37a	deletion of a test parameter	5	1, 6	AN
37b	addition of a test parameter	2–4, 7	1–6	AN
37c	tightening of an acceptance criterion	1–2	1, 6	AN
37d	relaxation of an acceptance criterion	2, 4, 6–7	1, 5–6	IN
37e	replacement of a test parameter	2–4, 6–7	1–6	IN

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. No additional impurity found over the ICH identification threshold.
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
6. The change to the specifications does not affect the stability and the performance of the product.
7. The change does not concern sterility testing.

Documentation required

1. (P.5.1) Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
4. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.

continues

Table *continued***Documentation required**

5. (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using currently accepted and proposed procedures, if new analytical procedures are implemented.

6. (P.5.6) Justification for the proposed FPP specifications.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
38	Change in the analytical procedures for the FPP involving:			
38a	deletion of an analytical procedure	5	1, 6	AN
38b	addition of an analytical procedure ^f	3–4, 6–7	1–5	AN
38c.1	modification or replacement of an analytical procedure	1–4, 6–7	1–5	AN
38c.2		2–4, 6–7	1–5	Vmin
38d	updating the analytical procedure with an officially recognized pharmacopoeial monograph as a result of an update to that monograph	None	1–5	AN
38e	change from an in-house analytical procedure to an analytical procedure in an officially recognized pharmacopoeial monograph or from the analytical procedure in one officially recognized pharmacopoeial monograph to an analytical procedure in another officially recognized pharmacopoeial monograph	2, 7	1–3, 5	IN

continues

Table *continued***Conditions to be fulfilled**

1. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected.
2. Comparative studies demonstrate that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. The change does not concern sterility testing.
5. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted analytical procedure.
6. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
7. No new impurities have been detected.

Documentation required

1. (P.5.1) A copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.3) Copies or summaries of validation reports, including verification data for assay or purity methods, if new analytical procedures are used.
4. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
5. (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using currently accepted and proposed analytical procedures.
6. Justification for the deletion of the analytical procedure, with supporting data.

3.2. P.7 Container-closure system

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
39a	Replacement or addition of a primary packaging type	1	1–2, 4–6	Vmin
39b		None	1–6	Vmaj

continues

Table *continued***Conditions to be fulfilled**

1. The change does not concern a sterile FPP.

Documentation required

1. Samples of the product as packaged in the new container-closure system.
2. (P.2) Data on the suitability of the container-closure system (e.g. extractable/leachable testing, permeation testing, light transmission) demonstrating equivalent or superior protection compared to the current packaging system. For changes to functional packaging, data to demonstrate the functioning of the new packaging.
3. (P.3.5) For sterile FPPs, process validation and/or evaluation studies.
4. (P.7) Information on the proposed primary packaging type (e.g. description, materials of construction of primary packaging components, specifications, and results of transportation studies, if appropriate).
5. (P.8.1) Stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and where applicable, results of photostability studies.
6. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme, unless data were provided in documentation 5.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
40	Change in the package size involving:			
40a	change in the number of units (e.g. tablets, ampoules, etc.) in a package	1–2	1–2	IN
40b.1	change in the fill weight or fill volume of non-parenteral multidose products	1–3	1–2	IN
40b.2		1–2	1–2	Vmin

Conditions to be fulfilled

1. The change is consistent with the posology and treatment duration accepted in the SmPC.
2. No change in the primary packaging material.
3. No increase in the headspace or surface/volume ratio.

Documentation required

1. Justification for the new pack-size, indicating that the new size is consistent with the dosage regimen and duration of use as accepted in the SmPC.

continues

Table *continued***Documentation required**

2. (P.8.2) A written commitment that stability studies will be conducted in accordance with the WHO guidelines for products where stability parameters could be affected.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
41	Change in the shape or dimensions of the container or closure for:			
41a	non-sterile FPPs	1–2	1–3	AN
41b	sterile FPPs	1–2	1–4	Vmin

Conditions to be fulfilled

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 FPP.

Documentation required

1. Samples of the product packaged in the new container-closure system.
2. (P.7) Information on the proposed container-closure system (e.g. description, materials of construction, and specifications).
3. (P.8.1) In the case of changes to the thickness of a packaging component or for sterile FPPs: stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and, where applicable, results of photostability studies. In the case of a change in the headspace or a change in the surface/volume ratio for non-sterile FPPs, a commitment for the above studies.
4. (P.3.5) Evidence of revalidation studies in the case of terminally sterilized products. The batch numbers of the batches used in the revalidation studies should be indicated, where applicable.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
42	Change in qualitative and/or quantitative composition of the immediate packaging material for:			
42a	solid FPPs	1–3	1–3	IN
42b	semisolid and liquid FPPs	1–3	1–3	Vmin

continues

Table *continued***Conditions to be fulfilled**

1. The change does not concern a sterile FPP.
2. No change in the packaging type and material (an example of an allowable change is blister to blister).
3. The relevant properties of the proposed packaging are at least equivalent to those of the currently accepted material.

Documentation required

1. (P.2) Data demonstrating the suitability of the proposed packaging material (e.g. extractable/leachable testing, light transmission, permeation testing for oxygen, carbon dioxide, and moisture).
2. (P.7) Information on the proposed packaging material (e.g. description, materials of construction, and specifications).
3. (P.8.1) Stability summary and conclusions, results of (or a commitment to study in the case of demonstrated equivalent or more protective packaging) a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and, where applicable, results of photostability studies.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
43	Change in the specifications of the immediate packaging involving:			
43a	tightening of specification limits	1–2	1	AN
43b	addition of a test parameter	2–3	1–2	AN
43c	deletion of a non-critical parameter	2	1, 3	AN

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.

Documentation required

1. (P.7) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.

continues

Table *continued***Documentation required**

2. (P.7) Description of the analytical procedure and summary of validation of the new analytical procedure.
3. Documentation to demonstrate that the parameter is not critical.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
44	Change to an analytical procedure on the immediate packaging involving:			
44a	minor change to an analytical procedure	1–3	1	AN
44b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2–4	1	AN
44c	deletion of an analytical procedure	5	2	AN

Conditions to be fulfilled

1. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method).
2. Appropriate (re)validation studies have been performed in accordance with the relevant guidelines.
3. Comparative studies indicate the new analytical procedure to be at least equivalent to the former procedure.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method.

Documentation required

1. (P.7) Description of the method and comparative validation results demonstrating that the currently accepted and proposed methods are at least equivalent.
2. Documentation to demonstrate the equivalence of the deleted method and a currently accepted method.

continues

Table *continued*

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
45 Change in any part of the (primary) packaging material not in contact with the FPP formulation (e.g. colour of flip-off caps, colour code rings on ampoules, or change of needle shield).	1	1–2	IN

Conditions to be fulfilled

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

Documentation required

1. (P.7) Information on the proposed packaging material (e.g. description, materials of construction, and specifications).
2. Sample of the FPP.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
46 Change to an administration or measuring device that is not an integral part of the primary packaging (excluding spacer devices for metered dose inhalers) involving:			
46a addition or replacement	1, 2	1–2	IN
46b deletion	3	3	IN

Conditions to be fulfilled

1. The proposed measuring device is designed to accurately deliver the required dose for the product concerned in line with the posology, and results of such studies are available.
2. The proposed device is compatible with the FPP.
3. The FPP can be accurately delivered in the absence of the device.

Documentation required

1. (P.2) Data to demonstrate accuracy, precision and compatibility of the device.
2. Sample of the device.
3. Justification for the deletion of the device.

3.2. P.8 Stability

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
47	Change in the shelf-life of the FPP (as packaged for sale) involving:			
47a	reduction	3	1–3	IN
47b	extension	1–2	1–3	Vmin

Conditions to be fulfilled

1. No change to the primary packaging type in direct contact with the FPP and to the recommended conditions of storage.
2. Stability data were generated in accordance with the currently accepted stability protocol.
3. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.

Documentation required

1. (P.5.1) Copy of the currently accepted shelf-life specifications.
2. (P 8.1) Proposed shelf-life, summary of long-term stability testing according to currently accepted protocol and test results for a minimum of two pilot- or production-scale batches for a period sufficient to support the proposed shelf-life.
3. (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type	
48	Change in the in-use period of the FPP (after first opening or after reconstitution or dilution):			
48a	reduction	1	1	IN
48b	extension	None	1–2	Vmin

Conditions to be fulfilled

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.

