WHO Expert Committee on Specifications for Pharmaceutical Preparations

Fiftieth report

This report contains the 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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WHO Expert Committee on Specifications for Pharmaceutical Preparations
Geneva, 12–16 October 2015

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Declarations of interest

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

Dr E. Adams, Dr M. Brits, Mr D. Churchward, Dr T. Dekker, Dr A. Garcia Arieta, Dr J. Gordon, Professor J. Hoogmartens, Professor Jin S., Dr O. Le Blaye, Dr J. Molzon, Dr A. Nicolas, Ms L. Paleshnuik, Dr J. Sabartova, Dr M. Da Luz Carvalho Soares and Mr S. Akbaralli Veljee reported no conflict of interest.

Professor S. Bawazir reported that he is in the process of establishing a new consultancy.

Professor H.G. Kristensen reported that he has provided testimonies as an independent expert in questions on validity and for infringement of patents at courts in Denmark, Norway and Sweden. In all cases testimony related to drug formulations. No items conflict with the subjects of the meeting.

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

Dr J. Miller reported that he has acted as a consultant for national authorities.

Ms C. Munyiamba-Yeta reported that she was employed by the Zambian Regulatory Authority for seven years until 2014. For the moment she works as an independent consultant.

Mr J. Wilkinson reported that he was employed with the European Medical Devices Industry Association until December 2012.

The interests summarized above do not give rise to a conflict of interest such that the expert concerned should be partially or totally excluded from participation in the Expert Committee on Specifications for Pharmaceutical Preparations. However, following WHO’s policy, they were disclosed within the Committee so that other members were aware of them. All other members of the Expert Committee declared no relevant interests.

Many of the Expert Committee Members have extensive governmental experience and expertise – including consulting with WHO – in the areas that are the subject of the Expert Committee agenda, and which were considered very relevant and important for the challenging tasks faced by the Committee. It was suggested that the Secretariat should provide more detail on the type of conflict to be reported in the declarations of interest for regulatory authorities. The Secretariat agreed to follow up this suggestion with the WHO Office of the Legal Counsel.
1. Introduction

The World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 12 to 16 October 2015. Mr Cornelius de Joncheere, Director of the Department of Essential Medicines and Health Products (EMP) at WHO, welcomed participants on behalf of the Director-General.

Mr de Joncheere welcomed the experts and advisers from all WHO regions, as well as observers and representatives from international organizations. He thanked them and their teams for their major contributions to the work of WHO in setting standards in the area of pharmaceuticals. He mentioned that this was the fiftieth anniversary of the Expert Committee’s meetings. The Committee held its first meeting in 1947 under the name of Expert Committee on Unification of Pharmacopoeias to continue the work of technical experts of the League of Nations. The Committee’s scope of work was extended from the maintenance of international pharmacopoeial standards to good manufacturing practices (GMP) and subsequently to other topics. Today it covers all aspects of medicines quality, with a strong focus on building quality assurance into the life cycle of products, from development to the supply to patients. A press event titled “Promoting quality medicines and saving lives – Commemorating the 50th anniversary of WHO programme to improve medicines quality worldwide” had been organized for 15 October 2015.

WHO’s standard-setting work today is more important than ever, and is conducted under strengthened rules for selection of experts and for declarations of interests. The Expert Committee system is the backbone of WHO’s normative function. The technical guidance is provided online and is widely used. The website, with the 75 medicines quality assurance-related guidelines adopted through the Committee and the online version of The International Pharmacopoeia, is at the top of the Organization’s list for web queries.¹

The Expert Committee has strong links with other WHO groups such as the Expert Committee on Biological Standardization (ECBS), the International Nonproprietary Names (INN) expert consultation, which met concurrently with this Committee, and the Expert Committee on the Selection and Use of Expert Medicines. Strong links also exist with global groups such as the world pharmacopoeias.

Health systems were a focus of the 2015 World Health Assembly. Besides the extensive work done to sustain the emergency response to the Ebola outbreak and to step up preparedness for future public health emergencies, other achievements included the adoption of a global action plan to combat antibiotic

resistance, and the adoption of the Global Vaccine Action Plan. In the area of medicines, innovative ways of developing new medicines are an important topic, as is the work of the mechanism to combat substandard/spurious/falsely-labeled/falsified/counterfeit (SSFFC) products. Health has also been recognized as a central topic for global development in the Sustainable Development Goals (SDGs) launched in September 2015. The health-related goal – SDG 3, “Ensure healthy lives and promote well-being for all at all ages” – includes targets for improving access to good quality, affordable medicines and promoting research for needed medicines.

The Committee elected Ms G.N. Mahlangu as Chairperson, Professor J. Hoogmartens as Co-chairperson, and Professor S.A. Bawazir and Dr J. Sabartova as Rapporteurs. Ms Mahlangu then took the chair. Declarations of interest as shown on page 10 of this report were presented to the meeting participants in accordance with strengthened WHO rules for Expert Committees.

**Open session**

The Chairperson welcomed the members, technical advisers and observers to the open session of the Expert Committee. The open session had been arranged in response to earlier expressions of interest by the diplomatic missions. It was noted that there were no representatives from the missions.

The Secretary of the Expert Committee described the Committee’s role in fulfilling WHO’s normative mandate, and explained how WHO’s Expert Committee system works. In its normative work the Committee sets rules for medicines quality assurance, and acts in response to global health emergencies and the needs of international organizations. An Expert Committee is the highest advisory body to the Director-General and is established in the constitution of the Organization. A set of strengthened rules and procedures, including new procedures for declaration of interests, govern invitations to and participation in an Expert Committee. The WHO Expert Committee on Specifications for Pharmaceutical Preparations maintains *The International Pharmacopoeia* and provides guidance on all topics relating to medicines quality assurance. The guidelines are developed in consultation with a wide range of international partners, including Collaborating Centres, international associations and organizations. Participants were reminded that they were acting in their personal capacity as experts.

The Secretary thanked all the partners for their major contributions to WHO’s standard-setting work.
2. General policy

2.1 Cross-cutting pharmaceutical quality assurance issues

Expert Committee on the Selection and Use of Essential Medicines

The Expert Committee on the Selection and Use of Essential Medicines selects the medicines that satisfy the priority health-care needs of the population, taking into account disease prevalence, efficacy and safety, and comparative cost-effectiveness. However, the absolute cost of treatment will not constitute a reason to exclude a medicine that is shown to otherwise meet the established selection criteria. The WHO Model Lists of Essential Medicines (EML) for adults and for children are updated every two years.

The current EMLs include 416 medicines for adults and 289 medicines for children. Important additions in 2015 include 16 new medicines for treatment of cancer, four single-ingredient antivirals and two combination antivirals to treat hepatitis C, as well as four medicines to treat multidrug-resistant tuberculosis and one medicine to treat latent tuberculosis infection. Other additions included new contraceptive formulations, medicines affecting coagulation, medicines for hepatitis B, and some new formulations of existing medicines. Notably, it was decided not to recommend inclusion on the EML of ranibizumab for neovascular eye diseases, novel oral anticoagulants and so-called polypill therapy for cardiovascular disease.

The EML includes a number of biological medicines, and a process for adding biosimilars will need to be defined in the future. All applications and recommendations of this Expert Committee are published on the WHO website.

The Committee noted the report.

Regulatory support

An update was provided about WHO’s regulatory support activities conducted on the basis of the Organization’s normative guidance. WHO is one of the largest global providers of regulatory training, covering all aspects of regulation, including inspections, assessment of product data and post-marketing control of medicines. The wide implementation of a common basis of norms and standards has facilitated the creation of a number of successful harmonization initiatives and cooperative networks, such as the East African Community harmonization project and similar initiatives in the Southern African Development Community region and elsewhere. Joint assessment and inspection activities are also increasing. These developments are further supported by good practices (GXP) documents for regulatory authorities that are being developed through the Committee, such as the good review practice document developed under the leadership of the Asia-Pacific Economic Cooperation Regulatory Harmonization
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Steering Committee and adopted by the Committee in 2014. A further overarching framework guidance document on good regulatory practices is being developed to promote regulatory consistency and collaboration.

The Committee noted the report.

Expert Committee on Biological Standardization (ECBS)
The ECBS met concurrently with the Expert Committee on Specifications for Pharmaceutical Preparations. Directions in biological standardization have been driven by three strategic aims that have shaped WHO’s work in the past year, namely to:

1) ensure preparedness for public health emergencies;
2) step up access to biotherapeutic products; and
3) strengthen global regulatory systems.

With regard to public health emergencies, lessons learnt during the Ebola outbreak have led to thought being given to the development of rapid regulatory pathways to make needed products available to affected populations. WHO has played a critical role in accelerating clinical trials for candidate products in Ebola-affected countries. With unprecedented support from the global regulatory community, efficacy data for vaccines, diagnostic products and potential treatments were generated in record time. Based on the lessons learnt during the Ebola outbreak a blueprint has been prepared for a new research and development (R & D) framework, with appropriate prioritization of suitable candidate products, enabling a swift and concerted global response in case of future emergencies. The development of a road map on R & D for Middle East respiratory syndrome (MERS) coronavirus will serve as a pilot. The blueprint was intended to be presented to the World Health Assembly (WHA) in 2016.

The Committee noted the report.

2.2 International collaboration
United Nations Children’s Fund (UNICEF)
UNICEF was established in 1946 to promote and protect children’s rights. Health and nutrition and the fight against HIV/AIDS are among UNICEF’s core commitments. The Supply Division in Copenhagen, Denmark, ensures that high-quality, good value medicines and other supplies reach children and their families quickly. In 2014, UNICEF supplied goods with a total value of US$ 3.38 billion, including US$ 1.48 billion worth of vaccines and US$ 251 million worth of pharmaceuticals. A web-based catalogue of products procured, including a wide range of medicines for all major health needs, is publicly available on the Internet.
UNICEF applies the WHO model quality assurance system for procurement agencies (MQAS) in inspections, assessment of product data and monitoring of supplier performance. The Committee was provided with a description of UNICEF’s systems for qualifying products and suppliers, which is based on product assessment and inspections. Products are assessed using a product questionnaire as published in the MQAS guidance. Vaccines, antiretrovirals, antimalarials and medicines for treatment of tuberculosis must be WHO-prequalified, with measures in place to verify that the goods supplied do in fact meet prequalification standards. UNICEF inspects manufacturers to verify compliance with WHO GMP guidelines and participates in joint inspections with the WHO prequalification team (WHO/PQT) and other organizations. Since 2006 UNICEF has been a partner of the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

Priority areas of UNICEF’s work in 2015 included performance management to ensure timely delivery, measures to support sourcing and regulation in recipient countries, long-term arrangements with suppliers, participation in meetings on essential medicines and relevant WHO disease programmes, targeted activities to ensure the availability and quality of specific products or product groups for use in WHO Member States, and the implementation of the outputs of the Expert Committee on Specifications for Pharmaceutical Preparations. The Committee noted the report.

Pharmacopoeial Discussion Group (PDG)

The PDG – consisting of the European Pharmacopoeia, the United States Pharmacopeia (USP) and the Japanese Pharmacopoeia (JP) – met in Tokyo, Japan, from 30 June to 1 July 2015. It was reported that 29 of the 36 general chapters and 48 of the 62 excipient monographs on the current work programme had been harmonized and that in-depth discussions on a number of additional items currently on the PDG work programme had taken place. Significant progress had been made, for example, with the harmonization of chromatographic methods for certain products. Chapters on colour, conductivity and protein determination had reached PDG Stage 4 (public consultation phase); a chapter on uniformity of delivered dose was being harmonized between the European Pharmacopoeia and the Japanese Pharmacopoeia. Methods for biotechnology products were also being harmonized. Stage 4 documents are posted on the websites of all three participating pharmacopoeias. WHO is an observer to PDG.

To provide increased transparency on its activities, PDG will offer an easy way to access information on its work programme to its sister pharmacopoeias, including the possibility to provide comments on draft texts during the consultation period. Information with respect to increasing transparency was shared at the sixth WHO international meeting of world pharmacopoeias.

The Committee noted the report.
Model regulatory framework for medical devices

Over the past 20 years, medical devices have become an extremely diverse and complex product group, with a significant manufacturer base and large global sales. Resolution WHA 67.20 urges Member States to strengthen national regulatory systems for medical products, including medical devices. A survey on the current status of regulatory systems in Member States has shown that regulatory systems for medical devices are nonexistent in almost half of the countries and very limited in many others.

Medical devices differ in several important ways from pharmaceuticals, although they are often regulated by the same national authorities. Opportunities exist for collaboration between regulatory authorities. There is currently limited WHO guidance available for medical devices, aside from that originating from the WHO/PQT for in vitro diagnostics (IVDs). To support Member States in establishing systems to regulate medical devices, WHO has initiated the development of a model regulatory framework for use by national regulatory authorities.

It has been proposed that the Expert Committee on Specifications for Pharmaceutical Preparations oversees the development of a model regulatory framework for medical devices. The Expert Committee noted that it does not currently have sufficient expertise and resources to perform this additional work. It was therefore suggested that a subgroup of suitably qualified experts should be created. The Secretariat will follow up accordingly and seek to identify the required expertise from the existing WHO Expert Advisory Panels.
3. Quality control – specifications and tests

3.1 The International Pharmacopoeia

3.1.1 Updates

Fifth edition of The International Pharmacopoeia

The fifth edition of *The International Pharmacopoeia* was published on the WHO website in August 2015 and has been made available on CD. The new edition includes 32 new or revised monographs on pharmaceutical substances and dosage forms as listed in the preface. Other updates include two texts reproduced with the permission of the *European Pharmacopoeia*. A function has been added to the electronic interface enabling users to generate PDF documents for saving or printing. The Secretariat expressed its sincere thanks to all who had contributed to this fifth edition.

The Committee noted the report and congratulated the Secretariat on this achievement.

Trade names of stationary phases

The Secretariat has started publishing trade names of stationary phases found suitable during monograph elaboration, for the information of users of the monographs. The list is available on the WHO website and will be updated continuously in accordance with new monographs included in *The International Pharmacopoeia*. It was agreed that a cross-reference to the list would be provided in *The International Pharmacopoeia* to direct users to this useful additional information.

3.1.2 Workplan 2015–2016

Priorities for new monographs

*The International Pharmacopoeia* specifies primarily the quality of essential medicines that are included on the WHO EML, on the invitations for expressions of interest for WHO prequalification, or in other United Nations (UN) and/or WHO documents recommending the use of medicines for treatment of specific diseases and/or for use by treatment programmes.

The Committee heard a description of the process used to establish a workplan for elaboration of monographs, which, while acknowledging limited resources, aimed to meet the expectations of the Member States, WHO

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programmes and other partners. For future monograph elaboration, priority has been assigned to medicines belonging to the categories covered by the WHO/PQT and to medicines considered as life-saving commodities for women and children as identified by the UN Commission on Life-Saving Commodities for Women and Children (UNCoLSC) and for which public standards are not yet available. General texts will be developed as the need arises in connection with the prioritized monographs.

The Secretariat will follow up on an earlier collaboration between WHO/PQT and the Chinese Pharmacopoeia under the Global Fund project, during which some 50 monographs were developed, with a view to making these available to WHO for possible inclusion in The International Pharmacopoeia.