Documentation required

1. (P 8) Proposed in-use period, test results and justification of change.
2. (P 5.1) Copy of currently accepted end of shelf-life FPP specifications and, where applicable, specifications after dilution or reconstitution.

continues

Table *continued*

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
49 Change in the labelled storage conditions of the FPP (as packaged for sale), the product during the in-use period or the product after reconstitution or dilution	1	1–2	Vmin

Conditions to be fulfilled

1. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

Documentation required

1. (P.8.1) If applicable, stability and/or compatibility test results to support the change to the storage conditions.
2. (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change.

Appendix 1

Examples of changes that make a new application or extension application necessary

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
1. Change of the API to a different API	None	1	New application/extension application
2. Inclusion of an additional API in a multicomponent product			
3. Removal of one API from a multicomponent product			
4. Change in the dose and/or strength of one or more APIs			
5. Change from an immediate-release product to an extended or delayed-release dosage form or vice versa			
6. Change from a liquid to a powder for reconstitution or vice versa			
7. Changes in the route of administration			
Conditions to be fulfilled			
None			
Documentation required			
1. Documents in fulfilment of the requirements outlined in the WHO <i>Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part</i> . ¹²			

¹² See footnote 3.

Appendix 2

Changes to excipients

Excipient	Percentage excipient (w/w) out of total target dosage form core weight
Filler	± 5.0
Disintegrant	
• starch	± 3.0
• other	± 1.0
Binder	± 0.5
Lubricant	
• Ca or Mg Stearate	± 0.25
• other	± 1.0
Glidant	
• talc	± 1.0
• other	± 0.1

- These percentages are based on the assumption that the active pharmaceutical ingredient (API) in the finished pharmaceutical product (FPP) is formulated to 100.0% of label/potency declaration. The total additive effect of all changes to excipients should be not more than 5.0% relative to the target dosage form weight (e.g. in a product consisting of API, lactose, microcrystalline cellulose and magnesium stearate, the lactose increases by 2.5% and microcrystalline cellulose decreases by 2.5%).
- If an excipient serves multiple functions (e.g. microcrystalline cellulose as a filler and as a disintegrant), then the most conservative recommended range should be applied (e.g. ± 1.0% for microcrystalline cellulose should be applied in this example). If a wider range is proposed, scientific justification and supporting data should be provided to demonstrate that the wider range will not affect the other function of the excipient.

Annex 4

Collaborative procedure between the World Health Organization Prequalification of Medicines Programme and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products

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1. Definitions

Collaborative procedure (Procedure)

Procedure for collaboration between the WHO Prequalification of Medicines Programme (WHO/PQP) and interested national medicines regulatory authorities (NMRAs) in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products.

Participating authorities or participating NMRAs

NMRAs that voluntarily agree to implement this collaborative procedure and accept the task of processing applications for registration of WHO-prequalified pharmaceutical products in accordance with the terms of the Procedure. A list of participating authorities is posted on the WHO/PQP web site (<http://www.who.int/prequal/>).

2. Background information

National assessment of applications for registration of pharmaceutical products (marketing authorization) is the key regulatory process that enables NMRAs to evaluate and monitor the quality, safety and efficacy of pharmaceutical products. For most countries the approach to registration of pharmaceutical products is a combination of two components:

- the NMRA's own assessment of application documentation combined with verification of compliance with relevant good practices by inspections (mostly focusing on good manufacturing practices (GMP) and inspections of manufacturing sites);
- consideration by the NMRA of decisions and outcomes of assessments and inspections made by NMRAs in other countries.

Consideration of the outcomes of assessments and inspections by trusted authorities substantially contributes to savings in regulatory resources and improvements in the quality of regulatory decisions, while retaining the prerogative of NMRAs to conclude their assessment by sovereign decisions, which reflect their own judgement of the benefit–risk balance as it relates to their specific country situation and the legislation in place.

Taking into consideration the regulatory decisions of other NMRAs requires setting up a system that will permit:

- identification of reference authorities whose regulatory decisions are based on acceptable standards and identification of documents

associated with such regulatory decisions, which are relevant to the regulatory environment in the country wishing to rely on such decisions;

- assurance that the product for which the decision has been taken by the reference NMRA is identical to the product being assessed, or, if it is not identical, that a clear understanding exists of the differences between the products subjected to assessment in the two regulatory environments;
- efficient use of available scientific expertise and human and financial resources to decide, with reasonable certainty, on the benefit–risk profile of an evaluated pharmaceutical product when used in a given country;
- the choice by each NMRA of the approaches that will make best use of the resources, workload and competence of individual NMRAs. Approaches could range from completely independent data reviews and inspections to adoption of regulatory decisions of trusted authorities without any further scientific review. A pragmatic approach is to assess only those areas which relate to use of the product in the country concerned and where failure to comply with regulatory standards could pose health risks. In the other areas, the outcomes of trusted authorities may be adopted.

This Procedure is based on the above-mentioned considerations. In line with the *Procedure for prequalification of pharmaceutical products*,¹ it aims at providing a convenient tool for NMRAs wishing to enhance their pre-marketing evaluation and registration system by taking advantage of the scientific assessment work conducted by WHO/PQP. The present procedure is complementary to the WHO/PQP collaboration procedure with NMRAs in inspection activities (<http://www.who.int/prequal>, “Inspections”).

It is expected that enhanced collaboration and information exchange between NMRAs and WHO/PQP will benefit both partners. Subject to the agreement of the WHO prequalification holders concerned, NMRAs will gain access to assessment outcomes that are not in the public domain and that have been prepared in conformity with the WHO recommended standards on which the *Procedure for prequalification of pharmaceutical products* is based. Such reports will help NMRAs to make their decisions and may also assist in educating national regulatory staff. At the same time, feedback from NMRAs on the information and documentation received from WHO/PQP under the Procedure

¹ Procedure for prequalification of pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report*. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 10.

will allow WHO/PQP to improve its work and to ensure that the outcomes of prequalification assessments are relevant to NMRAs. As a consequence patients will benefit from this collaboration by gaining faster access to medicines which have been found acceptable in principle for procurement by United Nations agencies. Depending on available resources, participating authorities may be given the opportunity to participate in the assessment process and in inspections organized by WHO/PQP.

This collaborative procedure also benefits manufacturers of prequalified medicines through faster and better harmonized regulatory approvals in participating countries. This Procedure, when combined with the *Collaboration Procedure with NMRAs in inspection activities*, may also alleviate the burden of national inspections on manufacturers.

3. Principles of collaboration

3.1 This collaborative procedure is limited to those pharmaceutical products that have been assessed and inspected by WHO/PQP in line with the procedures and standards available at www.who.int/prequal (“Information for applicants”) and have been found to be acceptable in principle for procurement by United Nations agencies as listed in the *List of WHO prequalified medicines* available at www.who.int/prequal. It is not, however, applicable to medicines which have been listed as prequalified on the basis of approval by stringent regulatory authorities.² Although it is expected that the Procedure will mostly serve to accelerate the assessment and registration of multisource (generic) pharmaceutical products,³ it is also applicable to any pharmaceutical product for which the safety and efficacy has been documented to WHO/PQP by the submission of preclinical and clinical data. The Procedure has three major stakeholders: WHO/PQP, interested NMRAs and those WHO prequalification holders/applicant⁴ who agree that this procedure is used for applications for national registration of their WHO-prequalified product submitted to an NMRA.

² Products listed as prequalified according to the procedures described in the *Guidelines on submission of documentation for prequalification of innovator finished pharmaceutical products approved by stringent regulatory authorities*.

³ *Guideline on submission of documentation for prequalification of multisource (generic) finished pharmaceutical products (FPPs) approved by stringent regulatory authorities* (<http://www.who.int/prequal/>); and in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report*. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 11.

⁴ If the applicant for national registration is not the same as the WHO prequalification holder, the WHO prequalification holder must confirm to the NMRA and WHO/PQP by an authorization letter (as per the template annexed to Appendix 3, Part A) that the applicant is acting for, or pursuant to rights derived from, the WHO prequalification holder and that the prequalification holder agrees with the application of the procedure in the country concerned.