Monographs proposed for elaboration or suppression

In line with the above-mentioned priorities, a list of 31 high priority monographs for finished pharmaceutical products (FPPs) was proposed for elaboration (Table 1). Additional monographs for the corresponding active pharmaceutical ingredient (API) will be required. Ten monographs were identified for suppression (Table 2) following their deletion from the WHO EML. As the medicines concerned may still be part of national lists of essential medicines, it was agreed that suppressed monographs should be transferred to a publicly accessible “Archived” section of The International Pharmacopoeia.

Table 1

<table>
<thead>
<tr>
<th>Dosage form monographs proposed for elaboration with high priority</th>
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<tbody>
<tr>
<td>abacavir, efavirenz and lamivudine tablets</td>
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<tr>
<td>abacavir, lamivudine and nevirapine dispersible tablets</td>
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<td>artemether and lumefantrine dispersible tablets</td>
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<td>atazanavir and ritonavir tablets</td>
</tr>
<tr>
<td>dolutegravir tablets</td>
</tr>
<tr>
<td>efavirenz, lamivudine and tenofovir tablets</td>
</tr>
<tr>
<td>entecavir oral solution</td>
</tr>
<tr>
<td>entecavir scored tablets</td>
</tr>
<tr>
<td>estradiol valerate and norethisterone enantate injection</td>
</tr>
</tbody>
</table>
Table 1 continued

<table>
<thead>
<tr>
<th>etravirine tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>flucytosine slow release tablets</td>
</tr>
<tr>
<td>lamivudine and tenofovir tablets</td>
</tr>
<tr>
<td>linezolid oral suspension</td>
</tr>
<tr>
<td>moxifloxacin tablets</td>
</tr>
<tr>
<td>norethisterone enantate injection</td>
</tr>
<tr>
<td>p-aminosalicylic acid granules for oral solution</td>
</tr>
<tr>
<td>protionamide tablets</td>
</tr>
<tr>
<td>pyrazinamide dispersible tablets</td>
</tr>
<tr>
<td>raltegravir tablets</td>
</tr>
<tr>
<td>ribavirin syrup</td>
</tr>
<tr>
<td>ritonavir oral solution</td>
</tr>
<tr>
<td>simeprevir capsule</td>
</tr>
<tr>
<td>sofosbuvir tablet</td>
</tr>
<tr>
<td>terizidone capsules</td>
</tr>
<tr>
<td>terizidone tablets</td>
</tr>
<tr>
<td>zanamivir powder for inhalation</td>
</tr>
</tbody>
</table>

Table 2

**Monographs proposed for suppression**

<table>
<thead>
<tr>
<th>ampicillin capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>colchicine tablets</td>
</tr>
<tr>
<td>ergometrine hydrogen maleate tablets</td>
</tr>
<tr>
<td>indometacin tablets</td>
</tr>
<tr>
<td>pethidine hydrochloride tablets</td>
</tr>
<tr>
<td>piperazine adipate tablets</td>
</tr>
<tr>
<td>piperazine citrate tablets</td>
</tr>
<tr>
<td>prednisolone sodium phosphate injection</td>
</tr>
<tr>
<td>prednisolone sodium succinate powder for injections</td>
</tr>
<tr>
<td>probenecid tablets</td>
</tr>
</tbody>
</table>

The Committee endorsed the workplan as presented.
3.2 Specifications for medicines, including children’s medicines and radiopharmaceuticals

3.2.1 Maternal, newborn, child and adolescent health medicines

Chlorhexidine digluconate solution and chlorhexidine digluconate topical solution/gel

The Committee was informed that work is ongoing to elaborate monographs for chlorhexidine digluconate solution and topical solution/gel for umbilical cord care. These medicines are listed in the 2010 report of the UNCoLSC as an important, low-cost intervention to reduce newborn mortality; the 7.1% chlorhexidine gluconate-containing solution or gel was added to the WHO EML for children in 2013. The Committee will be updated on the progress of the two monographs.

The Committee noted the report.

Estradiol cypionate

In accordance with the agreed workplan for The International Pharmacopoeia it was proposed to include a monograph on estradiol cypionate. A draft was received from a WHO Collaborating Centre in February 2015. The draft was discussed at the consultation on screening technology, sampling and specifications for medicines in April 2015 and circulated for comment in May 2015. Comments received were incorporated and the revised draft monograph was presented to the Committee.

The Committee adopted the monograph subject to the amendments agreed.

Levonorgestrel

Revision of the monograph on levonorgestrel in The International Pharmacopoeia was proposed in January 2015. A revised draft was discussed at the consultation on screening technology, sampling and specifications for medicines in April 2015 and sent out for public consultation in May 2015; comments were particularly sought on whether the monograph should include a limit test for dextronorgestrel. The revised monograph was presented to the Committee for discussion.

The monograph was adopted subject to the amendments agreed. The Committee also authorized the intended use of the reference substances Levonorgestrel for system suitability 1 CRS and Levonorgestrel for system suitability 2 CRS issued by the European Pharmacopoeia (see also 4.2.1).

Magnesium sulfate and magnesium sulfate injection

The Committee was informed that the suitability of the monographs on magnesium sulfate and magnesium sulfate injection had been re-evaluated by a
WHO Collaborating Centre, leading to the conclusion that the monographs are up to date and do not need revision.

The Committee endorsed this conclusion.

**Misoprostol, misoprostol dispersion and misoprostol tablets**

Access to monographs on misoprostol, misoprostol dispersion and misoprostol tablets is important for WHO Member States; misoprostol tablets have been identified as a life-saving product by the UNCoLSC. The first draft monograph on misoprostol was received from a WHO Collaborating Centre in 2014 and a preliminary version was presented to the Committee at its forty-ninth meeting. The draft was circulated for public consultation in January 2015, and was discussed and further revised at the informal consultation on screening technology, sampling and specifications for medicines in April 2015. At the same time, draft monographs for misoprostol tablets and dispersion were developed. All three drafts were presented to the Expert Committee at its fiftieth meeting, noting that it was proposed to send out all three texts again for public consultation after the Expert Committee meeting and to review the comments received with a subgroup of experts.

The Committee adopted the three monographs subject to amendments as agreed at the meeting and subject to the outcome of a further round of public consultation and subsequent review by a subgroup of experts as proposed. This will enable the Secretariat to publish the monographs in the next edition of *The International Pharmacopoeia*.

It was agreed that the monograph for misoprostol dispersion should be published in the section on monographs for pharmaceutical substances.

**Norethisterone and norethisterone tablets**

At the forty-ninth Expert Committee meeting in 2014 it was proposed to revise the monograph on norethisterone and to include a monograph on norethisterone tablets in *The International Pharmacopoeia*. Drafts were developed between October 2014 and June 2015 and were sent out for public consultation in July 2015. The drafts were revised according to comments received, and were presented to the Expert Committee.

The Committee accepted the two monographs and authorized the proposed intended use of the reference substance Norethisterone for system suitability issued by the *European Pharmacopoeia* (see also 4.2.1).

### 3.2.2 Antimalarial medicines

**Artemether injection**

The Committee was consulted regarding a proposed change that would widen the assay limits in the monograph on artemether injection in order to align
them with limits specified in similar monographs. The Committee was further informed of a proposal received from a manufacturer for improvement of the related substances test. A WHO Collaborating Centre kindly agreed to perform further investigations in this regard, and the Committee will be informed of the results.

The Committee supported the proposed widening of the assay limits and endorsed their inclusion in the next edition of *The International Pharmacopoeia*.

### 3.2.3 Antituberculosis medicines

**Cycloserine and cycloserine capsules**

Following up on information received from a manufacturer it was proposed to revise the monographs on cycloserine and cycloserine capsules. Extensive additional tests were performed by a collaborating laboratory to evaluate the proposed changes. Revised drafts of the two monographs were received from the collaborating laboratory in July 2015 and circulated for public comment in August 2015. The revised monographs were presented to the Committee for discussion.

The Expert Committee adopted the monographs subject to the amendments agreed.

### 3.2.4 Medicines for tropical diseases

**Mebendazole and mebendazole chewable tablets**

The Committee was informed of a number of planned revisions to the monographs on mebendazole and mebendazole chewable tablets. The Committee will be informed of progress.

The experts took note of this information.

### 3.2.5 Medicines for chronic diseases and for mental health

**Carbamazepine, carbamazepine tablets, carbamazepine chewable tablets and carbamazepine oral suspension**

Draft monographs on carbamazepine and related dosage forms were provided by a WHO Collaborating Centre in December 2014. The drafts were discussed at an informal consultation on screening technology, sampling and specifications for medicines held in April 2015. The text was published for comment in July 2015; comments were sought in particular as to whether the impurities listed under the section Impurities are degradation products or synthesis impurities.

The draft monograph on carbamazepine and the related dosage form monographs were presented to the Expert Committee. However, in light of new information about the nature of potential impurities, the Secretariat of *The International Pharmacopoeia* proposed to redesign the impurity specifications
and to circulate the monographs again for public consultation after the meeting, with a subsequent review of comments by a subgroup of experts in early 2016. The Committee adopted the monographs, subject to the amendments agreed and subject to a further round of consultation and revision as proposed.

3.2.6 Other anti-infective medicines

Clindamycin hydrochloride and clindamycin hydrochloride capsules

Initial draft monographs on clindamycin hydrochloride and clindamycin hydrochloride capsules were received from the responsible WHO Collaborating Centre in December 2014. The drafts were circulated for public comment in January 2015 and discussed at the informal consultation on screening technology, sampling and specifications for medicines in April 2015 before being presented to the Committee.

The Committee adopted the monographs subject to the amendments agreed.

Flucytosine and flucytosine intravenous infusion

Draft monographs on flucytosine and flucytosine intravenous infusion were circulated for comment in December 2014. The comments received were discussed at the consultation on screening technology, sampling and specifications for medicines in April 2015. The revised drafts were presented to the Committee.

The Committee adopted the proposed monographs.

3.2.7 Other medicines

Dextromethorphan hydrobromide and dextromethorphan oral solution

At the forty-ninth meeting of the Expert Committee it had been decided to revise the monograph on dextromethorphan hydrobromide in response to serious incidents that occurred after the consumption of dextromethorphan cough syrups contaminated with levomethorphan. As a result of these events, the Committee adopted a revised monograph on dextromethorphan hydrobromide, which included a statement that the substance must comply with a limit of not more than 0.1% levomethorphan hydrobromide using a suitable chiral method. A suitable test for levomethorphan had been elaborated and was included in the draft revised monograph on dextromethorphan hydrobromide. The draft was sent out for public consultation in January 2015 and was revised further at an informal consultation in April 2015. At the same time, a monograph on dextromethorphan oral solution was developed, and was sent out for public consultation in August 2015.

The limit test for levomethorphan is not part of the routine release testing of the dosage form, and was therefore not included in the monograph.
itself. Instead, the monograph includes a statement that samples, if tested, must comply with a levomethorphan limit of not more than 0.1%, and provides a reference to the levomethorphan limit test to be published in the Supplementary information section of *The International Pharmacopoeia* (see below).

The Committee adopted both monographs subject to the amendments agreed.

**Levomethorphan limit test for dextromethorphan-containing finished products**

An additional limit test for levomethorphan in dextromethorphan-containing dosage forms is to be included in the Supplementary information section of *The International Pharmacopoeia*, enabling quality control laboratories to test suspicious finished product samples for levomethorphan. In 2014 the Expert Committee members reviewed a laboratory report describing the elaboration of suitable procedures. A reference substance containing a mixture of levomethorphan and dextromethorphan is still under establishment. The proposed test was further discussed at an informal consultation in April 2015 and was confirmed by a national quality control laboratory before the proposed text was sent out for comment in August 2015. No comments had been received by 25 September 2015.

The Committee adopted the proposed text.

### 3.2.8 Radiopharmaceuticals

Review and update of radiopharmaceutical monographs by the International Atomic Energy Agency (IAEA) had been undertaken according to the update and submission process adopted by the Committee at its 2013 meeting. A coordination meeting was held at IAEA in 2014. In early 2015, the work priorities and time lines were aligned with the available expert time and resources. The final schedule for the updating of monographs was expected to be completed in October 2015.

A status update was provided on progress made in updating radiopharmaceutical monographs and associated documentation in *The International Pharmacopoeia*. A number of monographs had been submitted and circulated for comment in accordance with the Committee’s consultation process, namely those for technetium ($^{99m}$Tc) exametazime, thallous ($^{201}$Tl) chloride and sodium iodine ($^{131}$I) solution, as well as a general monograph on radiopharmaceuticals. The following monographs had been reviewed by the experts and were ready for submission to WHO for consultation: technetium

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3 The representative from the IAEA was unable to attend the meeting; the WHO Secretariat presented a written report received from IAEA to the Committee.
Quality control – specifications and tests

(\textsuperscript{99m}Tc) bicitate, technetium (\textsuperscript{99m}Tc) succimer, technetium (\textsuperscript{99m}Tc) sulfur colloid and technetium (\textsuperscript{99m}Tc) mebrofenin. The following monographs were ready for final verification by designated experts and expected to be completed in January 2016: technetium (\textsuperscript{99m}Tc) sestamibi, technetium (\textsuperscript{99m}Tc) tin colloid, technetium (\textsuperscript{99m}Tc) pertechnate, technetium (\textsuperscript{99m}Tc) pyrophosphate, technetium (\textsuperscript{99m}Tc) pentetate, technetium (\textsuperscript{99m}Tc) tetrafosmin, technetium (\textsuperscript{99m}Tc) medronate and technetium (\textsuperscript{99m}Tc) mertiatide.

Based on the outcome of the recent IAEA Coordinated Research Project (CRP), the IAEA planned to arrange a review, with help from the CRP participants, of the monograph on cyclotron-produced \textsuperscript{99m}Tc. Furthermore, a new monograph on extemporaneous preparation of radiopharmaceuticals would be drafted by the experts.

The Expert Committee noted the report.

3.3 General policy

Microbiological assay of antibiotics

There are currently five International Chemical Reference Substances (ICRS) which were established as secondary reference standards for tests according to Chapter 3.1, Microbiological assay of antibiotics, in \textit{The International Pharmacopoeia}. To ensure the continuous fitness for purpose of these reference substances, their assigned potencies have to be monitored regularly in extensive, resource-consuming collaborative trials. In addition, a total of 21 monographs prescribe a microbiological assay for antibiotics, but no suitable reference substance has yet been established.

At its meeting in 2009 the Expert Committee had decided that in monographs for antibiotics which specify a microbiological assay, this test should be replaced by a chromatographic method where possible and appropriate.

Since 2009, significant progress has been achieved in developing physicochemical assay methods for pharmaceutical products. In view of the information provided above, the Secretariat of \textit{The International Pharmacopoeia} proposed to:

\begin{enumerate}
  \item discontinue the use of five ICRS in microbiological assays of antibiotics and to delete the potency assignments in the ICRS leaflets;
  \item revise four monographs in order to replace the microbiological assay with liquid chromatography methods, considering methods already published in pharmacopoeias;
  \item revise four monographs in order to replace the ICRS by WHO International Standards for Antibiotics (ISA) or, preferably,
secondary standards derived from them and established by another pharmacopoeia for use in microbiological assay, which could foster work-sharing between pharmacopoeias;

(4) develop a concept document for the possible transition from microbiological to physicochemical assay in 14 monographs, considering in particular chromatographic methods published in the scientific domain, for discussion and possible endorsement by this Committee and the Expert Committee on Biological Standardization; and

(5) suppress the monographs for substances containing any of five active ingredients. Medicines containing these substances are no longer included in the WHO EML (19th edition) or in the relevant invitations for expression of interest to manufacturers.