- 3.2 WHO/PQP and participating authorities receive applications for the same pharmaceutical product. Within the context of this Procedure, the same pharmaceutical product is characterized by:
- the same product dossier;⁵
 - the same manufacturing chain, processes and control of materials;
 - the same active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) specifications;
 - the same essential elements of product information.⁶
- 3.3 WHO/PQP, with the agreement of the WHO prequalification holder, shares the full outcome, of prequalification assessments and inspections, including final assessment and inspection reports, with participating authorities, under appropriate obligations of confidentiality and restrictions on use (see below). As regards sharing the outcomes of assessments and inspections, only data owned by the WHO prequalification holder are shared. Sharing of any other data is subject to additional agreement of the data owners concerned.
- 3.4 For the purpose of this collaborative procedure, participating authorities accept the product documentation and reports, in the format in which they are routinely prepared by WHO in accordance with the *Procedure for prequalification of pharmaceutical products* published on WHO/PQP's web site at www.who.int/prequal, and as Annex 10 in WHO Technical Report Series, No. 961. It should be noted, however, that participating authorities may require applicants to comply with specific requirements for local regulatory review. Each participating authority should make such specific requirements public.
- 3.5 Fees to be paid by the applicants to participating authorities will continue to follow standard national procedures. Similarly, the submission by manufacturers of samples for laboratory testing – if required – will continue to follow standard procedures as defined in national legislation and/or as defined by national regulatory authorities.

⁵ Only the technical data included in the dossier must be the same. There may be country-specific differences in administrative data, or if required by NMRAs under exceptional circumstances, additional technical data can be provided (e.g. bioequivalence with a country-specific comparator).

⁶ The essential elements of product information include in particular the indications, contraindications, posology (dosing), special warnings and precautions for use, adverse reactions, storage conditions, primary packaging and shelf-life. Differences in brand name, the name of applicant or prequalification holder, language, format and degree of detail of the product information, labelling of internal and external packaging, among others, are not considered essential for the purposes of this procedure. The language of the product information may be different as long as the information content is the same as that approved by WHO/PQP.

3.6 Consistent with the terms of Appendix 1A and Appendix 3, Part B, each participating authority commits itself:

- to treat any information and documentation provided to it by WHO/PQP pursuant to this Procedure as confidential in accordance with the terms of Appendix 1A, and to allow access to such information and documentation only to persons:⁷
 - who have a need to know for the purpose of the assessment and accelerated registration of the product in question in the country and any post-registration processes that may be required;
 - who are bound by confidentiality undertakings in respect of such information and documentation which are no less stringent than those reproduced in Appendix 1A;
 - to issue its national regulatory decision on a given prequalified pharmaceutical product (whether positive or negative) within 90 calendar days after being given access to the confidential information and documentation concerning each product.⁸

These commitments are provided by each participating authority to WHO/PQP in writing by entering into the agreement for participation in this Procedure as reproduced in Appendix 1A and are reconfirmed for each pharmaceutical product for which collaboration is sought (see Appendix 3, Part B).

Each participating NMRA nominates a maximum of two focal points who will access the restricted-access web site, through which WHO/PQP will communicate all confidential information and documentation. Focal points designated by the NMRA must sign the undertaking reproduced in Appendix 1B before they will be granted access to the restricted-access web site. Any change in designated focal points must be communicated to WHO/PQP in writing without delay and must be accompanied by an undertaking (Appendix 1B) signed by the new focal point(s).

⁷ This includes the focal point(s) and all other persons in the NMRA who have access to any information and documentation provided by WHO/PQP.

⁸ Participating authorities should issue their national regulatory decisions at the earliest opportunity after being given access to the confidential information and documentation on a given prequalified product. Although a time limit of 90 days is defined in the Procedure, the decision should normally be taken within 60 days. This deadline can be extended to a maximum of 90 days if predefined dates of technical or decision-making meetings do not allow a participating authority to issue its decision within 60 days. If a participating authority does not issue its decision within 90 days and does not communicate valid reasons for the delay to WHO/PQP, WHO/PQP will follow up with the head of the NMRA to clarify the situation.

- 3.7 The decision whether or not to register a given product in a particular country remains the prerogative and responsibility of each participating authority. Accordingly, a participating authority may come to a different conclusion from that reached by WHO/PQP. Within 30 calendar days of having taken its decision, the participating authority reports this decision, together with the dates of submission and registration and, if applicable, any deviations from the WHO/PQP's decision on prequalification and the reasons for such deviations,⁹ to WHO/PQP. It does so through the restricted-access web site by completing the form in Part C of Appendix 3. The NMRA provides a copy of the completed form to the applicant.
- 3.8 Participation by WHO prequalification holders/applicants is voluntary, through the submission to a participating NMRA of the expression of interest reproduced in Part A of Appendix 3. For each product, such participation will be subject to the WHO prequalification holder/applicant accepting the terms of this Procedure, including the confidential exchange of information and documentation between WHO/PQP and the NMRA (see Appendix 2). The WHO prequalification holder/applicant can cease participation in this procedure at any time provided that he or she informs WHO/PQP and the participating NMRAs in writing of his or her decision. In such a case the NMRA shall cease all use of the information disclosed to it for the respective product(s) as per the terms of the participation agreement (see Appendix 1).
- 3.9 The requirements and procedures in case of a variation (as defined in the *WHO guidelines on variations to a prequalified product*¹⁰) may differ between NMRAs and WHO/PQP. The present collaborative procedure includes a variation procedure (see below under “Post-registration processes”) which is aimed at promoting consistency between variations accepted by WHO/PQP and variations accepted by participating authorities. There could be situations in which a manufacturer of a WHO-prequalified pharmaceutical product submits a variation application to a participating authority and not to WHO/PQP, or vice versa. In such a case, the conditions of the national registration, which were initially “harmonized” with the WHO prequalification decision,

⁹ This refers to a decision not to approve the marketing authorization of a WHO-prequalified product and to a decision to approve the marketing authorization, but with deviations in indications, contraindications, posology (dosing), special warnings and precautions for use, adverse drug reactions, storage conditions and shelf-life. Differences in brand name, name of applicant or prequalification holder, format of product information, level of detail of product information, labelling of internal and external packaging and language of product information are not considered to be deviations from the prequalification conclusions.

¹⁰ WHO guidelines on variations to a prequalified product. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh report*. Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3 (and any updates thereto).

may become essentially different through the product life-cycle. In such a case a pharmaceutical product registered and procured in a participating country would no longer be the same as the “WHO-prequalified” product because the specifications and/or other essential parameters would no longer be the ones accepted by WHO/PQP. As a result, applicants are required to submit the variations which are submitted to WHO/PQP without delay to participating authorities, and participating authorities are encouraged to follow the outcomes of the WHO variation procedures for nationally-approved WHO-prequalified products. WHO/PQP will inform the NMRA which registered individual prequalified products, through the restricted-access web site, about variations to the prequalification status of such products, if and when regulatory action is deemed to be justified. If a national variation procedure results in the nationally registered product being no longer the same¹¹ as the WHO-prequalified product, or in the event that a variation of a WHO-prequalified product is not followed by the same variation of the nationally registered product, the participating authority informs WHO/PQP of the situation by submitting the form in Appendix 4, clearly specifying the deviations. Other participating NMRAs, which have registered the WHO-prequalified product in question pursuant to this Procedure, will be made aware of such deviations through the restricted-access web site. In addition, if the fact that a WHO-prequalified product has been registered in a particular country pursuant to this Procedure has been made public, any subsequent deviations should also be made public.

- 3.10 If a prequalified product is withdrawn by the WHO prequalification holder, or is suspended or delisted by WHO/PQP, WHO/PQP will inform each participating authority which has approved, or is in the process of reviewing, the product pursuant to this collaborative procedure, of the withdrawal, suspension or delisting and the reasons for taking this action, through the restricted-access web site and subject to the obligations of confidentiality contained in Appendix 1A. Similarly, when an NMRA deregisters or suspends the registration of a prequalified pharmaceutical product for any reason, it will inform WHO/PQP of this decision and of its reasons through the restricted-access web site. Other participating NMRAs which have registered the WHO-prequalified product in question pursuant to this Procedure will be made aware of such national deregistration or suspension through the restricted-access web site. In addition, if the fact

¹¹ Within the context of this Procedure, the same pharmaceutical product is characterized by the same product dossier, the same manufacturing chain, processes and control of materials, the same API and FPP specifications and the same essential elements of product information, as further described in paragraph 3.2 above.

that a WHO-prequalified product has been registered in a country pursuant to this Procedure has been made public, any subsequent deregistration or suspension should also be made public.

- 3.11 Participation in this Procedure does not exempt applicants for national registration and holders of national registration from the respective national regulatory requirements. Participating authorities retain the right to assess submitted data and organize site inspections to the extent they deem appropriate.