The Committee agreed to the proposals described under points (1), (2), (4) and (5) above (see Table 3). With regard to the proposal outlined in point (3), the Committee agreed that the experts should be given more time to identify possible reference standards that can be referred to in each of the monographs. The relevant ICRS and monographs affected by these decisions are listed in Table 3.

Table 3
Recommendations relating to the use of microbiological assays for antibiotics

<table>
<thead>
<tr>
<th>(1)</th>
<th>ICRS no longer to be used for microbiological assays of antibiotics, and potency assignments to be deleted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nystatin (ICRS0369)</td>
</tr>
<tr>
<td></td>
<td>framycetin sulfate (neomycin B) (ICRS0355)</td>
</tr>
<tr>
<td></td>
<td>gentamicin sulfate (ICRS0319)</td>
</tr>
<tr>
<td></td>
<td>spectinomycin hydrochloride (ICRS0415)</td>
</tr>
<tr>
<td></td>
<td>streptomycin sulfate (ICRS0416)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(2)</th>
<th>Monographs in which microbiological assay should be replaced by liquid chromatography methods</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>erythromycin ethylsuccinate</td>
</tr>
<tr>
<td></td>
<td>erythromycin lactobionate</td>
</tr>
<tr>
<td></td>
<td>erythromycin stearate</td>
</tr>
<tr>
<td></td>
<td>tetracycline hydrochloride</td>
</tr>
</tbody>
</table>
Table 3 continued

(3) Monographs for which suitable standards other than ICRS should be identified*

- amphotericin B
- amphotericin B for injection
- bleomycin sulfate
- kanamycin for injection
- kanamycin monosulfate

(4) Monographs for which a concept paper should be developed on the possible transition from microbiological to physicochemical methods

<table>
<thead>
<tr>
<th>Amphotericin B</th>
<th>Kanamycin acid sulfate</th>
<th>Gentamicin sulfate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B for injection</td>
<td>Kanamycin for injection</td>
<td>Streptomycin sulfate</td>
</tr>
<tr>
<td>Bleomycin sulfate</td>
<td>Kanamycin monosulfate</td>
<td>Streptomycin for injection</td>
</tr>
<tr>
<td>Erythromycin ethylsuccinate tablets</td>
<td>Nystatin</td>
<td>Paromomycin sulfate</td>
</tr>
<tr>
<td>Erythromycin stearate tablets</td>
<td>Nystatin tablets</td>
<td></td>
</tr>
</tbody>
</table>

(5) Monographs that should be suppressed

- bacitracin
- bacitracin zinc
- bleomycin hydrochloride
- chlorotetracycline hydrochloride
- erythromycin (base)
- neomycin sulfate
- oxytetracycline dehydrate
- oxytetracycline hydrochloride

* The Committee agreed that the experts should be given more time to identify possible reference standards that can be referred to in the monographs.

Replacement of mercuric acetate

The Secretariat of The International Pharmacopoeia is committed to eliminating the use of mercury salts in currently recommended methods in order to reduce the risk to analysts and the environment. In the past, mercuric acetate was used to titrate weak bases; however, such titrations are now obsolete and can be replaced with safer and better titration techniques, such as the direct titration with perchloric acid in anhydrous acetic acid. As a first step in phasing out mercury-based methods, a WHO Collaborating Centre has identified 47 monographs in which mercuric acetate is used as a reagent and has listed alternative methods used in other pharmacopoeias. As a possible next step, the Secretariat proposed that a concept should be developed to guide the replacement of obsolete titrations of pharmaceutical substances in The International Pharmacopoeia and the elaboration of the related assays.

The Committee took note of the update.
Draft note for guidance on organic impurities in active pharmaceutical ingredients and finished pharmaceutical products

Taking into account current practices in the use of *The International Pharmacopoeia* and available guidance on how to establish limits for impurities, a note for guidance on organic impurities in active pharmaceutical substances and FPPs was drafted.

The proposed note for guidance is intended to replace the text on “Related substances in finished pharmaceutical product monographs” in the Supplementary information section of *The International Pharmacopoeia*. The first draft was prepared by the Secretariat of *The International Pharmacopoeia* in January–March 2015 with input from a group of experts, and was discussed at the consultation on screening technology, sampling and specifications for medicines in April 2015. The draft was sent out for public consultation in April 2015, and the comments received were collated by the Secretariat. The revised proposed draft was presented to the Committee.

The Committee reviewed the proposed revised draft and provided further feedback. It was agreed to form a small working group to address a number of specific comments raised in the discussion. The working group met during the meeting and reported back to the Committee with a proposal for further revisions. The Committee agreed that the revised document should be discussed further within the small working group and with relevant experts. It should then be discussed at an informal consultation before being sent out again for public consultation, together with a brief explanatory note about the nature of the revisions. The Committee will review a revised draft at its next meeting.

4.1 Update on International Chemical Reference Substances (ICRS), including report of the ICRS Board

International Chemical Reference Substances (ICRS) are used as primary standards in physical and chemical tests that are described in *The International Pharmacopoeia*, as well as for setting official secondary standards. ICRS are used to identify and determine the purity or assay of pharmaceutical substances and preparations or to verify the performance of test methods. The standards are officially adopted by the Expert Committee.

The European Directorate for the Quality of Medicines & HealthCare (EDQM) is the custodian centre in charge of establishment, storage, distribution and monitoring of ICRS in *The International Pharmacopoeia*. Three steering committee telephone conferences were held in 2014, and two in 2015. In accordance with the work programme as agreed in March 2014, the ICRS listed below were established and released by the ICRS Board.

Routine monitoring of fitness for purpose was done on 17 ICRS in 2014, and no negative findings were reported; for 2015, 13 substances had been monitored with no negative findings. The EDQM welcomed the decisions to add dates and version numbers to monographs in *The International Pharmacopoeia*, as this facilitates quality assurance verification of ICRS batches in relation to their intended *International Pharmacopoeia* use.

Work is in progress to establish reference substances for capreomycin sulfate, enabling testing according to the recently adopted monographs on capreomycin, and for dextromethorphan for system suitability, enabling the performance of the limit test for levomethorphan adopted by the Committee at this meeting.

The Secretariat expressed its sincere thanks to EDQM for establishing, storing and distributing ICRS and providing related guidance, to the ICRS Board for reviewing establishment reports and releasing ICRS, and to the laboratories that participated in collaborative trials. The Expert Committee noted the report and joined the Secretariat in thanking the custodian centre for this major contribution. The Expert Committee noted the report and endorsed the release of the ICRS shown in Table 4.
Table 4
ICRS released by the ICRS Board

<table>
<thead>
<tr>
<th>Substance</th>
<th>ICRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-artemether</td>
<td>1</td>
</tr>
<tr>
<td>efavirenz</td>
<td>2</td>
</tr>
<tr>
<td>efavirenz impurity B</td>
<td>1</td>
</tr>
<tr>
<td>ritonavir</td>
<td>2</td>
</tr>
<tr>
<td>abacavir sulfate</td>
<td>2</td>
</tr>
<tr>
<td>paracetamol</td>
<td>3</td>
</tr>
<tr>
<td>artemether</td>
<td>2</td>
</tr>
<tr>
<td>rifampicin</td>
<td>3</td>
</tr>
<tr>
<td>stavudine impurity F</td>
<td>1</td>
</tr>
</tbody>
</table>

4.2 General policy

4.2.1 Chapter on reference substances and reference spectra

Following up on a recommendation made by the Expert Committee at its fortieth meeting to use in The International Pharmacopoeia, where appropriate, ultraviolet (UV) absorptivity values for assays and other quantification purposes with a view to limiting reference to ICRS, it was proposed to revise the chapter on reference substances and reference spectra.

Additional changes were proposed to reflect recent discussions within the ICRS Board and with the custodian centre for ICRS. A draft revised chapter was prepared by the Secretariat of The International Pharmacopoeia in January–March 2015 with feedback from a group of experts. The draft was discussed at the consultation on screening technology, sampling and specifications for medicines held from 13 to 15 April 2015 before being circulated for public consultation in May 2015. Comments received were duly collated before presentation of the draft to the Expert Committee at its meeting in October 2015.

Besides other changes, the revised chapter sets out the principles to be applied when reference substances are included in monographs that have been established by other pharmacopoeias for use according to The International Pharmacopoeia. A list of reference standards found suitable for such a use is included as an appendix to the draft revised chapter. The list includes the reference substances mentioned in the monographs on norethisterone and levonorgestrel (see 3.2.1). To facilitate continuous updating, the Committee recommended that the list should be maintained as a living document on the WHO website and referred to in the chapter on reference substances.

The Committee adopted the text subject to the amendments agreed.
5. Quality control – national laboratories

5.1 External quality assurance assessment scheme

The external quality assurance assessment scheme (EQAAS) is a proficiency testing scheme offered by WHO for the external evaluation of quality control management systems in chemical quality control laboratories. Since 2010 it has been organized with assistance from the EDQM.

The Committee was given an update on Phase 6 of the EQAAS studies. Unlike in Phase 5 studies, the samples sent out were used for two studies, reducing the burden of sending and receiving samples. Approximately 40 laboratories participated in Phase 6 studies. Analysis of samples was ongoing, with results expected at the end of 2015.

The Secretariat maintains close links with the WHO/PQT prequalifying quality control laboratories when carrying out the EQAAS studies. Preparations were beginning for Phase 7 of the EQAAS scheme.

The Committee noted the report.

5.2 Guidance on testing of “suspect” substandard/spurious/falsely-labelled/falsified/counterfeit medicines

In October 2014, the Committee had provided advice and endorsed a draft outline for Guidance on testing of “suspect” substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medicines.

Various related texts were reviewed at the informal consultation on screening technology, sampling and specifications for medicines held in April 2015, and work is in progress to draft concise guidelines on testing of “suspect” SSFFC medicines. A first draft was produced after the consultation and circulated for comment among the relevant experts.

The Committee noted the update and recommended that work on developing the guidelines be continued.
6. Prequalification of quality control laboratories

6.1 **Update on the prequalification of quality control laboratories**

The prequalification procedure for quality control laboratories was established in 2004. Participation is voluntary and is open to both public and private quality control laboratories. In October 2015 there were a total of 38 WHO-prequalified laboratories distributed among all six WHO regions. Two laboratories became prequalified in 2015, one in Uganda and one in India.

A peer audit scheme has been introduced as a capacity-building measure for laboratories involved in the prequalification procedure. Training has been conducted under this scheme in Armenia, Ghana and Nigeria and a further training programme is planned in Madagascar. Applications are currently also being received from manufacturer-linked laboratories, and in any future revision of the procedures consideration should be given to whether the prequalification procedure should be applicable to this type of laboratory.

The Committee noted the report.

6.2 **Update on WHO quality monitoring projects**

A quality monitoring survey of antiretrovirals started in the third quarter of 2015 and is ongoing, with samples being collected in five countries. A survey on antimalarials would start in the first quarter of 2016. It is planned that this survey will include artemisinin combination therapies in the initial phase of developing a spectral library for FPPs to support the use of screening methods for the detection of potential SSFFC products.

The Expert Committee expressed its appreciation for the report.
7. Quality assurance – collaboration initiatives

7.1 International meetings of world pharmacopoeias

In 2012, WHO brought together representatives from 23 national and regional pharmacopoeia authorities at the first meeting of world pharmacopoeias. The participants committed to working towards harmonization of pharmacopoeial standards in the global context by developing a guidance text on good pharmacopoeial practices (GPhP) aiming at convergence of approaches in defining pharmacopoeial standards (see 7.2). Harmonization of standards has become increasingly important for public health for several reasons. It will support the global fight against falsified and substandard medicines and will reduce the costs arising from meeting the different standards used in the production and testing of medicines, thus making good quality medicines accessible to more people.

The international meeting of world pharmacopoeias has become a recurring event which is co-hosted by WHO and a pharmacopoeia. Two meetings were held in 2015: the fifth International Meeting of World Pharmacopoeias co-hosted by the United States Pharmacopeia (USP) and WHO from 20 to 22 April 2015 in Rockville, USA, and the sixth International Meeting of World Pharmacopoeias co-hosted by the Chinese Pharmacopoeia (ChP) and WHO in Suzhou, China on 21–22 September 2015. Achieving global standards to expand access to medicines globally was key to the discussions at the September meeting, which was held in connection with the 2015 ChP Annual Scientific Symposium.

Representatives from 12 WHO Member States’ pharmacopoeias attended, and more than 30 official pharmacopoeial authorities were represented. During this sixth international meeting the new guidelines on GPhP were prepared for finalization, based on feedback received during wide global consultation (see 7.2).

The representative of the Japanese Pharmacopoeia (JP) announced that the seventh WHO International Pharmacopoeia meeting would be co-hosted by the JP and WHO, and would be held in Tokyo from 13 to 15 September 2016 in conjunction with the 130th anniversary of the JP.

The Expert Committee noted the report and thanked the pharmacopoeias and the Secretariat for their major contributions to this achievement.

7.2 Good pharmacopoeial practices

The primary objective of the GPhP is to define approaches and policies on establishing pharmacopoeial standards with the ultimate goal of harmonization. The GPhP describe a set of guiding principles for national pharmacopoeial authorities and regional pharmacopoeial authorities, which facilitates the appropriate design, development and maintenance of pharmacopoeial standards.
A GPhP text has been drafted over the past three years at successive meetings of world pharmacopoeias (see 7.1). In view of the length of the third draft it was decided in 2014 to split it into a main text and a detailed technical annex to be developed by a separate drafting group. A technical annex was drafted on the basis of parts of the previous GPhP text with input from the JP, the *European Pharmacopoeia* and other pharmacopoeias. The significantly shortened fourth draft of the main text was then circulated for comments in September 2014, and was discussed at the fourth meeting of world pharmacopoeias held in Strasbourg, France, in October 2014. It was subject to further consultation with world pharmacopoeias from October 2014 to March 2015 and was discussed at the fifth international meeting of world pharmacopoeias, held in Washington, DC, USA in April 2015. Feedback received on the draft text at that meeting was discussed from 20 to 22 April 2015, leading to preparation of a fifth draft, which was circulated for further consultation among world pharmacopoeias. Comments were received from 15 parties, including five international associations, and were discussed at the sixth international meeting of world pharmacopoeias held in China in September 2015, leading to a sixth draft, which was subjected to the usual public consultation process.

At its forty-ninth meeting, the Expert Committee had been briefed on progress made on developing a GPhP text and had endorsed a concept paper on the purpose and benefits of GPhP. The final revised draft of the main guidance text and comments received during the public consultation process were presented to the Expert Committee at its fiftieth meeting.

The Committee provided its feedback in response to the comments received. The Committee adopted the guidance (Annex 1) with agreed amendments reflecting the comments received, subject to final concurrence being granted by the pharmacopoeias. Work will continue on drafting possible additional chapters and to develop the technical annex further, taking into account its complexity and the resources available. The Committee congratulated the Secretariat on facilitating the development of this document, which is a major step forward towards prospective harmonization of pharmacopoeial practices.

### 7.3 FIP–WHO technical guidelines: points to consider in the provision by health-care professionals of children-specific preparations that are not available as authorized products

The draft of a guidance document on extemporaneous preparation of medicines for children, which had been commissioned by WHO, was considered in 2011 by the WHO Expert Committee on the Selection and Use of Essential Medicines, which has a subcommittee on paediatric medicines. The Committee felt that extemporaneous preparation of medicines for children may be necessary in some situations but was concerned about the risks of inappropriate preparations.
Revisions of the document were submitted to the forty-sixth, forty-seventh, forty-eighth and forty-ninth meetings of the Expert Committee on Specifications for Pharmaceutical Preparations.

The draft was brought into balance with the contents of the WHO document *Development of paediatric medicines: points to consider in formulation* and includes parts from earlier drafts, e.g. the draft appendix on potential problems in compounding, a section on aspects of GMP and a glossary intended to facilitate a common interpretation of the guidance by a wide audience of practitioners. At its 2014 meeting the Expert Committee reviewed the draft and the comments received, and decided that a further meeting should be held between WHO, the International Pharmaceutical Federation (FIP) and other interested parties in order to discuss the text. The draft was then discussed at the informal consultation on paediatric formulations for medicines from 13 to 14 May 2015, and a revised draft was sent out for comment in June 2015. Feedback was received and collated and the draft was further revised in line with comments received. The proposed revised draft was presented to the Committee at its fiftieth meeting in October 2015, with a note that some points raised in the comments would require expert advice beyond the scope of advice from the Committee.

The Committee discussed the proposed draft and the comments, and adopted the guidance with amendments as agreed (Annex 2), subject to a future revision of remaining points with input from suitably qualified experts. The Committee thanked the main author and the experts who contributed to this very useful and relevant guidance. FIP expressed its appreciation to WHO for facilitating the preparation and adoption of this guidance through the Expert Committee.
8. Quality assurance – good manufacturing practices

8.1 Update of WHO good manufacturing practices for biologicals

The guidance on Good manufacturing practices (GMP) for biological products was first adopted by the Expert Committee on Biological Standardization (ECBS) as an annex to the GMP for pharmaceutical products, and was published in the WHO Technical Report Series in 1992. The guidance is widely used by regulators and is mandatory for prequalification of vaccines. To reflect the considerable developments since the adoption of the guidelines as well as current perspectives regarding GMP for manufacturers of biological products, a preliminary draft revision was prepared in 2008. A revised draft was prepared by a drafting group and was discussed at a consultation on GMP for biological products held in July 2014. The text was circulated for public consultation in 2015 before being presented to the ECBS at its October 2015 meeting, held concurrently with the meeting of the Expert Committee on Specifications for Pharmaceutical Preparations.

The proposed guidelines are intended to be an annex to WHO Good manufacturing practices for pharmaceutical products: main principles (WHO Technical Report Series, No. 986, 2014, Annex 2), and should be read in conjunction with other specific WHO guidelines and recommendations for specific classes of biological products (e.g. vaccines). An outline of the proposed revised guidelines and key changes and updates was presented to the Committee. The draft was also presented to the ECBS during its meeting.

The Expert Committee noted the report, and adopted the guidance text (Annex 3) following its adoption by the ECBS.

8.2 Update of questions and answers for WHO good manufacturing practices for active pharmaceutical ingredients

The WHO good manufacturing practices for active pharmaceutical ingredients (WHO Technical Report Series, No. 957, 2010, Annex 2), adopted by the Expert Committee in 2010, are in line with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) text adopted by numerous national and regional authorities. An Appendix 2 to this GMP text approved at the time was intended to eliminate ambiguities and uncertainties and help harmonize the inspections of both small molecules and biotech APIs.

To clarify technical issues and harmonize expectations during inspections, the Pharmaceutical Inspection Co-operation Scheme (PIC/S) through its Expert Circle on APIs and later the ICH, set up working groups to develop questions and answers (Q&As) on the API GMP guidance. WHO has
been involved both as an observer and through technical advice in the PIC/S as well as the ICH-related working groups. The ICH Q&As were adopted on 10 June 2015. During the consultation on data management, bioequivalence, GMP and medicines’ inspection, held from 29 June to 1 July 2015, a draft working document titled *WHO good manufacturing practice guide for active pharmaceutical ingredients* (working document QAS/15.626) was discussed, and the participants unanimously recommended that the current Appendix 2 should be replaced by a cross-reference to the ICH website with the Q&As on *Q7: Good manufacturing practice guide for active pharmaceutical ingredients*.

The Expert Committee endorsed this proposal.

### 8.3 Update of WHO good manufacturing practices: validation

The need for revision of the published *Supplementary guidelines on good manufacturing practices: validation* (WHO Technical Report Series, No. 937, 2006, Annex 4) had been identified by PQT and a draft document was circulated for comment in early 2013. The focus of the revision was Appendix 7 (non-sterile process validation), which had been revised and was adopted by the Committee at its forty-ninth meeting in October 2014.

The Committee was informed that work is ongoing to revise the validation guidance and its appendices as relevant. The Committee noted the update and recommended that this work should be continued.

### 8.4 Update of model inspection report


An outline of an update of the model inspection report prepared by PQT was submitted to the Expert Committee in October 2014; the Committee discussed the outline and endorsed the proposals of the informal consultation. A draft proposal for revision was prepared by the inspectors of the WHO/

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PQT, and was discussed at an informal consultation on data management, bioequivalence, GMP and medicines’ inspection held in Geneva from 29 June to 1 July 2015. The revised draft guidance and model inspection report format were sent out for comment in August 2015. The comments received and a proposed revised draft were presented to the Committee at its fiftieth meeting.

The experts discussed the draft revised guidance and the model inspection report template and provided their input. It was agreed that the template should include subsections for inspection observations corresponding to the subsections of the WHO GMP text with cross-references to the set of six systems incorporating the general scheme of pharmaceutical manufacturing operations, as reflected, e.g. in the inspectional approach of the United States Food and Drug Authority.

The Committee adopted the guidance (Annex 4), subject to the amendments agreed.

8.5 Update and recommendations from the inspectors’ meeting
8.5.1 Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms

The Committee was briefed about progress on updating the Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms (WHO Technical Report Series, No. 961, 2011, Annex 5). A revised draft of these guidelines was discussed at a consultation on data management, bioequivalence, GMP and medicines’ inspection held from 29 June to 1 July 2015. The revision takes into account current trends in engineering as well as experience gained from the implementation of this guidance during inspections.

The guidelines were further revised by a consultant, based on the feedback received during the consultation and from the inspectors of PQT. On this occasion the text was also aligned with other relevant guidelines, notably the proposed revisions to Supplementary guidelines on good manufacturing practices: validation (WHO Technical Report Series, No. 937, 2006, Annex 4). The revised draft was circulated for public comment in September 2015. A large number of comments had been received, which will be discussed at a further technical consultation.

The Expert Committee noted the report.

8.5.2 Risk classification of inspection observations

Observations noted during inspections of manufacturing sites, contract research organizations and quality control laboratories need to be classified according
to the risk to patients and level of compliance with relevant GXPs. Guidance on classification of observations will facilitate harmonization and increase the uniformity of approaches taken by inspectors, as well as the overall rating of GXP compliance by the site. During the consultation on data management, bioequivalence, GMP and medicines’ inspection held on 29 June–1 July 2015, a draft working document on *Risk classification of inspection observations* was discussed. The draft was submitted to the Committee at its fiftieth meeting. Considering that other organizations were also drafting guidance in this area, the participants at the informal consultation recommended that WHO should join in with the ongoing activities in order to enable consistency between inspectorates, facilitating the sharing of information and inspection reports.

The Committee endorsed this proposal.

8.6 Guidance on good data and record management practices

In recent years the number of observations made regarding good data management practices during inspections of GMP, good clinical practice (GCP) and good laboratory practices (GLP) has been increasing. There is increased regulatory awareness of the need for integrity of data submitted as a basis for regulatory decisions. Good data management in line with scientific advances and regulatory developments is crucial for all stakeholders in regulation of health products, including patients, industry and regulators.

A proposal for a new guidance document on good data management was first discussed at an informal consultation held in April 2014. At its forty-ninth meeting the Committee discussed and endorsed a concept paper and the proposed structure of the guidance. A document was then drafted by the inspectors of PQT in close cooperation with a data management expert and national inspectors, and was discussed at the consultation on data management, bioequivalence, GMP and medicines’ inspection held from 29 June to 1 July 2015. The draft was further revised on the basis of feedback received during the consultation, taking into account principles laid down in related WHO guidance as well as industry norms and regulatory requirements. The guidance promotes a risk-based approach and provides illustrative examples of good data management in practice. The draft was sent out for comments in September 2015 before being presented to the Committee at its fiftieth meeting. The Committee’s view was sought on future collaboration with PIC/S to enable future revisions of the proposed guidance, aiming for convergence with PIC/S data management norms, which are at an early stage of development.

Recognizing the wide interest in and urgent need for this guidance, the Committee adopted the guidance (Annex 5), subject to the review of current and forthcoming comments by a subgroup and subject to circulation of the finalized document to the Expert Committee prior to publication.
9. Quality assurance – distribution and trade of pharmaceuticals

9.1 Good trade and distribution practices for starting materials

WHO guidance on good trade and distribution practices (GTDP) was developed in order to ensure the quality and integrity of starting materials and pharmaceutical products circulating in the global pharmaceutical market. The guidance was adopted in 2003. At the forty-seventh meeting of the Expert Committee in 2012 it was felt that there was a need to include new developments and concepts in both the WHO guidelines on GTDP for pharmaceutical starting materials and the good distribution practices (GDP) guide for pharmaceutical excipients issued by the International Pharmaceutical Excipients Council (IPEC), which is aligned with the WHO document. In July 2013 the IPEC Federation provided a proposed revision and update of the WHO guidelines, which then underwent several rounds of comments and was discussed at the forty-eighth and forty-ninth meetings of the Expert Committee. The draft document was revised in line with the experts’ input and was circulated again for comment in March 2015. Comments were collated and reviewed by a subgroup of the Committee in July and August 2015. The revised draft was submitted to the Expert Committee at its fiftieth meeting.

It was agreed that a subgroup of experts should review the comments received and revise the guidance further. A revised draft was presented to the Committee members during the meeting. The Committee adopted the guidance subject to further review by a subgroup of experts. The final revised text is included in Annex 6.

9.2 WHO Certification scheme on the quality of pharmaceutical products moving in international commerce – questions and answers

The WHO Certification Scheme for finished pharmaceutical products is an international voluntary agreement, originally endorsed by the World Health Assembly in 1969, to provide information about the quality of pharmaceutical products moving in international commerce to countries which participate in the Scheme using model format templates provided by WHO, notably the Certificate of Pharmaceutical Product (CPP).

The Scheme has been revised several times, with each revision being endorsed by the World Health Assembly. A questions and answers (Q&A) document was developed as an interim measure in line with recommendations for revision of the Scheme. In 2010, WHO initiated a survey among its Member States about their use of the Scheme. The responses received indicated that the Scheme is appreciated as a valuable tool for exchange of regulatory information
between Member States, but that it may need further adaptation and more active participation by a number of member countries to enable its useful application in the current regulatory and industry environment. At its forty-ninth meeting in 2014, the Expert Committee had therefore recommended that the Q&As should be updated. The CPP Network team of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) proposed a revised document, which was circulated for comment in August 2015. The comments were reviewed by a small working group in September 2015, and the proposed revision was presented to the Committee in October 2015. The Committee reviewed the revised Q&As and heard from the WHO Regulatory Systems Strengthening Team and from a number of organizations represented at the meeting session about their experience with the use of the Scheme.

The Committee adopted the proposed revised Q&A document. Furthermore it was recommended that the 17th International Conference of Drug Regulatory Authorities (ICDRA) to be held in Cape Town, South Africa, from 27 November to 2 December 2016 should be used as an opportunity to advocate for active support of the effective functioning of the Scheme by Member States.

9.3 **Guidance on medicines quality surveys**

Following recommendations made by the Committee at its meetings in 2010 and 2011, two draft guidance documents were produced. These documents reflected the extensive experience of the WHO/PQT with the conduct of quality control testing surveys to monitor the quality of pharmaceutical products circulating in the markets of Member States. The *Proposal for a procedure on sampling and market surveillance* was drafted in 2012 in response to the Committee’s recommendation to develop a sampling procedure. A second draft document entitled *Recommendations on the content of a survey protocol for surveys of the quality of medicines* was prepared in 2014. It describes the steps necessary for conducting quality surveys and proposes examples and standard operating procedures that can be adapted to different situations. This document was presented to the Expert Committee at its 2014 meeting. Noting its comprehensive nature the Committee had recommended in 2014 that it should be retained as a scientific background reference and that a shorter practical guide should be prepared.

A concise draft of the guidelines on the conduct of surveys of the quality of medicines was sent out for public consultation in July 2015. Comments received were consolidated and presented together with the revised draft text to the Committee in October 2015.

The Committee reviewed the document and the comments and provided its input. The Expert Committee adopted the proposed guidance, subject to amendments agreed (Annex 7).
9.4 Update on the monitoring and surveillance project

A pilot study of the WHO global monitoring and surveillance system was conducted between September 2012 and January 2013 and is now part of the workplan of the Member States mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products established by the World Health Assembly Resolution WHA65.19. Participation has steadily increased and was reported to encompass 112 Member States in October 2015.

A rapid alert form with a minimum set of questions is used for reporting. Reports are submitted to WHO through focal points at national regulatory authorities (NRAs). Since 2012 there have been 900 reports of potential SSFFC products, leading to 12 International Drug Alerts being issued for SSFFC medical products presenting an immediate and significant threat to public health. Potential SSFFC products have been reported for all types of medicines. Frequently reported categories include antimalarials and antibiotics. This is a worrying finding in view of the emerging resistance to both.

Upon receipt of a report, WHO provides immediate technical support with a response time of 24–72 hours. The reports are uploaded to a database, and the data are analysed in order to detect patterns and to assess the scale, scope, extent and harm from SSFFC products. Detection and reporting are also used to prevent future harm. Evidence-driven action is taken to strengthen regulatory systems, raise awareness and engage stakeholders in combating SSFFC medical products. Future actions will involve strengthening the communication with focal points in participating NRAs and strengthening networks of NRAs globally.

The Expert Committee noted the report.
10. Prequalification of priority essential medicines and active pharmaceutical ingredients

10.1 Update on the Prequalification Team managed by WHO


The Committee was given an overview of the different workstreams and activities within PQT.

In terms of pharmaceutical products, medicines for hepatitis B and C have become eligible for prequalification, with two finished product applications undergoing screening and preparatory meetings having been held with several companies. Prequalification may also be opened up to other therapeutic areas if there is a need. WHO assessment times have decreased substantially in recent years. Additional guidance to applicants has been provided for specific product types and specific prequalification requirements. A total of 426 products were prequalified as of 12 October 2015. A collaborative registration procedure, which started in 2013, supports speedy registration of prequalified products in participating countries based on sharing of prequalification information.