4. Steps in the collaboration for national registration of a pharmaceutical product¹²

- 4.1 The applicant submits the product dossier for a WHO-prequalified pharmaceutical product to a participating NMRA. The technical part of the dossier is updated to reflect the data submitted to WHO/PQP during the initial prequalification procedure, and consecutive variation procedures and requalification (where applicable). The applicant must provide the participating authority with:

- an application dossier complying with established national requirements, including the same technical information as that submitted to WHO/PQP. To the extent that national regulatory requirements allow, the technical part of the dossier will be identical to the current version of the WHO/PQP dossier;
- an expression of interest reproduced in Part A of Appendix 3;
- country-specific data;
- any fees that may be payable to the NMRA pursuant to national requirements.

Wherever possible, to minimize the workload of the NMRA and facilitate the process, applicants should ensure that they express their interest to use the Procedure (Appendix 3, Part A) to the NMRA and to WHO/PQP before submitting a national application for registration. If acceptable to NMRAs, not only should the technical content of the dossiers be the same, but also the format in which data are presented should closely follow the common technical document (CTD) format in which dossiers are submitted to WHO/PQP.

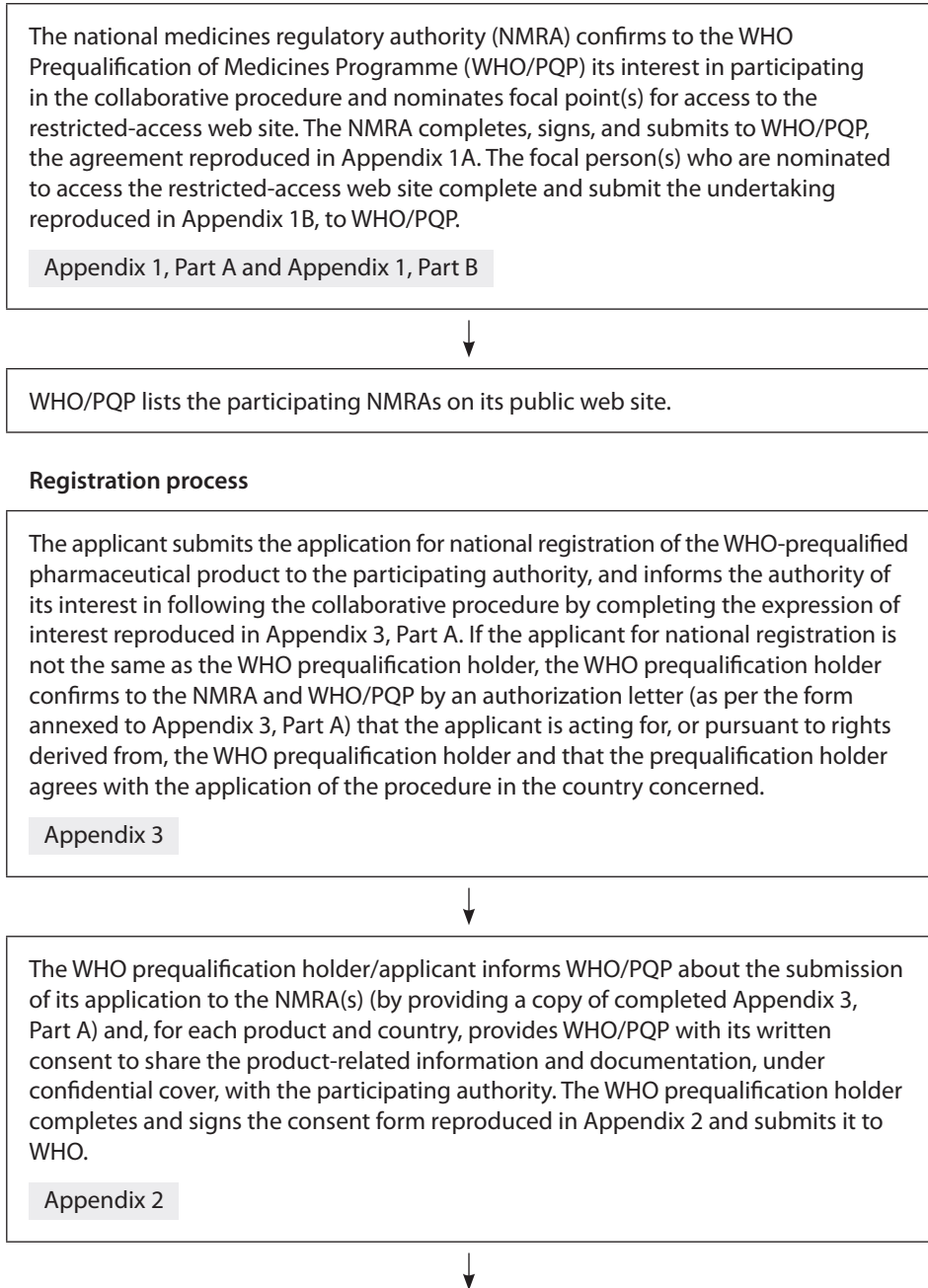
In situations where the applicant wishes to apply the Procedure to an application which is already pending within the NMRA, the applicant should

¹² In addition, to complement the steps of this collaborative procedure, joint inspections may be arranged under the collaborative procedure for joint inspections posted on the WHO/PQP web site (www.who.int/prequal/Inspections).

first update the dossier to ensure that the technical part of the information is the same as that submitted to WHO/PQP. It is the decision of individual NMRAs whether to apply the Procedure in such cases.

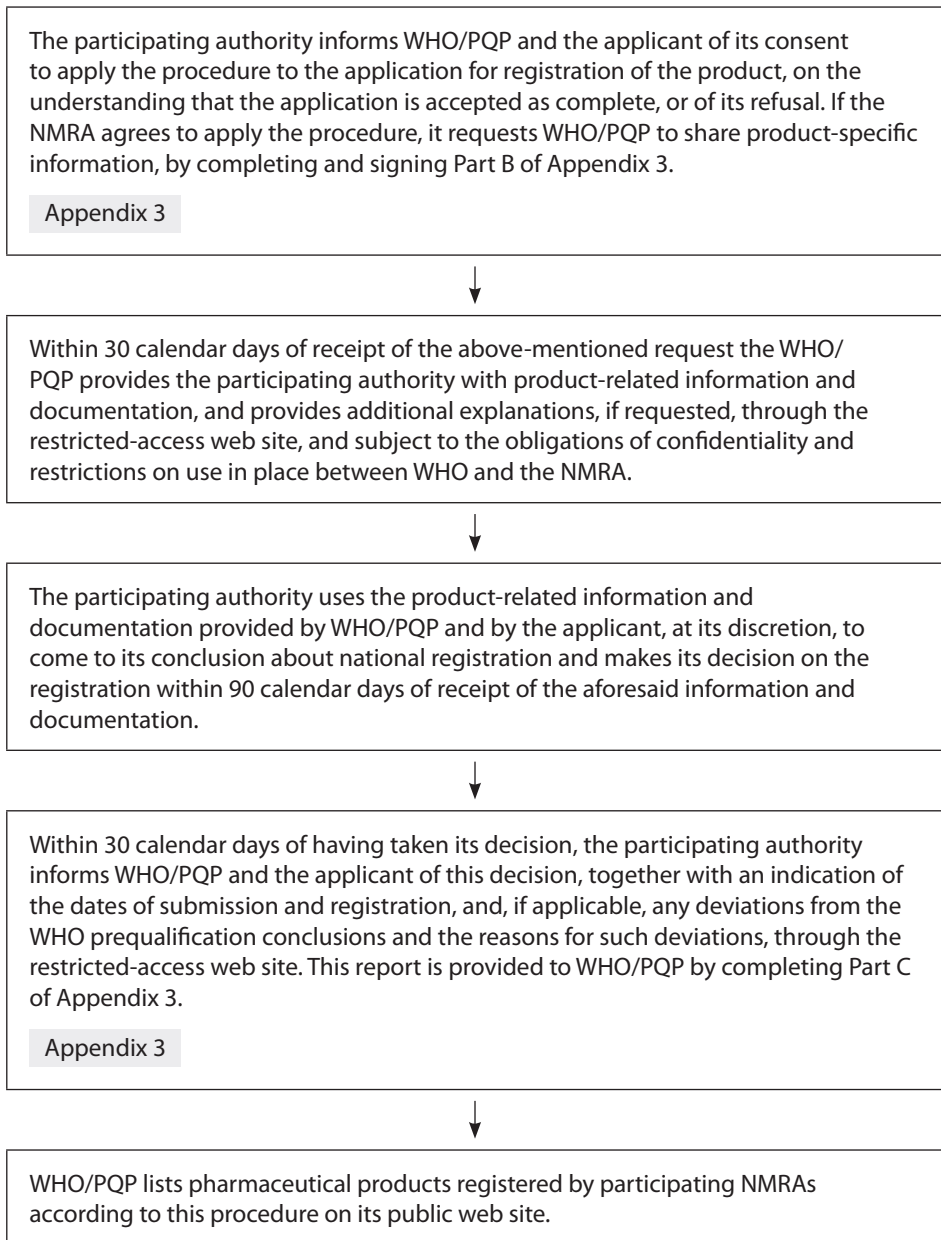
- 4.2 For each application under this Procedure, WHO/PQP is informed by the WHO prequalification holder/applicant about the submission to the participating NMRA by providing a copy of completed Appendix 3, Part A. The WHO prequalification holder provides WHO at this time with its written consent for WHO/PQP to provide the product-related information in compliance with the applicable confidentiality requirements to the NMRA of the country concerned (see Appendix 2).
- 4.3 The participating NMRA informs WHO/PQP and the respective applicant of each application which it accepts or declines to include in this Procedure, and requests WHO/PQP to provide it with the necessary information and documentation (Appendix 3, Part B). The Procedure applies only to applications that the NMRA has accepted as complete.
- 4.4 Within 30 calendar days of receipt of the above-mentioned request WHO/PQP shares the most recent product-related information and assessment and inspection outcomes through the restricted-access web site with the participating authority. This information is subject to the obligations of confidentiality and restrictions on use and may include assessment report(s), variation assessment report(s) if applicable, full inspection report(s) of the most recent inspection(s) and the letter of prequalification or requalification. At the request of the participating authority, WHO/PQP provides explanations and/or more detailed information.
- 4.5 After receiving the information and documentation from WHO/PQP, the participating authority undertakes an accelerated assessment of the product in question. For each application, the participating authority is required to issue the relevant national decision within 90 calendar days from the day it received access to the complete prequalification documentation. Within 30 days of having taken its decision, the participating authority reports this decision, together with an indication of the dates of submission and registration, and, if applicable, any deviations from the WHO prequalification conclusion and the reasons for such deviations, to WHO/PQP through the restricted-access web site. This report is provided to WHO/PQP using Part C of Appendix 3 and is copied to the applicant. WHO/PQP lists pharmaceutical products registered according to this Procedure by participating NMRAs on its public web site. The steps in the collaboration for national registrations of a pharmaceutical product are summarized in Figure 1.