Regarding prequalification of APIs, the Committee was informed that a total of 82 APIs have been prequalified to date. New API manufacturers had come forward in 2015 thus improving the prospects of continued access and competitiveness. Three applications for hepatitis C-related APIs are being processed. In general the number of applications for prequalification of both APIs and finished products has been stable, demonstrating continued interest.

PQT is involved in a wide range of collaborative initiatives. Within WHO, PQT maintains close links with many other programmes and units, including The International Pharmacopoeia. A standard text has been included in the API prequalification sign-off form to permit access by The International Pharmacopoeia to relevant data in the API master file. Monographs in The International Pharmacopoeia strongly support manufacturers working towards prequalification of their products; for example, the revised cycloserine monograph has been much appreciated by applicants. PQT offers a rotational fellowship programme, under which regulators from Member States spend three or six months working at WHO with the prequalification assessor team or inspectorate. This programme has greatly contributed to capacity-building and to the success of collaborative activities.

The Secretariat thanked PQT for its important input to, and feedback on, the guidance developed through the Expert Committee.

The Expert Committee noted the report.
10.2 **Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines**

The **Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products** aims to make use of work done by the WHO/PQT to support efficient assessment for granting of marketing authorization by participating regulatory authorities. It is based on sharing of prequalification assessment and inspection reports with the consent of the prequalification holder. The procedure was first adopted in 2012 (WHO Technical Report Series, No. 981, 2013, Annex 4), and has been successfully implemented for medicines.

It was proposed to update the procedure and to extend it to vaccines. The revision was discussed with stakeholders and the Expert Committee was informed of the proposed revision at its 2014 meeting. A working document was sent out for public consultation in July 2015. The revised document, together with the comments received, was submitted to the Expert Committee in October 2015.

The Expert Committee adopted the proposed revision of the collaborative procedure, now titled **Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines (revision)** (Annex 8), subject to the amendments agreed.
11. Regulatory guidance

11.1 Guidance for organizations performing in vivo bioequivalence studies

The performance of a bioequivalence study is usually a requirement for registration and prequalification of a multisource (“generic”) product to ensure interchangeability of the product. Such studies should be undertaken in compliance with WHO GCP and considering relevant elements from WHO GLP and good practices for quality control laboratories.

An update of WHO’s 2006 Guidance for organizations performing in vivo bioequivalence studies (WHO Technical Report Series, No. 937, 2006, Annex 9) in line with new developments was discussed at an informal consultation in April 2014. A working document was presented to the Expert Committee in October 2014, and the Committee supported the revision of the guidelines. The draft was then further revised by the inspectors of the WHO/PQT in collaboration with national inspectors and was circulated for public comment in May 2015. Comments received were discussed at an information consultation on data management, bioequivalence, GMP and medicines’ inspection held from 29 June to 1 July 2015. A second draft was prepared taking into consideration the revised text on Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (WHO Technical Report Series, No. 992, 2015, Annex 7), the new proposed guidelines on good data management (see 8.6), and PQT’s experience of assessing and inspecting bioequivalence studies since 2006. Guidance was added on bioanalytical analysis, and areas with recurrent inspection findings were clarified. The updated draft was presented to the Committee in October 2015. The guidelines emphasize management responsibilities to ensure that adequate premises, equipment and quality systems are available to conduct good quality studies.

The Committee discussed the revised guidelines and agreed to the changes proposed in response to the comments. The revised guidelines (Annex 9) were adopted as presented.

11.2 WHO general guidance on variations to multisource pharmaceutical products

A marketing authorization holder is responsible for the quality, safety and efficacy of an FPP that is placed on the market throughout its life cycle. After the FPP has been authorized for marketing the manufacturer will often wish to make changes (variations) to the product for a number of reasons. Such changes may require the approval of the national medicines regulatory authority. The extent
and nature of regulatory control of variations to registered pharmaceutical products varies considerably between WHO Member States.

In October 2013 the Expert Committee endorsed the development of *Guidelines for regulatory authorities on variations for multisource products*. A draft of the guidelines was developed between October 2013 and February 2014 and circulated for comment and feedback before being discussed by the Committee at its forty-ninth meeting. Based on feedback received, the guidance was revised to describe the main principles for variation procedures for implementation by regulatory authorities in accordance with risk–benefit and legal considerations specific to each authority. The guidance is intended to assist regulatory authorities to establish national requirements for the regulation of post-approval changes. It proposes categories of changes and reporting procedures for adaptation by regulatory authorities. The revised document was sent out for another round of comments in June 2015. Feedback was collated and the revised draft was presented to the Committee at its fiftieth meeting. The Committee discussed the proposal to revise the title of the guidance and to delete the term “multisource”, as it was noted that a wider audience may use the document as written. However, it was concluded that the original name should be retained.

The Committee reviewed the guidance and the comments received, and adopted the guidance subject to the amendments agreed (Annex 10).

### 11.3 Update of biowaiver principles for assessment of interchangeable multisource (generic) products

Revised guidelines on interchangeability of multisource products were adopted by the Committee in 2014. The safety and efficacy of a multisource (generic) product is usually demonstrated through an in vivo bioequivalence study that establishes its therapeutic equivalence to a comparator product. A biowaiver is a regulatory approval process based on evidence of equivalence other than through in vivo bioequivalence testing. Existing guidance on whether a biowaiver can be granted – based on the permeability and solubility of the API according to the Biopharmaceutics Classification System (BCS) – is provided in the *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). The proposal includes a section describing the general biowaiver principles as well as three tables listing information on various categories of APIs included in the WHO EML.

In 2014 the Committee reviewed progress and endorsed the proposed approach to separate the guidance text from the tables, which will be maintained in a separate living document that can be updated in line with each new version of the EML (see 11.4). This is analogous to the approach suggested for the list of comparator products (see 11.5).
Following these discussions, the WHO Secretariat requested a WHO Collaborating Centre in Germany to provide a draft revised version of the guidance on the biowaiver principles. The draft text was presented to the Committee at its fiftieth meeting.

The Committee discussed the revised guidance and provided its feedback. The document will be further revised and sent out as a working document for comment.

11.4 **Update of biowaiver list based on the WHO Model List of Essential Medicines**

Following the forty-eighth meeting of the Expert Committee the Secretariat contacted a WHO Collaborating Centre in Germany to discuss the additional studies needed for the update of the currently published biowaiver list in line with successive updates of the WHO EML. A list of all APIs for which additional studies are necessary in view of the various updates of the EML, was collated and prioritized. The WHO Collaborating Centre submitted the proposed tables to be attached as separate, living documents to the revised guidance on biowaivers (see 11.3). The importance of providing well documented, reliable references and study data for the BCS classifications assigned in the list was noted. New references on the outcomes of existing studies have been added. The Collaborating Centre is continuing to carry out further studies and the list will be updated accordingly. The tables were presented to the Committee with a view to obtaining further feedback before the lists are circulated for comment.

The Committee recommended that the list should be further reviewed in line with comments made at the meeting and should be made available for public consultation. The list will be presented to the Committee for consideration at its next meeting.

11.5 **Update of international comparator products list for equivalence assessment of interchangeable multisource (generic) 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 containing a list of international comparator pharmaceutical products for bioequivalence testing and included a decision-tree for use in identifying comparator pharmaceutical products.

In 2014 the Expert Committee endorsed the decision that the guidance on general principles for selecting comparator products should be separated from the lists of comparator products and endorsed the revised *Guidance on the selection of comparator pharmaceutical products for equivalence assessment*
of interchangeable multisource (generic) products (WHO Technical Report Series No. 992, 2015, Annex 8). The Committee further supported the proposal to seek the assistance of members of the International Generic Drug Regulators Pilot (IGDRP) – a collaborative network of medicines regulatory authorities aiming at work-sharing in approval of generic products – in validating the entries in the international comparator products list. Members of the Expert Committee were also invited to review the current international comparator products list and to submit comments and amendments to the Secretariat.

Based on these discussions and inputs, the experts prepared an updated draft list of comparator products, together with explanatory notes on the updating process and selection criteria for the products listed. The main difference from the existing approach is that there can be more than one acceptable market from which to source a comparator product, because many products are marketed in countries other than their countries of manufacture. The list and explanatory notes were presented to the Committee for discussion and feedback on the proposed updating approach.

The Committee recommended that the table should be reviewed and updated further to ensure its consistency and applicability before it is circulated for comment to all interested parties, and subsequently posted as a working document on the WHO website. The Committee will discuss maintenance of the list at its next meeting.

11.6 **Good regulatory practices**

Good governance principles and legal frameworks for health product regulation are critically needed in Member States. Following the recommendation made in 2010 at the 14th ICDRA to collect examples of best regulatory practice, and based on feedback gained from national regulatory authorities during WHO assessments, a project was initiated to develop WHO guidelines on good regulatory practices (GRP). WHO has facilitated collaborative activities between regulatory authorities and has reviewed feedback gathered from national regulatory authorities over more than a decade to identify the authorities’ main needs.

The scope of the proposed GRP guidelines is intended to include all health products and health technologies, and set out high-level principles from which a series of companion documents – similar to the Good review practices document adopted by the Committee in 2014 – could be developed according to need, timing and available resources. The concept of leveraging the work of other authorities or good cooperation practices will be an important aspect of this work. The draft guidance will go through the usual consultation process and it is planned to present it for review to both the ECBS and the Expert Committee on Specifications for Pharmaceutical Preparations in 2016.
The Committee discussed the proposal and noted the importance of having such a framework. The Committee expressed its support for the plans to develop this guidance.
12. Nomenclature, terminology and databases

Quality assurance terminology
The Secretariat maintains a collection of terms and definitions included in the guidance documents adopted by the Committee, with references to the respective guidelines. The Secretariat reported that this database is being kept up to date. An updated version is in the process of being verified and finalized for publication on the WHO website.

The Committee took note of the update.

International Nonproprietary Names (INN) for pharmaceutical substances
The International Nonproprietary Name (INN) Programme assigns unique names to pharmaceutical substances to enable global consistency and identification. A record number of 239 requests for assignment of an INN had been received from manufacturers in 2015. A total of 196 INNs were published in 2015, 94 of which were for biological substances. The total number of requests, as well as the proportion of requests received for INNs for biologicals, has been increasing.

A biological qualifier (BQ) scheme is proposed by the INN Programme to identify a substance manufactured by a specific process under a specific quality system. The BQ would be assigned as a second qualifier in addition to the INN. The scheme is intended to apply to all biological substances, including both innovators and biosimilars. Discussion is ongoing among a wide range of partners. The BQ proposal, together with a Q&A document providing the detailed technical information, was to be presented to the INN Expert Group at its 61st Consultation in October 2015 for discussion.

Cell therapies are another complex and growing product group for which there is currently no global naming system. Names have been assigned to cell therapies in some regulatory systems. The INN Expert Group is discussing a naming scheme applicable to cell therapies.

The Expert Committee noted the report.

Revision of guidance on representation of graphic formulae
Guidance on how to represent graphic formulae in *The International Pharmacopoeia* and within the INN list was developed and adopted by the Expert Committee at its thirty-fourth meeting (TRS 863, Annex 1, 1996). A discussion took place on whether an update of this guidance would be useful to bring it into line with current practices. Such updated guidance could promote convergence in this area.
The Committee supported the proposal and recommended that work should start promptly to update WHO guidance on representation of graphic formulae.
13. Summary and recommendations

The World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations advises the Director-General of WHO on pharmaceutical quality assurance. Based on a wide consultation process, it provides independent expert recommendations and guidance to ensure that medicines meet identical standards of quality, safety and efficacy in all WHO Member States. The Committee held its first meeting in 1947 under the name of the Expert Committee on Unification of Pharmacopoeias. Over time, it expanded the scope of its standard-setting work from quality-control-testing specifications to all arrangements that must be made in the development, production, regulation and supply of medicines to ensure that the medicines reaching the patients are of the quality required for their intended use.

At its fiftieth meeting from 12 to 16 October 2015, the Expert Committee heard updates from the WHO Expert Committee on Biological Standardization, the WHO Expert Committee on the Selection and Use of Essential Medicines and the International Nonproprietary Names (INN) Expert Group, all of which met in Geneva. With respect to international collaboration, updates were presented by the United Nations Children’s Fund (UNICEF) about the supply and quality assurance of health products in line with WHO guidance, and by the Pharmacopoeial Discussion Group (PDG) about progress achieved with the harmonization of pharmacopoeial standards.

In the area of quality control the Expert Committee adopted the proposed workplan for elaboration of monographs and reviewed new and revised specifications and general texts for quality control testing of medicines for inclusion in The International Pharmacopoeia. The Committee was informed that the fifth edition of The International Pharmacopoeia was published on the WHO website in August 2015 as well as being made available as a CD. A total of 22 texts, as listed below, were adopted. The Committee also endorsed nine International Chemical Reference Substances (ICRS) established by the custodian centre, the European Directorate for the Quality of Medicines & HealthCare (EDQM). The Expert Committee further noted the progress report of the external quality assurance assessment scheme (EQAAS), which has successfully completed six phases of proficiency testing studies and will begin Phase 7 in 2016. An update was given on the international meetings of world pharmacopoeias, which are co-hosted in turn by one of the participating pharmacopoeias together with WHO. These meetings had been instrumental in developing the good pharmacopoeial practices document adopted by the Committee at its fiftieth meeting, subject to concurrence of the world pharmacopoeias. This text provides guidance on the appropriate design, development and maintenance of pharmacopoeial standards and will facilitate prospective harmonization of standards among pharmacopoeias globally.
In the various quality assurance-related areas, the Expert Committee adopted new guidance on good data and record management, on establishing national requirements for the regulation of post-approval changes to pharmaceutical products and on the conduct of surveys of the quality of medicines, as well as a guidance text developed in collaboration with the International Pharmaceutical Federation (FIP) on the provision of children-specific preparations that are not available as authorized products. The Expert Committee was briefed on WHO prequalification of medicines, which has continued to attract the interest of applicants, including additional manufacturers of APIs. Additional medicines have become eligible for prequalification, notably treatments for hepatitis B and C. A collaborative procedure for speedy registration of medicines that have been fully assessed and prequalified by WHO is currently offered by 26 regulatory authorities in collaboration with WHO, and a revision of this procedure to extend it to prequalified vaccines was discussed and adopted at the meeting. Prequalification of quality control laboratories is also ongoing and two quality monitoring surveys – one on HIV/AIDS medicines and one on antimalarials – are under way. The Committee also heard updates from the WHO regulatory support unit, which offers a modular assessment tool and capacity-building advice for regulatory systems, and from the WHO monitoring and surveillance project for reporting of medicines quality problems by Member States. Acknowledging the need for a model regulatory framework for medical devices the Committee discussed possibilities for WHO to oversee this work through its Expert Committee structure.

A list of decisions and recommendations made by the Expert Committee at its fiftieth meeting is given below.

The following guidelines were adopted and recommended for use:

- Good pharmacopoeial practices (Annex 1)
- FIP–WHO technical guidelines: Points to consider in the provision by health-care professionals of children-specific preparations that are not available as authorized products (Annex 2)
- Guidance on good manufacturing practices: inspection report, including Appendix 1: Model certificate of good manufacturing practices (revision) (Annex 4)
- Guidance on good data and record management practices (Annex 5)
- Good trade and distribution practices for pharmaceutical starting materials (revision) (Annex 6)
- WHO Certification scheme on the quality of pharmaceutical products moving in international commerce: questions and answers (Q&A) (revision)
- Guidelines on the conduct of surveys of the quality of medicines (Annex 7)
- Collaborative procedure between the World Health Organization (WHO) prequalification team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines (revision) (Annex 8)
- Guidance for organizations performing in vivo bioequivalence studies (revision) (Annex 9)
- WHO general guidance on variations to multisource pharmaceutical products (Annex 10)

The Committee also adopted the revised guidance on good manufacturing practices for biological products (Annex 3), following its adoption by the Expert Committee on Biological Standardization on 16 October 2015.

The following monographs were adopted for inclusion in *The International Pharmacopoeia*:

**For maternal, newborn, child and adolescent health medicines**
- estradiol cypionate
- levonorgestrel (revision), including the use of the reference substances Levonorgestrel for system suitability 1 CRS and Levonorgestrel for system suitability 2 CRS issued by the *European Pharmacopoeia*
- misoprostol
- misoprostol dispersion
- misoprostol tablets
- norethisterone (revision), including the use of the reference substance Norethisterone for system suitability issued by the *European Pharmacopoeia*
- norethisterone tablets, including the use of the reference substance Norethisterone for system suitability issued by the *European Pharmacopoeia*

**For antimalarial medicines**
- artemether injection (revision)

**For antituberculosis medicines**
- cycloserine (revision)
- cycloserine capsules (revision)
Summary and recommendations

For medicines for chronic diseases and for mental health
- carbamazepine
- carbamazepine tablets
- carbamazepine chewable tablets
- carbamazepine oral suspension

For other anti-infective medicines
- clindamycin hydrochloride
- clindamycin hydrochloride capsules
- flucytosine
- flucytosine intravenous infusion

For other medicines
- dextromethorphan hydrobromide
- dextromethorphan oral solution

For the Supplementary section of The International Pharmacopoeia:
- levomethorphan limit tests for dextromethorphan-containing finished products

General policy
- Chapter on Reference substances and reference spectra

The Committee also agreed to proposals to discontinue the use of certain ICRS for the purpose of microbiological assays, to replace microbiological assays by physicochemical methods in certain monographs, to suppress a number of monographs that currently prescribe microbiological assays but pertain to medicines no longer included in the WHO Model List of Essential Medicines (19th edition) or in the relevant invitations for expression of interest from manufacturers.

International Chemical Reference Substances (ICRS)
The Committee endorsed the release of the following ICRS newly characterized by the custodian centre, the European Directorate for the Quality of Medicines & HealthCare (EDQM) and released by the ICRS Board:
- α-Artemether ICRS 1
- Efavirenz ICRS 2
- Efavirenz impurity B ICRS 1
- Ritonavir ICRS 2
- Abacavir sulfate ICRS 2
- Paracetamol ICRS 3
- Artemether ICRS 2
- Rifampicin ICRS 3
- Stavudine impurity F ICRS 1.

Recommendations
The Expert Committee made the recommendations listed below in the various quality assurance-related areas. Progress on the suggested actions will be reported to the Committee at its next meeting. The Committee recommended that the Secretariat, in collaboration with experts as appropriate, should carry out the following activities.

The International Pharmacopoeia
- Continue the development of monographs, general methods and texts and general supplementary information, including radiopharmaceutical monographs elaborated by the International Atomic Energy Agency (IAEA), in accordance with the workplan.
- Identify possible reference standards that can be referred to in five specific monographs which currently prescribe microbiological assays using ICRS, and for which no suitable alternative reference standard or physicochemical assay method has yet been identified.
- Proceed with the revision of the draft *Note for guidance on organic impurities in active pharmaceutical ingredients and finished pharmaceutical products*, intended to replace the text on *Related substances in finished pharmaceutical product monographs* in the Supplementary information section of *The International Pharmacopoeia*.

Quality control – national laboratories
- Continue with the development of guidelines on testing of “suspect” substandard/spurious/falsely-labelled/falsified/counterfeit medicines.

Quality assurance – good manufacturing practices
- Add a cross-reference to the *WHO good manufacturing practices for active pharmaceutical ingredients* to the *ICH Q7 Guideline: Good manufacturing practice guide for active pharmaceutical ingredients – questions and answers*. 
Proceed with revising the Supplementary guidelines on good manufacturing practices: validation including the appendices as relevant.

Continue with the revision of the Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms.

Pursue the revision of the draft working document on Risk classification of inspection observations in collaboration with the Brazilian Health Surveillance Agency (ANVISA), the European Medicines Agency (EMA), the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and other organizations currently drafting guidance in this area.

Regulation and regulatory collaboration

Continue revising the proposed Prerequisites for waiver of in vivo bioequivalence requirements for the WHO Model List of Essential Medicines immediate-release, solid oral dosage forms

Further review the biowaver list and make the draft updated list available for public consultation.

Further review the proposed updated international comparator products list to ensure its consistency and applicability before circulating it for comment to all interested parties and subsequently posting it as a working document on the WHO website.

Pursue the ongoing initiative to develop a high-level guidance document on good regulatory practices for health products and health technologies, for adoption through both the Expert Committee on Specifications for Pharmaceutical Preparations and the Expert Committee on Biological Standardization.

Investigate possibilities to set up an expert group on regulation of medical devices, composed of suitably qualified experts appointed to existing Expert Advisory Panels.

Nomenclature, terminology and databases

Continue to provide the database of terms and definitions covered by this Expert Committee on the WHO website.

Proceed with the proposed update of guidance on graphic representation of chemical formulae used, for example, in The International Pharmacopoeia.
Acknowledgements

Special acknowledgement was made by the Committee to:
Mrs W. Bonny, Medicines Quality Assurance (MQA), Technologies Standards and Norms (TSN), Mr H. Chen, MQA, Ms M. Gaspard, MQA, Dr S. Kopp, Group Lead, MQA, Dr H. Schmidt, MQA; Dr D.J. Wood, Coordinator, TSN; Mr D. Mubangizi, Group Lead, Inspection Services, Prequalification Team (PQT), Ms J.K. Sawyer, Liaison Officer, PQT; Dr M.M. Stahl, Group Lead, Medicines Assessment, PQT, Mr I.R. Thrussell, Expert Inspector, PQT; Dr L. Rägo, Head, Regulation of Medicines and other Health Technologies; Mr C. de Joncheere, Director, Department of Essential Medicines and Health Products, WHO, Geneva, Switzerland; and Ms M. Zweygarth, Geneva, Switzerland, who were instrumental in the preparation and proceedings of the meeting.

Technical guidance included in this report has been produced with the financial assistance of the European Union, the Bill & Melinda Gates Foundation, the Reproductive, Maternal, Newborn and Child Health Fund and UNITAID.

The Committee also acknowledged with thanks the valuable contributions made to its work by the following agencies, institutions, organizations, pharmacopoeias, WHO Collaborating Centres, WHO Programmes, especially PQT, and persons:

Acknowledgements


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 et consommables médicaux, Cotonou, Benin; Agency for Medicinal Products and Medical Devices, Control Laboratory, Sarajevo, Bosnia and Herzegovina; Instituto Nacional de Controle de Qualidade em Saúde, Rio de Janeiro, Brazil; Laboratoire National de Santé Publique, Ouagadougou, Burkina Faso; National Product Quality Control Centre, Ministry of Health, Phnom Penh, Cambodia; Laboratoire National de Contrôle de Qualité des Médicaments et d’Expertise, Yaoundé, Cameroon; Departamento de Control Nacional, Unidad de Control de Calidad de Medicamentos comercializados, Instituto de Salud Pública, Santiago de Chile, Chile; National Institutes for Food and Drug Control, Beijing, People’s Republic of China; Medicamentos y Productos Biológicos del INVIMA, Bogotá, Colombia; Laboratorio de Análisis y Asesoría Farmacéutica, Facultad de Farmacia, Universidad de Costa Rica, San José, Costa Rica; Laboratorio de Normas y Calidad de Medicamentos, Caja Costarricense de Seguro Social, Universidad de Costa Rica, Alajuela, Costa Rica; Laboratoire National de la Santé Publique, Abidjan, Côte d’Ivoire; Oficina Sanitaria Panamericana, OPS/OMS, Havana, Cuba; National Organization for Drug Control and Research, Cairo, Egypt; Drug Quality Control and Toxicology Laboratory, Drug Administration and Control Authority, Addis Ababa, Ethiopia; Centrale Humanitaire Médico-Pharmaceutique, Clermont-Ferrand, France; Food and Drugs Board, Quality Control Laboratory, Accra, Ghana; Laboratoire national de contrôle de qualité des medicaments, Conakry, Guinea; Laboratory for Quality Evaluation and Control, National Institute of Pharmacy, Budapest, Hungary; Central Drugs Laboratory, Kolkata, India; Provincial Drug and Food Quality Control Laboratory, Yogyakarta, Indonesia; Food and Drugs Control Laboratories, Ministry of Health and Medical Education, Tehran, Islamic Republic of Iran; Caribbean Regional
Drug Testing Laboratory, Kingston, Jamaica; Mission for Essential Drugs and Supplies, Nairobi, Kenya; National Quality Control Laboratory for Drugs and Medical Devices, Nairobi, Kenya; Food and Drug Quality Control Center, Ministry of Health, Vientiane, Lao People's Democratic Republic; Laboratoire de Contrôle de Qualité des Médicaments, Agence du Médicament de Madagascar, Antananarivo, Madagascar; Centre for Quality Control, National Pharmaceutical Control Bureau, Petaling Jaya, Selangor, Malaysia; Laboratoire National de la Santé du Mali, Bamako, Mali; Laboratoire National de Contrôle des Médicaments, Rabat, Morocco; Quality Surveillance Laboratory, Windhoek, Namibia; National Medicines Laboratory, Department of Drug Administration, Kathmandu, Nepal; Laboratoire National de Santé Publique et d’Expertise, Niamey, Niger; Central Quality Control Laboratory, Directorate General of Pharmaceutical Affairs and Drug Control, Ministry of Health, Muscat, Oman; Drug Control and Traditional Medicine Division, National Institute of Health, Islamabad, Pakistan; Instituto Especializado de Análisis, Universidad de Panamá, Panama; Centro Nacional de Control de Calidad, Instituto Nacional de Salud, Lima, Peru; Bureau of Food and Drugs, Department of Health, Muntinlupa City, Philippines; Laboratory for Quality Control of Medicines, Medicines Agency, Ministry of Health, Chisinau, Republic of Moldova; National Drug and Cosmetic Control Laboratories, Drug Sector, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; Laboratoire National de Contrôle des Médicaments, Dakar Etoile, Senegal; Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; Centre for Quality Assurance of Medicines, Faculty of Pharmacy, North-West University, Potchefstroom, South Africa; Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa; National Drug Quality Assurance Laboratory, Ministry of Health, Colombo, Sri Lanka; National Drug Quality Control Laboratory, Directorate General of Pharmacy, Federal Ministry of Health, Khartoum, Sudan; Pharmaceutical Analysis Laboratory, R&D, The School of Pharmacy, Muhimbili University of Health and Allied Sciences, Dar-es-Salaam, United Republic of Tanzania; Tanzania Food and Drug Authority, Dar-es-Salaam, United Republic of Tanzania; Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Laboratoire National de Contrôle des Médicaments, Tunis, Tunisia; National Drug Quality Control Laboratory, National Drug Authority, Kampala, Uganda; Central Laboratory for Quality Control of Medicines of the Ministry of Health of Ukraine, Kiev, Ukraine; Laboratory of Pharmaceutical Analysis, State Pharmacological Centre, Ministry of Health of Ukraine, Kiev, Ukraine; Laboratorio Control de Productos MSP, Comisión Para El Control de Calidad de Medicamentos, Montevideo, Uruguay; Instituto Nacional de Higiene “Rafael Rangel”, Caracas, Venezuela; National Institute of Drug Quality Control, Hanoi, Viet Nam; Medicines Control Authority, Control Laboratory of Zimbabwe, Harare, Zimbabwe.
Farmacopea Argentina, Buenos Aires, Argentina; Farmacopeia Brasileira, Brasilia, DF, Brazil; British Pharmacopoeia Commission, Medicines and Healthcare Products Regulatory Agency, London, England; Farmacopea Chilena, Valparaíso, Chile; Pharmacopoeia of the People’s Republic of China, Beijing, People’s Republic of China; Croatian Pharmacopoeia, Zagreb, Croatia; Czech Pharmacopoeia, Prague, Czech Republic; Danish Pharmacopoeia Commission, Copenhagen, Denmark; European Pharmacopoeia, European Directorate for the Quality of Medicines & HealthCare, Council of Europe, Strasbourg, France; Finnish Medicines Agency, Helsinki, Finland; Pharmacopée française, Agence nationale de sécurité sanitaire des produits de santé, Saint-Denis, France; German Pharmacopoeia Commission, Bonn, Germany; Indian Pharmacopoeia Commission, Raj Nagar, Ghaziabad, India; Indonesian Pharmacopoeia Commission, Jakarta, Indonesia; Iranian Pharmacopoeia, Iranian Association of Pharmaceutical Scientists, Tehran, Islamic Republic of Iran; Committee of the Japanese Pharmacopoeia, Tokyo, Japan; Kazakhstan Pharmacopoeia, Pharmacopoeia Centre of the Republic of Kazakhstani, Almaty, Kazakhstan; Pharmacopoeia of the Republic of Korea, Cheongwon-gun, Chungcheongbuk-do, Republic of Korea; Lithuanian Pharmacopoeia Commission, Vilnius, Lithuania; Mexican Pharmacopoeia, México DF, Mexico; Philippines Pharmacopoeia, Manila, Philippines; Polish Pharmacopoeia Commission, Warsaw, Poland; Portuguese Pharmacopoeia, Lisbon, Portugal; State Pharmacopoeia of the Russian Federation, Moscow, Russian Federation; Serbian Pharmacopoeia, Belgrade, Serbia; Slovakian Pharmacopoeia Commission, Bratislava, Slovakia; Spanish Pharmacopoeia, Royal, Madrid, Spain; Swedish Pharmacopoeia, Uppsala, Sweden; Swiss Pharmacopoeia, Berne, Switzerland; Thai Pharmacopoeia, Nonthaburi, Thailand; Pharmacopoeia of Ukraine, Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines, Kharkov, Ukraine; United States Pharmacopeia, Rockville, MD, USA; Vietnamese Pharmacopoeia, Hanoi, Viet Nam.