Figure 1
Flowchart showing the principal steps of the collaborative procedure



continues

Figure 1 *continued*



continues

Figure 1 *continued***Post-registration processes**

The WHO prequalification holder/applicant submits variations simultaneously to WHO/PQP and relevant participating authorities. If regulatory action is deemed to be justified, WHO/PQP promptly provides the participating authorities concerned, through the restricted-access web site, and subject to the above-mentioned obligations of confidentiality and restrictions on use, with variation assessment reports and post-prequalification inspection reports, and any related information it considers relevant. If a national variation procedure results in the nationally-registered product being no longer the same¹³ as the WHO-prequalified product, or in the event that a variation of a WHO-prequalified product is not followed by the same variation of the nationally-registered product, the participating authority informs WHO of the situation within 30 calendar days of obtaining access to the information and documentation provided by WHO/PQP, by submitting the form reproduced in Appendix 4, clearly specifying the deviations. Other participating NMRA which have registered the WHO-prequalified product in question pursuant to this procedure will be made aware of such deviations through the restricted-access web site.

Appendix 4



WHO/PQP informs the participating authority, through the restricted-access web site, and subject to the above-mentioned obligations of confidentiality and restrictions on use, about withdrawals, suspensions or delistings of prequalified pharmaceutical products. The participating authority informs WHO/PQP, through the restricted-access web site, of national deregistration or suspension (for any reason) of a prequalified pharmaceutical product and the reasons for doing so.

Other participating NMRA which have registered the WHO-prequalified product in question pursuant to this procedure will be made aware of such national deregistration or suspension, through the restricted-access web site.

Appendix 4



WHO/PQP removes a product from the list published in line with this procedure:

- if the nationally-registered product is no longer the same¹⁴ as the WHO-prequalified product, or
- if the NMRA deregisters a WHO-prequalified product, or
- if WHO/PQP delists a WHO-prequalified product.

WHO/PQP will also publish the reasons for the removal from the list.

¹³ See footnote 11.

¹⁴ See footnote 11.

5. Collaboration mechanisms for post-registration variations

- 5.1 Post-prequalification variations submitted to WHO/PQP are expected to be submitted simultaneously to any relevant participating authorities, and vice versa. Submission of variations to NMRAs should respect national regulatory requirements.
- 5.2 WHO/PQP promptly shares the variation assessment reports and post-prequalification inspection reports, through the restricted-access web site, and subject to the above-mentioned obligations of confidentiality and restrictions on use, with the relevant participating authorities, in all cases in which variation (including “notification” according to WHO/PQP’s variation procedure¹⁵) requires regulatory action (e.g. where product safety, efficacy or patient information materials are concerned). Within 30 days of obtaining access to the information and documentation from WHO/PQP, each participating authority informs WHO/PQP through the restricted-access web site if and to what extent a variation of a WHO-prequalified product is not followed by the same variation of the nationally-registered product and, as a consequence, the nationally-registered product is no longer the same¹⁶ as the WHO-prequalified product.
- 5.3 If a national variation procedure results in the nationally-registered product being no longer the same¹⁷ as the WHO-prequalified product, the participating authority informs WHO/PQP within 30 days about the subject and outcome of this national variation procedure.
- 5.4 Deviations under 5.2 and 5.3 above may include change of source of active ingredients and/or manufacturing sites, product specifications, testing methods, storage conditions, shelf-life, packaging material, indications, contraindications, posology (dosing), special warnings and precautions for use, and adverse reactions. Differences in brand name, name of applicant or WHO prequalification holder, format of product information, level of detail of product information, labelling of internal and external packaging and language of product information are not considered to be deviations from the prequalification conclusions.

¹⁵ Guidance on variations to prequalified dossiers is available at: http://www.who.int/prequal/info_applicants/info_for_applicants_guidelines.htm

¹⁶ See footnote 11.

¹⁷ See footnote 11.

- 5.5 WHO/PQP removes a product from the list published in line with this procedure if the nationally-registered product is no longer the same¹⁸ as the WHO-prequalified product.

6. Withdrawals, suspensions or delistings of prequalified pharmaceutical products and national deregistrations

- 6.1 If a WHO-prequalified product is withdrawn from prequalification by the WHO prequalification holder, or if a product is suspended or delisted by WHO/PQP, WHO/PQP will promptly, through the restricted-access web site, and subject to the above-mentioned obligations of confidentiality and restrictions on use, inform relevant participating authorities accordingly, providing the reasons whenever needed.
- 6.2 In the case that a participating NMRA deregisters or suspends the registration of a prequalified pharmaceutical product for any reason, the participating authority informs WHO/PQP of the decision (together with an indication of the reasons), through the restricted-access web site. The information should be provided promptly whenever product quality, safety or efficacy are concerned and in all other cases within 30 working days. A participating authority is encouraged to consult WHO/PQP before adopting a decision about deregistration or suspension of registration of a WHO-prequalified product.
- 6.3 In case a WHO-prequalified product is deregistered at the national level, or in case WHO/PQP delists a prequalified product, WHO/PQP adjusts the information about this product on its web site accordingly.

¹⁸ See footnote 11.

Appendix 1

NMRA participation agreement and undertaking for NMRA focal point(s)

Appendix 1, Part A

Agreement to participate in the collaborative procedure between the World Health Organization Prequalification of Medicines Programme and national medicines regulatory authorities (NMRAs) in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products

Details of national medicines regulatory authority (NMRA)

Name of NMRA _____ (“the NMRA”)

Postal address: _____

Country: _____ (“the Country”)

Telephone number (please include codes): _____

E-mail: _____

Scope of agreement

Applicants for national registration of a WHO-prequalified pharmaceutical product (hereafter referred to as “Applicants”) may express their interest to the NMRA for the assessment and accelerated registration of this product (“the Product”) in the Country under the “collaborative procedure between the World Health Organization Prequalification of Medicines Programme (WHO/PQP) and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products” (hereafter referred to as “the Procedure”).¹

Subject to the NMRA agreeing to conduct such assessment and consider such accelerated registration of the Product under the Procedure (by submitting the form reproduced in Part B of Appendix 3 attached to the Procedure to WHO/PQP through the restricted-access web site), the NMRA hereby confirms for each

¹ If the applicant for national registration is not the same as the WHO prequalification holder, the WHO prequalification holder must confirm to the NMRA and to WHO/PQP by an authorization letter (as per the template annexed to Appendix 3, Part A) that the applicant is acting for, or pursuant to rights derived from, the WHO prequalification holder, and that the WHO prequalification holder agrees with the application of the Procedure in the country concerned.

such Product that it will adhere to, and collaborate with the WHO/PQP and the applicant of the Product in accordance with, the terms of the Procedure.

Confidentiality of information

Any information and documentation relating to the Product and provided by WHO/PQP to the NMRA under the Procedure may include but shall not necessarily be limited to:

- the full WHO/PQP assessment and inspection outcomes (reports);
- information and documentation on variations (as defined in the *WHO guidelines on variations to a prequalified product*, WHO Technical Report Series, No. 981, and any updates thereto), as well as information and documentation on any actions taken by WHO/PQP or NMRAs post-prequalification of the Product;
- all such data, reports, information and documentation being hereinafter referred to as “the Information”.

As regards sharing the outcomes of assessments and inspections, only data owned by the WHO prequalification holder are shared. Sharing of any other data is subject to additional agreement of the data owners concerned.

WHO/PQP agrees to make such Information available to the NMRA through a restricted-access web site exclusively for the purpose of the assessment and accelerated registration of the Product in the Country and any post-registration processes that may be required, in accordance with and subject to the terms of the Procedure (“the Purpose”). The NMRA agrees to treat any Information provided by WHO/PQP as aforesaid as strictly confidential and proprietary to WHO/PQP, the WHO prequalification holder/applicant and/or parties collaborating with WHO/PQP and/or the WHO prequalification holder/applicant. In this regard, the NMRA agrees to use such Information only for the Purpose and to make no other use thereof. Thus, the NMRA undertakes to maintain the Information received from WHO/PQP in strict confidence, and to take all reasonable measures to ensure that:

- the Information received from WHO/PQP shall not be used for any purpose other than the Purpose;
- the Information shall only be disclosed to persons who have a need to know for the aforesaid Purpose and are bound by confidentiality undertakings in respect of such information and documentation which are no less stringent than those contained herein.

The NMRA warrants and represents that it has adequate procedures in place to ensure compliance with its aforesaid obligations.

The obligations of confidentiality and restrictions on use contained herein shall not cease on completion of the Purpose.

The obligations of confidentiality and restrictions on use contained herein shall not apply to any part of the Information which the NMRA is clearly able to demonstrate:

- was in the public domain or the subject of public knowledge at the time of disclosure by WHO/PQP to the NMRA under the Procedure; or
- becomes part of the public domain or the subject of public knowledge through no fault of the NMRA; or
- is required to be disclosed by law, provided that the NMRA shall in such event immediately notify WHO/PQP and the applicant in writing of such obligation and shall provide adequate opportunity to WHO/PQP and/or the applicant to object to such disclosure or request confidential treatment thereof (provided always, however, that nothing contained herein shall be construed as a waiver of the privileges and immunities enjoyed by WHO/PQP and/or as submitting WHO/PQP to any national court jurisdiction).

Upon completion of the Purpose, the NMRA shall cease all use and make no further use of the Information disclosed to it under the Procedure, and shall promptly destroy all of the Information received from WHO/PQP which is in tangible or other form, except that the NMRA may retain copies of the Information in accordance with its established archival procedures, subject always, however, to the above-mentioned obligations of confidentiality and restrictions on use.

The Purpose for each product shall be deemed completed as soon as:

- the WHO prequalification holder/Applicant discontinues participation in the Procedure for the particular product;
- the Product is deregistered by the NMRA and/or delisted by WHO/PQP.

The access right of the NMRA's focal person(s) to the restricted-access web site will cease automatically upon the NMRA ceasing to participate in the Procedure. If and as soon as an NMRA focal point is replaced by a new focal point or ceases to be an employee of the NMRA, such focal point's access to the restricted-access web site shall automatically terminate.

The NMRA agrees that it has no right in or to the Information and that nothing contained herein shall be construed, by implication or otherwise, as the grant of a licence to the NMRA to use the Information other than for the Purpose.

Timelines

In respect of each Product which the NMRA accepts to assess and consider for accelerated registration under the Procedure, the NMRA undertakes to abide by the terms of the Procedure, including but not limited to the following timelines for processing each application:

- within 90 calendar days of obtaining access (through the restricted-access web site) to:
 - the data submitted to WHO/PQP for prequalification of the Product and owned by the WHO prequalification holder,
 - the full WHO/PQP assessment and inspection outcomes (reports), the NMRA undertakes to take a decision on the national registration of the Product;
- within 30 working days of the NMRA's decision on national registration of the Product, the NMRA undertakes to inform WHO/PQP of this decision and of any deviations from the WHO prequalification conclusions (with an indication of the reasons for such deviations) by completing and submitting the form attached as Appendix 3, Part C to the Procedure to WHO/PQP through the restricted-access web site;
- if a national variation procedure results in the nationally registered product being no longer the same² as the WHO-prequalified product, or if and to the extent a variation of a WHO-prequalified product is not followed by a variation of the nationally-registered product and as a consequence, the nationally-registered product is no longer the same² as the WHO-prequalified product, the NMRA undertakes to inform WHO/PQP thereof (together with an indication of the reasons for such deviations) within 30 days of the conclusion of the national variation procedure or within 30 days of having received access to the information and documentation provided by WHO/PQP, as the case may be (i.e. by completing and submitting the form attached to the Procedure as Appendix 4 to WHO/PQP through the restricted-access web site);³

² Within the context of this Procedure, the same pharmaceutical product is characterized by the same product dossier, the same manufacturing chain, processes and control of materials, the same API and FPP specifications and the same essential elements of product information, as further described in paragraph 3.2 of the Procedure.

³ If the fact that a WHO-prequalified product has been registered in a country pursuant to this Procedure has been made public any subsequent deviations should be made public also.

- the NMRA undertakes to inform WHO/PQP in case the NMRA deregisters or suspends the registration of the Product in the Country, by completing and submitting the form attached to the Procedure as an Appendix 4 to WHO/PQP through the restricted-access web site, and to do so promptly if this decision is based on quality, safety of efficacy concerns, and within 30 working days if this decision is based on other reasons.

Focal points for access to restricted-access web site

The NMRA has designated the person(s) listed below to act as focal point(s) for access to WHO/PQP's restricted-access web site. The undertaking(s) completed and signed by the focal point(s) is(are) attached hereto as an Appendix to this agreement.

Any change in designated focal points must be communicated to WHO/PQP without delay in writing and will be subject to the new focal point having signed and submitted to WHO the undertaking reproduced in Appendix 1B to the Procedure. The NMRA also undertakes to inform WHO/PQP if and as soon as a designated focal point ceases to be an employee of the NMRA.

Focal point for inspections

If applicable, this should be the same focal point as for the “WHO/PQP collaborative procedure between WHO/PQP and selected NMRAs in inspection activities” (<http://who.int/prequal>).

Mr/Ms/Dr:

First name (and initials): _____

Surname/family name: _____

Title in NMRA: _____

E-mail: _____

Phone: _____

A signed undertaking is attached

Focal point for dossier assessment

The same person as above may be nominated. If a different person is nominated, please complete details below.

Mr/Ms/Dr:

First name (and initials): _____

Surname/family name: _____

Title in NMRA: _____

E-mail: _____

Phone: _____

A signed undertaking is attached

Miscellaneous

The NMRA agrees that WHO/PQP may list its name on the WHO/PQP web site as a participant in the Procedure. Except as provided hereinbefore, neither party shall, without the prior written consent of the other party, refer to the relationship of the parties under this Agreement and/or to the relationship of the other party to the Product, the Information and/or the Purpose, in any statement or material of an advertising or promotional nature.

This Agreement shall not be modified except by mutual agreement of WHO and the NMRA in writing. The NMRA furthermore undertakes to promptly inform WHO/PQP of any circumstances or change in circumstances that may affect the implementation of this Agreement.

The parties shall use their best efforts to settle amicably any dispute relating to the interpretation or execution of this Agreement. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties or in the absence of agreement, with the UNCITRAL Arbitration Rules in effect on the date of this Agreement. The parties shall accept the arbitral award as final.

It is agreed furthermore that nothing contained in this Agreement shall be construed as a waiver of any of the privileges and immunities enjoyed by WHO under national and international law, and/or as submitting WHO to any national court jurisdiction.