WHO Centre Collaborateur pour la Conformité des Médicaments, Laboratoire national de Contrôle des Produits Pharmaceutiques, Alger, Algeria; WHO Collaborating Centre for Drug Quality Assurance, Therapeutic Goods Administration Laboratories, Woden, ACT, Australia; WHO Collaborating Centre for Drug Quality Assurance, National Institute for the Control of Pharmaceutical and Biological Products, Beijing, People’s Republic of China; WHO Collaborating Centre for Research on Bioequivalence Testing of Medicines, Frankfurt am Main, Germany; WHO Collaborating Centre for Drug Information and Quality Assurance, National Institute of Pharmacy, Budapest, Hungary; WHO Collaborating Centre for Quality Assurance of Essential Drugs, Central Drugs Laboratory, Calcutta, India; WHO Collaborating Centre for Regulatory Control of Pharmaceuticals, National Pharmaceutical Control Bureau, Jalan University, Ministry of Health, Petaling Jaya, Malaysia; WHO Collaborating
Centre for Drug Quality Assurance, Pharmaceutical Laboratory, Centre for Analytical Science, Health Sciences Authority, Singapore; WHO Collaborating Centre for Quality Assurance of Drugs, North-West University, Potchefstroom, South Africa; WHO Collaborating Centre for Quality Assurance of Essential Drugs, Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand.


Abbott, Allschwil, Switzerland; Abbott Laboratories, Abbott Quality & Regulatory, Dept. 03QY, Abbott Park, IL, USA; Dr F. Abiodun, Benin City, Nigeria; Professor E. Adams, Laboratorium voor Farmaceutische Chemie en Analyse van Geneesmiddelen, Leuven, Belgium; Dr M. Adarkwah-Yiadom, Standard Officer, Ghana Standards Board, Drugs, Cosmetics and Forensic Laboratory Testing Division, Accra, Ghana; Professor I. Addae-Mensah, Department of Chemistry, University of Ghana, Legon, Ghana; División de Química y Tecnología Farmacéutica, AEMPS. Madrid, Spain; Dr K. Agravat, Regulatory Affairs, Unimark Remedies Limited, Ahmedabad, India; Ms R. Ahmad, Centre for Product Registration, National Pharmaceutical Control Bureau, Ministry of Health, Petaling Jaya, Malaysia; Ajanta Pharma Ltd, Kandivli (West), Mumbai, India; Apotex Inc., Toronto, Ontario, Canada; Amgen Inc., Thousand Oaks, CA, USA; Amgen Inc., Engineering, West Greenwich, RI, USA; Dr P. Aprea, Director, Directorate of Evaluation and Control of Biologicals and Radiopharmaceuticals, National Administration of Medicines, Food and Medical Technology, Buenos Aires, Argentina; Dr N. Aquino, Inspector and Specialist in GMP and Risk Management, Brazilian Health Surveillance Agency, Brasilia, DF,
Brazil; Dr A.C. Moreira Marino Araujo, Health Expert, Drugs Office, Post Approval Changes of Synthetic Drugs, Brazilian Health Surveillance Agency, Brasilia, DF, Brazil; Dr H. Arentsen, Regulatory Intelligence and Policy Specialist, Regulatory Development Strategy, H. Lundbeck A/S, Copenhagen-Valby, Denmark; Astellas Pharma Europe BV, Leiderdorp, Netherlands; AstraZeneca Pharmaceuticals (China) Co., Ltd, Taizhou City, Jiangsu Province, China; AstraZeneca, Alderley Park, Cheshire, England; Dr C. Athlan, Quality Reviewer, Swissmedic, Swiss Agency for Therapeutic Products, Berne, Switzerland; Dr A. Ba, Directeur, Qualité et Développement, Centrale Humanitaire Medico-Pharmaceutique, Clermont-Ferrand, France; Dr H. Baião, Infarmed, Portugal; Dr P. Baker, United States of America Food and Drug Administration, China Office, USA; Dr J.R. Ballinger, Guy’s and St Thomas Hospital, London, England; Dr E. Bamanyekanye, Département de la Pharmacie, du Médicament et des Laboratoires (DPML), Burundi; Mr N. Banerjee, Cipla Limited, Goa, India; Dr H. Batista, US Food and Drug Administration, Silver Spring, MD, USA; Mr B. Baudrand, OTECI, Paris, France; Dr R. Bauer, Head of Institute, Institute Surveillance, Austrian Federal Office for Safety in Health Care, Austrian Agency for Health and Food Safety, Vienna, Austria; Dr O.P. Baula, Deputy Director, State Pharmacological Center, Ministry of Health, Kiev, Ukraine; Professor S.A. Bawazir, Advisor to the Executive President, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; Bayer Health Care Pharmaceuticals, Bayer Pharma AG, Berlin, Germany; Dr M.G. Beatrice, Vice President, Corporate Regulatory and Quality Science, Abbott, Abbott Park, IL, USA; Dr T.L. Bedane, Drug Administration and Control, Addis Ababa, Ethiopia; Ms T.J. Bell, WHO Focal Point, US Food and Drug Administration, Silver Spring, MD, USA; Dr M. Silvana Bellini, EDQM Laboratory, Strasbourg, France; Dr J.B.G. Bernstein, Director, Pharmacy Affairs, Office of the Commissioner/Office of Policy, US Food and Drug Administration, Silver Spring, MD, USA; Mr L. Besançon, General Secretary and CEO, International Pharmaceutical Federation, The Hague, Netherlands; Dr R.P. Best, President and CEO, International Society for Pharmaceutical Engineering, Tampa, FL, USA; Dr A. Bevilacqua, US Pharmacopeia, Bedford, MA, USA; Dr J. Bishop III, Review Management Staff, Office of the Director, Center for Biologics Evaluation and Research, United States Food and Drug Administration, Silver Spring, MD, USA; Dr L. Bonthuys, Pretoria, South Africa; Mr M.H. Boon, Deputy Director, Overseas Audit Unit – Audit Branch, Audit & Licensing Division, Health Products Regulation Group, Singapore; Dr G. Born, Institute of Pharmaceutical Technology, Johann Wolfgang Goethe-University, Frankfurt, Germany; Professor R. Boudet-Dalbin, Paris, France; Dr B. Blum, Sandoz, France; Dr G. Bourdeau, Méréville, France; Dr S.K. Branch, Acting Group Manager, Special Populations Group, Medicines and Healthcare Products Regulatory Agency, London, England; Dr E. Brendel, Bayer HealthCare AG, Elberfeld, Germany; Dr M. Brits, Director, WHO Collaborating
Centre for the Quality Assurance of Medicines, North-West University, Potchefstroom Campus, Potchefstroom, South Africa; Mr C. Brown, Inspections Enforcement and Standards Division, Medicines and Healthcare Products Regulatory Agency, London, England; Dr W. Bukachi, Project Coordinator, International Affairs, US Pharmacopeia, Rockville, MD, USA; Ms A. Bukirwa, National (Food and) Drug Authority, Kampala, Uganda; Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Dr F. Burnett, Managing Director, Pharmaceutical Procurement Service, Organization of Eastern Caribbean States, Casties, St Lucia; Dr W. Cabri, Research and Development, Director, Chemistry and Analytical Development, Sigma-tau Industrie Farmaceutiche Riunite SpA, Pomezia, Italy; Dr M. Cahilly, Warren, Vermont, USA; Dr. D. Calam, Wiltshire, England; Dr N. Cappuccino, Lambertville, NJ, USA; Dr L. Cargill, Director, Caribbean Regional Drug Testing Laboratory, Kingston, Jamaica; Professor (Madame) R. Jiménez-Castellanos, Department of Pharmaceuticals and Pharmaceutical Technology, Faculty of Pharmacy, Seville, Spain; Dr A. Castro, Regulatory Affairs Director and Senior Pharmacist, Roche Servicios SA, Heredia, Costa Rica; Dr D. Catsoulacos, Scientific Administrator, Manufacturing and Quality Compliance, Compliance and Inspection, European Medicines Agency, London, England; European Medicines Agency, London, England; Mr J.-M. Caudron, Braine-le-Château, Belgium; Mr P. Cenizo, Southern African Pharmaceutical Regulatory Affairs Association (SAPRAA), Randburg, South Africa; Dr A.N.K. Chali, Chemical and Pharmaceutical Assessor, Uppsala, Sweden; Dr B. Chapart, Pharma Review Manager, Global Analytical Development, Sanofi-Aventis Pharma, Anthony, France; Ms Cheah Nuan Ping, Director, Cosmetics & Cigarette Testing Laboratory, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; Dr X. Chen, Director, Division of Drug Distribution Supervision, State Food and Drug Administration, Beijing, People’s Republic of China; Professor Y. Cherrah, Faculté de Médecine et Pharmacie, Rabat, Morocco; Dr B.K. Choi, Director, Pharmaceutical Standardization, Osong Health Technology Administration Complex, Research and Testing Division of the Ministry of Food and Drug Safety, Cheongwon-gun, Chungbuk, Republic of Korea; Dr Y.H. Choi, Scientific Officer, Korea Food & Drug Administration, Cheongwon-gun, Chungbuk, Republic of Korea; Dr D. Churchward, Expert GMPD Inspector, Inspection Enforcement and Standards, Medicines & Healthcare products Regulatory Agency, London, England; Cipla Limited, Mumbai, India; Ms I. Clamou, Assistant Manager, Scientific, Technical and Regulatory Affairs, European Federation of Pharmaceutical Industries and Associations, Brussels, Belgium; Dr M. Cooke, Senior Manager, Global Quality, Operations, AstraZeneca, Macclesfield, Cheshire, England; Dr C. Craft, Member, United States Pharmacopeia International Health Expert Committee, Rockville, MD, USA; Ms J. Crawford, Inpatients Pharmacy, Waitakere Hospital, Auckland,
New Zealand; Ms T. Crescenzi, United States of America Food and Drug Administration, Silver Spring, MD, USA; Critical Paths to TB Regimens (CPTR), Global Regulatory Pathways Work Group, Tucson, AZ, USA; Dr R.L. Dana, Senior Vice President, Regulatory Affairs and Parenteral Drug Association Training and Research Institute, Parenteral Drug Association, Bethesda, MD, USA; Mr M.M. Das, Barisha, Kolkata, India; Dr V. Davoust, Quality & Regulatory Policy, Pharmaceutical Sciences, Pfizer Global Research & Development, Paris, France; Dr D. de Kaste, National Institute for Public Health and the Environment, Bilthoven, Netherlands; Professor T. Dekker, Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa; Dr M. Derecque-Pois, Director General, European Association of Pharmaceutical Full-line Wholesalers, Brussels, Belgium; Directorate General of Pharmaceutical Affairs and Drug Control, Ministry of Health, Muscat, Oman; Dr R. Diyana, Senior Bioavailability/Bioequivalence Evaluator, National Authority for Food and Drug Control, Indonesia; DMB (French association of data management professionals), Suresnes, France; Professor E. Doelker, University of Geneva, Geneva, Switzerland; Professor J.B. Dressman, Director, Institut für Pharmazeutische Technologie, Biozentrum, Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany; Mrs S. Dube-Mwedzi, Consultant Regulatory Officer, Medicines Control Authority of Zimbabwe, Harare, Zimbabwe; Dr A.T. Ducca, Senior Director, Regulatory Affairs, Healthcare Distribution Management Association, Arlington, VA, USA; Dr T.D. Duffy, Lowden International, Tunstall, Richmond, N. Yorks, England; Dr P. Ellis, Director, External Advocacy, Quality Centre of Excellence, GlaxoSmithKline, Brentford, Middlesex, England; European Compliance Academy Foundation, Heidelberg, Germany; European Medicines Agency, London, England; Fedefarma, Ciudad, Guatemala; F. Hoffman-La Roche Ltd, Basel, Switzerland; Dr A. Falodun, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Benin, Benin City, Nigeria; Federal Ministry of Health, Berlin, Germany; Dr R. Fendt, Head, Global Regulatory & GMP Compliance Pharma, Care Chemicals Division, BASF, Limburgerhof, Germany; Mr A. Ferreira do Nascimento, Agência Nacional de Vigilância, Brasília, Brazil; Mr M. FitzGerald, European Association of Pharmaceutical Full-line Wholesalers, Brussels, Belgium; Dr A. Flueckiger, Head, Corporate Health Protection, Corporate Safety, Health & Environmental Protection, F. Hoffmann-La Roche, Basel, Switzerland; Dr G.L. France, Head, Q&A Compliance, EU Region, Novartis Consumer Health Services SA, Nyon, Switzerland; Dr B. Fritschel, Johnson & Johnson, New Brunswick, NJ, USA; Dr A. Fuglsang, Haderslev, Denmark; Mr T. Fujino, Director, International Affairs, Japan Generic Medicines Association, Tokyo, Japan; Mr A. Garcia Arieta, Head, Service on Pharmacokinetics and Generic Medicines, Division of Pharmacology and Clinical Evaluation, Department of Human Use Medicines, Spanish Agency of Medicines and Medical Devices, Madrid, Spain; Miss Y. Gao, Project Manager, Chinese Pharmacopoeia
Commission, Beijing, People’s Republic of China; Dr M. Garvin, Senior Director, Scientific and Regulatory Affairs, Pharmaceutical Research and Manufacturers of America, Washington, DC, USA; Dr A. Gayot, Faculté de Pharmacie de Lille, Lille, France; Dr X. Ge, Senior Analytical Scientist, Pharmaceutical Laboratory, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; German Expert Group on Computerized, Darmstadt, Germany; Dr L. Gibril, Compliance Coordinator, Novartis Pharma SAE, Amiria, Cairo, Egypt; Gilead Sciences International Ltd, Abington, Cambridge, England; Dr F. Giorgi, Research and Development, Analytical Development Manager, Sigma-tau Industrie Farmaceutiche Riunite SpA, Pomezia, Italy; Dr L. Girard, Head, Global Pharmacopoeial Affairs, Novartis Group Quality, Quality Systems and Standards, Basel, Switzerland; GlaxoSmithKline, Brentford, Middlesex, England; GlaxoSmithKline Biologicals SA, Wavre, Belgium; GlaxoSmithKline, Sales Training Centre, Research Triangle Park, NC, USA; Dr C. Sánchez González, Coordinator of Policies and Regulatory Affairs Centro para el Control de Medicamentos, Equipos y Dispositivos Médicos, La Habana, Cuba; Dr J. Gordon, Nova Scotia, Canada; Dr T. Gould, Brighton East, Victoria, Australia; Ms J. Gouws, Department of Health, Medicines Control Council, Pretoria, South Africa; Dr M. Goverde, QC Expert Microbiology, Novartis Pharma AG, Basel, Switzerland; Ms R. Govithavatangaphong, Director, Bureau of Drug and Narcotics, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Dr L. Graham, Medicines & Healthcare products Regulatory Agency, London, England; Dr J. Grande, Manager, Regulatory Affairs, McNeil Consumer Healthcare, Markham, England; Dr A. Gray, Senior Lecturer, Department of Therapeutics and Medicines Management and Consultant Pharmacist, Centre for the AIDS Programme of Research in South Africa (CAPRISA), Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Congella, South Africa; Dr M. Guazzaroni Jacobs, Director, Quality and Regulatory Policy, Pfizer Inc., New York, NY, USA; Ms N. M. Guerrero Rivas, Radiofarmacia de Centroamérica, SA, Ciudad del Saber, Panamá, Panamá; Guilin Pharmaceutical Company Ltd, Guilin, People’s Republic of China; Dr R. Guinet, Agence nationale de sécurité du médicament et des produits de santé, Saint-Denis, France; Dr S. Gupta, Mankind Pharma Limited, Unit-II, Vill. Kishanpura, Paonta Sahib, Disst. Sirmour, India; Professor R. Guy, Professor of Pharmaceutical Sciences, Department of Pharmacy & Pharmacology, University of Bath, Bath, England; Mr L. Gwaza, Medicines Regulation, Evaluations & Registration Division, Medicines Control Authority of Zimbabwe, Harare, Zimbabwe; Dr N. Habib, Director General of Medical Supplies, Ministry of Health, Oman; Dr S. Haidar, Acting Director, Division of Generic Drug Bioequivalence Evaluation, Office of Study Integrity and Surveillance, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA; Mr B.J. Hamid, Jakarta, Indonesia; Dr N. Hamilton, Industrial Quality and Compliance,
Acknowledgements