Agreed and accepted

For the NMRA

Signature: _____

Name: _____

Title: _____

Place and date: _____

Attachments:

1. Signed undertakings of NMRA focal point(s) (Appendix 1, Part B).

Appendix 1, Part B

Undertaking for NMRA focal point(s)

The undersigned:

Mr/Ms/Dr:

First name (and initials): _____

Surname/family name: _____

Title in NMRA: _____

Name of NMRA _____ (“the NMRA”)

Country: _____ (“the Country”)

E-mail: _____

Phone: _____

Applicants for national registration of WHO-prequalified pharmaceutical products (hereafter referred to as “Applicants”) may express their interest to the NMRA for the assessment and accelerated national registration of such products under the “collaborative procedure between the World Health Organization Prequalification of Medicines Programme (WHO/PQP) and national medicines regulatory authorities (NMRAs) in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products” (hereafter referred to as “the Procedure”).¹

Subject to the NMRA agreeing to conduct such assessment and consider such accelerated registration of a WHO-prequalified product under the Procedure, WHO/PQP will communicate confidential Information (as hereinafter defined) relating to each such product to the NMRA, and the NMRA will communicate outcomes of the national registration procedure and post-registration actions in respect of such products to WHO/PQP, through a restricted-access web site, which can be accessed only by the focal points designated by the NMRA, including the undersigned. For the purpose of accessing the restricted-access web site and downloading Information and uploading reports in accordance with and subject to the terms of the Procedure, WHO/PQP will provide the undersigned with a secret access code. The undersigned undertakes to treat this access code as strictly confidential and not to disclose it to any other person whatsoever. The undersigned furthermore undertakes to take all precautionary measures that may be needed to prevent any other person whatsoever from obtaining the aforesaid

¹ If the applicant for national registration is not the same as the WHO prequalification holder, the WHO prequalification holder must confirm to the NMRA and to WHO/PQP by an authorization letter (as per the template annexed to Appendix 3, Part A) that the applicant is acting for, or pursuant to rights derived from, the WHO prequalification holder, and that the prequalification holder agrees with the application of the Procedure in the country concerned.

secret access code and from accessing the restricted-access web site (i.e. except for the other designated focal points who have signed this undertaking).

“Information” as aforesaid means any information and documentation relating to a WHO-prequalified product to be provided by WHO/PQP to the NMRA under the Procedure, including but not necessarily limited to:

- the full WHO/PQP assessment and inspection outcomes (reports);
- information and documentation on subsequent variations (as defined in the *WHO guidelines on variations to a prequalified product*, WHO Technical Report Series, No. 981, and any updates thereto), as well as information and documentation on any actions taken by WHO/PQP or NMRAs post-prequalification of the Product.

As regards sharing the outcomes of assessments and inspections, only data owned by the WHO prequalification holder are shared. Sharing of any other data is subject to additional agreement of the data owners concerned.

The undersigned confirms that:

1. the NMRA has bound him or her to obligations of confidentiality and restrictions on use no less stringent than those contained in Appendix 1A to the Procedure; and that
2. the aforesaid obligations of confidentiality and restrictions on use shall not cease on completion of the assessment and accelerated registration of any product in the Country, nor on completion of any post-registration processes that may be required, nor on the undersigned ceasing to be an employee of (or ceasing to have another relationship with) the NMRA.

The undersigned shall automatically cease having the right to access the restricted-access web site when the NMRA designates a new focal point to replace the undersigned or when the undersigned ceases to be an employee of the NMRA.

This Undertaking shall not be modified except by mutual agreement of WHO and the undersigned in writing. The undersigned furthermore undertakes to promptly inform WHO/PQP of any circumstances or change in circumstances that may affect the implementation of this Undertaking.

The parties shall use their best efforts to settle amicably any dispute relating to the interpretation or execution of this Undertaking. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties or in the absence of agreement, with the UNCITRAL Arbitration Rules in effect on the date of this Undertaking. The parties shall accept the arbitral award as final.

It is agreed furthermore that nothing contained in this Undertaking shall be construed as a waiver of any of the privileges and immunities enjoyed by WHO under national and international law, and/or as submitting WHO to any national court jurisdiction.

Agreed and accepted by the Undersigned:

Signature: _____

Name: _____

Title in NMRA: _____

Place and date: _____

Appendix 2

Consent of WHO prequalification holder for WHO to share information with NMRA confidentially under the Procedure

Reference is made to the attached expression of interest for the assessment and accelerated national registration under the Procedure of the following WHO-prequalified pharmaceutical product (hereafter referred to as "the Product") in _____ [country].¹

WHO prequalification details:

WHO prequalification reference number: _____

Date of prequalification (dd/mm/yyyy): _____

Date of requalification (if applicable): _____

WHO prequalification holder:² _____

Application details:

Name of entity: _____ ("the Applicant")

Street: _____

City and country: _____

E-mail: _____

Phone: _____

The WHO prequalification holder hereby consents to WHO/PQP providing the following information and documentation to the NMRA of _____ [country] ("the NMRA") for the assessment and accelerated registration of the Product in the country under the Procedure and to freely discuss the same with the aforesaid NMRA for this purpose:

- the full WHO/PQP assessment and inspection outcomes (reports);

¹ Please complete a separate form of this Annex for each country.

² If the applicant for national registration is not the same as the WHO prequalification holder, the WHO prequalification holder must confirm to the NMRA and to WHO/PQP by an authorization letter (as per the template annexed to Appendix 3, Part A) that the applicant is acting for, or pursuant to rights derived from, the WHO prequalification holder, and that the prequalification holder agrees with the application of the Procedure in the country concerned.

- information and documentation on subsequent variations (as defined in the *WHO guidelines on variations to a prequalified product*, WHO Technical Report Series, No. 981, and any updates thereto), as well as information and documentation on any actions taken by WHO/PQP post-prequalification of the Product.
- all such data, reports, information and documentation being hereinafter referred to as “the Information”.

As regards sharing the outcomes of assessments and inspections, only data owned by the WHO prequalification holder are shared. Sharing of any other data is subject to additional agreement of the data owners concerned.³

Such consent is subject to the NMRA having entered into an agreement with WHO/PQP as per Appendix 1A to the Procedure and having agreed to conduct the assessment and consider the accelerated registration of the Product under the Procedure, by having submitted the form reproduced in Part B of Appendix 3 to the Procedure to WHO.

If a national variation procedure results in the nationally-registered product being no longer the same⁴ as the WHO-prequalified Product, or if a variation of the WHO-prequalified Product is not followed by a variation of the nationally-registered product and, as a consequence, the nationally-registered product is no longer the same, the WHO prequalification holder/Applicant will inform WHO/PQP of the differences and their reasons.

For the WHO prequalification holder

Signature: _____

Name: _____

Title: _____

Place: _____

Date (dd/mm/yyyy): _____

³ In case that certain data submitted to WHO/PQP by the WHO prequalification holder in relation to prequalification of the Product are not in his/her ownership, the WHO prequalification holder specifies such data in an annex to this declaration of consent.

⁴ Within the context of this Procedure, the same pharmaceutical product is characterized by the same product dossier, the same manufacturing chain, processes and control of materials, the same API and FPP specifications and the same essential elements of product information, as further described in paragraph 3.2 of the Procedure.

Appendix 3

Expression of interest to NMRA for the assessment and accelerated national registration, acceptance by NMRA and notification of Procedure outcomes

Appendix 3, Part A

Expression of interest to the national medicines regulatory authority (NMRAs) for the assessment and accelerated national registration of a WHO-prequalified pharmaceutical product

In line with the Procedure, the undersigned Applicant¹ expresses its interest in the application of the above-mentioned Procedure by the NMRA of _____ [country] (“the NMRA”) in respect of the following submission for national registration:

Application details:

Name of entity: _____ (“the Applicant”)

Street: _____

City and country: _____

E-mail: _____

Phone: _____

Date of application: _____

(dd/mm/yyyy, e.g. 31/07/2011): _____

Product name in national system (if known): _____

National reference number (if known): _____

Product details:

API(s) (INN): _____

Dosage form and strength: _____

Packaging: _____

Manufacturing site(s), including block(s)/unit(s)

if appropriate: _____

¹ If the applicant for national registration is not the same as the WHO prequalification holder, the WHO prequalification holder must confirm to the NMRA and to WHO/PQP by an authorization letter (as per the template annexed to Appendix 3, Part A) that the applicant is acting for, or pursuant to rights derived from, the WHO prequalification holder, and that the prequalification holder agrees with the application of the Procedure in the country concerned.

WHO prequalification details:

WHO prequalification reference number: _____

Date of prequalification (dd/mm/yyyy): _____

WHO prequalification holder: _____

The Applicant confirms that the information and documentation provided in support of the above-mentioned submission for national registration is true and correct, that the pharmaceutical product submitted for national registration is the same² as the WHO-prequalified product and that the technical part of the information is the same³ as that submitted to the WHO Prequalification of Medicines Programme (WHO/PQP). Non-essential differences⁴ from the information submitted to WHO/PQP, are the following: _____

Subject to the NMRA agreeing to conduct the assessment and consider the accelerated registration of the Product under the Procedure, the Applicant:

1. undertakes to adhere to, and collaborate with the NMRA and WHO/PQP in accordance with the terms of the Procedure; and
2. will authorize WHO/PQP⁵ to provide the NMRA confidential access to the following information and documentation and to freely discuss the same with the aforesaid NMRA for the above-mentioned Purpose:
 - the full WHO/PQP assessment and inspection outcomes (reports);

² Within the context of this Procedure, the same pharmaceutical product is characterized by the same product dossier, the same manufacturing chain, processes and control of materials, the same API and FPP specifications and the same essential elements of product information, as further described in paragraph 3.2 of the Procedure.

³ Only the technical data included in the dossier must be the same. There may be country-specific differences in administrative data, or if required by NMRAs under exceptional circumstances, additional technical data can be provided (e.g. bioequivalence with a country-specific comparator).

⁴ As defined in Section 3.2 of the Procedure, differences in administrative information, brand name, name of applicant/prequalification holder (provided that the applicant is acting for, and has the authority to represent the WHO prequalification holder), format of product information, level of detail of product information, labelling of internal and external packaging and language of product information are not considered to be essential differences.

⁵ If the applicant for national registration is not the same as the WHO prequalification holder, then the authorization to WHO/PQP must be provided by the WHO prequalification holder or their legal representative.

- information and documentation on subsequent variations (as defined in the *WHO guidelines on variations to a prequalified product*, WHO Technical Report Series, No. 981, and any updates thereto), as well as information and documentation on any actions taken by WHO/PQP post-prequalification of the Product.

As regards sharing the outcomes of assessments and inspections, only data owned by the WHO prequalification holder are shared. Sharing of any other data is subject to additional agreement of the data owners concerned.

3. authorizes the NMRA to freely share and discuss all registration and the Product related information provided by the Applicant to the NMRA, with WHO/PQP, subject to the obligations of confidentiality and restrictions on use as contained in the NMRA's participation agreement and focal points' undertakings.
- The application for national registration was submitted before the Applicant decided to apply the Procedure to the Product and therefore at the time of submission the registration dossier did not respect conditions of the Procedure. Steps taken to update the submission to the NMRA to make the dossier “the same” as required by the Procedure, are listed and referenced in the attached letter.
- The applicant is not the WHO prequalification holder. An authorization letter from the WHO prequalification holder is attached.

For the Applicant

Signature: _____

Name: _____

Title: _____

Place: _____

Date (dd/mm/yyyy): _____

Template for authorization letter

(To be provided if the applicant is not the WHO prequalification holder. Please provide a separate letter for each NMRA concerned, with a copy to WHO/PQP).

This is to confirm that _____ (*name of applicant*) _____ seeking registration for prequalified product number _____ (*WHO/PQ number*) _____ in _____ (*name country*) _____ under the WHO collaborative procedure for accelerated registration of WHO prequalified products, is acting for, or pursuant to rights derived from _____ (*name of WHO prequalification holder*)

_____ and that _____ (*name of WHO prequalification holder*) _____ agrees with the application of the procedure in the country concerned.

For _____ (*name of WHO Prequalification holder*) _____ :

Signature _____

Name _____

Title _____

Date _____

Appendix 3, Part B

Acceptance by the NMRA to apply the Procedure to a specified WHO-prequalified pharmaceutical product and request for access to product-specific information and documentation

If there have been changes to the details as completed in Part A, please complete the relevant fields below. Where fields below are left blank, the data in Part A are considered to be valid.

Application details:

Name of entity: _____ (“the Applicant”)

Street: _____

City and country: _____

E-mail: _____

Phone: _____

Date of application: _____

(dd/mm/yyyy, e.g. 31/07/2011): _____

Product name in national system (if known): _____

National reference number (if known): _____

Product details:

API(s) (INN): _____

Dosage form and strength: _____

Packaging: _____

Manufacturing site(s), including block(s)/unit(s)
if appropriate: _____

WHO prequalification details:

WHO prequalification reference number: _____

Date of prequalification (dd/mm/yyyy): _____
 WHO prequalification holder _____

Please complete either section A or section B below:

Section A

The NMRA agrees to conduct the assessment and the accelerated registration of the above-mentioned product (“the Product”) under the Procedure and requests access to product-specific information, in accordance with and subject to the terms of the Procedure and the Agreement between WHO/PQP and the NMRA dated ____ / ____ / ____ (dd/mm/yyyy).

Section B

The NMRA has decided not to apply the Procedure to the above-mentioned Product for the following reasons: _____

For the NMRA

Signature: _____
 Name: _____
 Title: _____
 Place: _____
 Date (dd/mm/yyyy): _____

Appendix 3, Part C

Notification of outcomes of national registration procedure by the NMRA

Product and application details as completed in Parts A and B above apply.

Please complete either Section A or B below:

Section A

Registration has been granted, and the above-mentioned product (“the Product”) is identified as follows in the national medicines register:

Name of the Product _____
National registration number _____
Date of registration _____ (dd/mm/yyyy)
Product details (if different from those specified in Parts A and B): _____
 API(s) (INN) _____
 Dosage form and strength _____
 Packaging _____

Manufacturing site(s), including block(s)/unit(s)
 if appropriate _____
 Registration holder (if different from the Applicant as
 specified in Parts A and B: _____
 Name of entity _____
 Street _____
 City and country _____
 E-mail _____
 Phone _____

Are the national registration conclusions different from prequalification outcomes?⁶

_____ (Yes/No)

If you answered Yes to the above question:

Deviation	Reason

Please specify whether registration is subject to specific commitments, the registration is provisional or conditional, use of the Product is limited by specific prescribing restrictions, or additional clinical trials or additional data are required:

Section B

The application for registration of the Product was rejected for the following reasons: _____

For the NMRA

Signature: _____

Name: _____

Title: _____

Place: _____

Date: (dd/mm/yyyy) _____

⁶ This refers to deviations in indications, contraindications, posology (dosing), special warnings and precautions for use, adverse drug reactions, storage conditions and shelf-life. Differences in brand name, name of applicant/prequalification holder, format of a product information, level of detail of product information, labelling of internal and external packaging and language of product information are not considered to be a deviation from the prequalification conclusions.

Appendix 4

Report on post-registration actions in respect of a product registered under the Procedure

- Variation of the national registration resulting in the national registration conditions being inconsistent with the WHO/PQP prequalification conclusions
- Deregistration or suspension of the registration of the product

Product details:

Product name in national system: _____ (“the Product”)

National registration number: _____

Date of registration (dd/mm/yyyy): _____

WHO prequalification details:

WHO prequalification reference number: _____

Date of prequalification (dd/mm/yyyy): _____

WHO prequalification holder: _____

- The national variation procedure has resulted in the nationally-registered Product being no longer the same¹ as the WHO-prequalified product.

Deviations ²	Reasons

¹ Within the context of this Procedure, the same pharmaceutical product is characterized by the same product dossier, the same manufacturing chain, processes and control of materials, the same API and FPP specifications and the same essential elements of product information, as further described in paragraph 3.2 of the Procedure.

² This refers to deviations in indications, contraindications, posology (dosing), special warnings and precautions for use, adverse drug reactions, storage conditions and shelf-life. Differences in brand name, name of applicant/prequalification holder, format of product information, level of detail of product information, labelling of internal and external packaging and language of product information are not considered to be a deviation from the prequalification conclusions.

- The variation notified to NMRA by WHO/PQP has not been followed by a variation of the nationally-registered Product and, as a consequence, the nationally-registered product is no longer the same³ as the WHO-prequalified product.

Deviations ⁴	Reasons

- The Product has been deregistered or the registration of the Product has been suspended.

Deregistration (Yes/No): _____

Suspension of registration: (Yes/No): _____

Effective date (dd/mm/yyyy): ____ / ____ / ____

Reasons: _____

For the NMRA

Signature: _____

Name: _____

Title: _____

Place: _____

Date: (dd/mm/yyyy) _____

³ See footnote 1.

⁴ See footnote 2.