Industrial Affairs, Sanofi Aventis, West Malling, Kent, England; Ms J. Hantzunikolas, Therapeutic Goods Administration, Department of Health, Woden, ACT, Australia; Dr S. Harada, International Affairs Division, Minister’s Secretariat, Ministry of Health, Labour and Welfare, Tokyo, Japan; Dr B. Hasselbalch, Acting Associate Director, Policy and Communications, and Director, Division of Policy, Collaboration & Data Operations, Office of Compliance, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, MD, USA; Dr A. Hawwa, Lecturer in Pharmacy (Medicines in Children), Medical Biology Centre, Queen’s University Belfast, Belfast, Northern Ireland; Dr M. Hayes-Bachmeyer, Technical Regulatory Affairs, Pharmaceuticals Division, F. Hoffmann-la Roche, Basel, Switzerland; Mr Y. Hebron, Manager, Medicines and Cosmetics Analysis Department, Tanzania Food and Drugs Authority, Dar-es-Salaam, United Republic of Tanzania; Dr G.W. Heddell, Director, Inspection Enforcement & Standards Division, Medicines and Healthcare Products Regulatory Agency, London, England; Dr D. Hege-Voelksen, Swissmedic, Swiss Agency for Therapeutic Products, Berne, Switzerland; Ms J. Hiep, QA Pharmacist and Auditor, Adcock Ingram, Bryanston, South Africa; Ms M. Hirschhorn, Head, Quality and Chemistry Sector, Comisión para el Control de Calidad de Medicamentos (Drug and Control Commission), Montevideo, Uruguay; Mrs Hong J., Senior Pharmacist and Director of Hubei Provincial Institutes for Food and Drug Control, Wuhan Hubei, China; Mrs Hong L., Senior Pharmacist and Director of Zhejiang Provincial Institutes for Food and Drug Control, Hangzhou, China; Professor J. Hoogmartens, Leuven, Belgium; Dr K. Horn, Managing Director, Institute for Pharmaceutical and Applied Analytics, Official Medicines Control Laboratory, Bremen, Germany; F. Hoffmann-La Roche Ltd, Basel, Switzerland; Dr K. Hoppu, Director, Poison Information Centre, Helsinki University Central Hospital, Helsinki, Finland; Dr H. Hoseh, Head of Registration Unit, Drug Directorate, Jordan Food and Drug Administration, Jordan; Dr X. Hou, Chemical & Materials, Singapore; Dr N. Ibrahim, National Pharmaceutical Control Bureau, Ministry of Health, Jalan University, Petaling Jaya, Indonesia; Indian Drug Manufacturers’ Association, Mumbai, India; Infarmed, Lisbon, Portugal; Ipsen Pharma, Dreux, France; Dr J. Isasi Rocos, Pharmaceutical Chemist, Lima, Peru; Professor R. Jachowicz, Head, Department of Pharmaceutical Technology and Biopharmaceutics, Jagiellonian University Medical College, Faculty of Pharmacy, Kraków, Poland; Mr I. Jackson, Operations Manager, GMDP Inspections, Inspection, Enforcement & Standards Division, Medicines and Healthcare Products Regulatory Agency, London, England; Dr S.A. Jaffar, Director General, Directorate General of Pharmaceutical Affairs and Drug Control, Ministry of Health, Muscat, Oman; Johnson & Johnson, Latina, Italy; Dr R. Jähnke, Global Pharma Health Fund e.V., Frankfurt, Germany; Dr M. James, GlaxoSmithKline, Brentford, Middlesex, England; Dr A. Janssen, Manager, Regulatory Affairs,
DMV Fonterra Excipients, FrieslandCampina Ingredients Innovation, Goeh, Germany; Professor S. Jin, Chief Expert for Pharmaceutical Products, National Institutes for Food and Drug Control, Beijing, People’s Republic of China; Dr P. Jones, Director, Analytical Control, Pharmaceutical Sciences, Pfizer Global R&D, Sandwich, England; Dr H. de Jong, International Pharmaceutical Federation, The Hague, Netherlands; Dr Y. Juillet, Consultant, Paris, France; Mr D. Jünemann, Teaching Assistant; Institut für Pharmazeutische Technologie, Biozentrum, Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany; Ms A. Junttonen, Senior Pharmaceutical Inspector, National Agency for Medicines, Helsinki, Finland; Dr S. Kafkala, Analytical Development Director, GenePharm S.A., Pallini, Greece; Dr V. Kamde, Quality Management, Oman Pharmaceuticals, Oman; Dr M. Kaplan, Director, Institute for Standardization and Control of Pharmaceuticals, Jerusalem, Israel; Dr M. Karga-Hinds, Director, Barbados Drug Service, Christchurch, Barbados; Dr A.M. Kaukonen, National Agency for Medicines, Helsinki, Finland; Ms H. Kavale, Cipla, Mumbai, India; Dr T. Kawanishi, Director General, National Institute of Health Sciences, Tokyo, Japan; Dr S. Keitel, Director, European Directorate for the Quality of Medicines and Healthcare, Strasbourg, France; Dr K. Keller, Director and Professor, Federal Ministry of Health, Bonn, Germany; Dr M. Keller, Inspector, Division of Certificates and Licencing, Swissmedic, Swiss Agency for Therapeutic Products, Berne, Switzerland; Dr L. Kerr, Scientific Operations Adviser, Office of Laboratories and Scientific Services, Therapeutic Goods Administration, Woden, ACT, Australia; Mr M. Khan, United States of America Food and Drug Administration, Silver Spring, MD, USA; Dr M. Khan, Director, Federal Research Center Life Sciences, US Food and Drug Administration, Silver Spring, MD, USA; Dr S. Khoja, Vapi, Gujarat, India; Professor K. Kimura, Drug Management and Policy, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa-city, Japan; Dr W. Kongsuk, Bureau of Drug and Narcotic, Department of Medical Sciences, Nonthaburi, Thailand; Dr H. Köszegi-Szalai, Head, Department for Quality Assessment and Control, National Institute of Pharmacy, Budapest, Hungary; Dr S. Kouakap, Ministère de la Santé, Cameroon; Dr A. Kovacs, Secretariat, Pharmaceutical Inspection Co-operation Scheme, Geneva, Switzerland; Ms S. Kox, Senior Director Scientific Affairs, European Generic Medicines Association, Brussels, Belgium; Dr P. Kozarewicz, Scientific Administrator, Quality of Medicines Sector, Human Unit Pre-Authorization, European Medicines Agency, London, England; Dr A. Krauss, Principal Chemist, Office of Laboratories and Scientific Services, Therapeutic Goods Administration, Woden, ACT, Australia; Professor H.G. Kristensen, Vedbaek, Denmark; Dr J. Kumar, HLL Lifecare Ltd., Kanagala, Belgaum, India; Mr A. Kupferman, Bangkok, Thailand; Dr S. Kumar, Assistant Drugs Controller, Central Drugs Standard Control Organization, Food and Drug Administration Bhawan, New Delhi, India; Professor S. Läer, Institut für Klinische Pharmazie und Pharmakotherapie,
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Government of Pakistan, Islamabad, Pakistan; Ministry of Health and Welfare, Tokyo, Japan; Dr J. Mitchell, GlaxoSmithKline, Belgium; Dr S. Moglate, United Nations Population Fund, UN City, Copenhagen, Denmark; Dr N.H. Mohd, Director General of Medical Supplies, Ministry of Health, Muscat, Oman; Ms N.H. Mohd Potri, Senior Assistant, Director, GMP and Licensing Division, Centre for Compliance and Licensing, National Pharmaceutical Control Bureau, Ministry of Health Malaysia, Petaling Jaya, Malaysia; Dr J.A. Molzon, Bethesda, MD, USA; Dr I. Moore, Product and Quality Assurance Manager, Croda Europe, Snaith, England; Dr J. Morénas, Assistant Director, Inspection and Companies Department, Agence nationale de sécurité du médicament et des produits de santé, Saint Denis, France; Dr K. Morimoto, Expert, Office of Review Management, Review Planning Division, Pharmaceutical and Medical Devices Agency, Tokyo, Japan; Direction of Medicine and Pharmacy, Ministry of Health, Rabat, Morocco; Dr J.M. Morris, Irish Medicines Board, Dublin, Ireland; Mr T. Moser, Galenica, Berne, Switzerland; Dr M. Mugad, HLL Lifecare Ltd, Kanagala, Belgaum, Karnataka, India; Dr A.E. Muhairwe, Executive Secretary and Registrar, National Drug Authority, Kampala, Uganda; Dr. S. Mülbach, Director, Senior Regulatory Counsellor, Vifor Pharma, Glattbrugg, Switzerland; Ms C. Munyimba-Yeta, Director, Inspectorate and Licensing, Pharmaceutical Regulatory Authority, Lusaka, Zambia; Dr Murthi, Accutest Research Laboratory Ltd, Navi Mumbai, Maharashtra, India; Mylan, Allschwil, Switzerland; Mylan Laboratories Limited, Drug Regulatory Affairs, Jinnaram Mandal, Andhra Pradesh, India; Dr D.A. van Riet-Nales, Member Quality Working Party, European Medicines Agency, Senior Assessor, Department of Chemical Pharmaceutical Assessments, College ter Beoordeling van Geneesmiddelen, Utrecht, Netherlands; Ms N. Nan, Chief Pharmacist, National Institutes for Food and Drug Control, Beijing, People's Republic of China; Miss X. Nan, Project Officer, China Center for Pharmaceutical International Exchange, Beijing, People's Republic of China; Mr N. Nanerjee, Cipla Ltd, Goa, India; Dr E. Narciandi, Head, Technology Transfer Department, Center for Genetic Engineering & Biotechnology, Havana, Cuba; National Agency of Drug and Food Control, Jakarta Pusat, Indonesia; National Authority of Medicines and Health Products (INFARMED), Directorate for the Evaluation of Medicinal Products, Lisbon, Portugal; National Institute of Drug Quality Control of Vietnam, Hanoi, Viet Nam; NBCD Working Group, Leiden, Netherlands; Starship Hospital, New Zealand; Dr R. Neri, Sanofi, Antony, France; Dr E. Nickličková, Inspector, State Institute for Drug Control, Prague, Czech Republic; Professor A. Nicolas, Radiopharmacist, Expert analyse, Pharmacie, Hôpital Brabois Adultes, Vandoeuvre, France; Dr H.K. Nielsen, Technical Specialist, Essential Medicines, Medicines and Nutrition Centre, UNICEF Supply Division, Copenhagen, Denmark; Professor B. Ning, Deputy Director, Division of Chemical Drugs, National Institutes for Food and Drug Control, Beijing, People's Republic of China; Dr P. Njaria, Head, Quality Assurance Unit and
Acknowledgements

Instrumentation, National Quality Control Laboratory, Nairobi, Kenya; Dr C. dos Santos Nogueira, Especialista em Regulação e Vigilância Sanitária, ANVISA, Brasilia, Brazil; Dr K. Nodop, Inspections, European Medicines Agency, London, England; Novartis Group Quality, Novartis, Basel, Switzerland; Professor A. Nunn, Formby, Liverpool, England; Dr A. Ojoo, Technical Specialist, Paediatric Formulations, United Nations Children’s Fund Supply Division, Nordhavn, Copenhagen, Denmark; Mr S. O’Neill, Managing Director, The Compliance Group, Dublin, Ireland; Dr L. Oresic, Head, Quality Assurance Department, Croatian Agency for Medicinal Products and Medical Devices, Zagreb, Croatia; Dr P.B. Orhii, Director-General, National Agency for Food and Drug Administration and Control, Abuja, Nigeria; Dr N. Orphanos, International Programs Division, Bureau of Policy, Science, and International Programs, Therapeutic Products Directorate, Health Products & Food Branch, Health Canada, Ottawa, Canada; Professor T.L. Paál, Director-General, National Institute of Pharmacy, Budapest, Hungary; Dr P.R. Pabrai, New Delhi, India; Dr R. Pai, Johannesburg, South Africa; Mrs L. Paleshnuik, Arnprior, Ontario, Canada; Dr S. Parra, Manager, Generic Drugs Quality Division 1, Bureau of Pharmaceutical Sciences, Therapeutic Products Directorate, Health Canada, Ottawa, Ontario, Canada; Mr B. Passek, BMG, Germany; Dr D.B. Patel, Secretary-General, Indian Drug Manufacturers’ Association, Mumbai, India; Dr P.S. Patil, Umedica Laboratories Pvt Ltd, Vapi, Gujarat, India; Dr S.R. Srinivas Patnala, Grahamstown, South Africa; Dr S. Patnala, Professor, Pharmaceutical Analysis and Coordinator, University Instrumentation Facility, KLE University, Belgaum, India; Paul-Ehrlich-Institut, Langen, Germany; Dr A. Pazhayattil, Apotex Inc., Toronto, Ontario, Canada; Mr C. Perrin, Pharmacist, International Union Against Tuberculosis and Lung Disease, Paris, France; Dr M. Phadke, Senior Manager, Analytical Research, IPCA Laboratories, Mumbai, India; Pharmaceutical Inspection Co-operation Scheme, Geneva, Switzerland; Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan; Dr B. Phillips, Medicines and Healthcare Products Regulatory Agency, London, England; Dr R.D. Pickett, Supanet, Bucks, England; Dr B. Pimentel, European Chemical Industry Council, Brussels, Belgium; Polychromix, Inc., Wilmington, MA, USA; Dr A. Pontén-Engelhardt, Head of Stability Management, Global Quality, Operations, AstraZeneca, Södertälje, Sweden; Ms A. Poompanich, Bangkok, Thailand; Dr H. Potthast, Federal Institute for Drugs and Medical Devices, Berlin, Germany; Dr R. Prabhu, Regulatory Affairs Department, Cipla, Mumbai, India; Dr J. Prakash, Principal Scientific Officer, Indian Pharmacopoeia Commission, Raj Najar, Ghaziabad, India; Dr P.B.N. Prasad, Deputy Drugs Controller (India), Central Drugs Standard Control Organisation, Bhavan, S.R.Nagr, Hyderabad, India; Dr R.P. Prasad, Director, Department of Drug Administration, Kathmandu, Nepal; Ms S.J. Putter, Walmer, Port Elizabeth, South Africa; Quality Systems and Standards – Group Quality, Novartis Pharma AG, Basel, Switzerland;
Ms M.-L. Rabouhans, Chiswick, London, England; Dr M. Rafi, Assistant Manager (Regulatory Affairs), HLL Lifecare Limited, Belgaum, Karnataka, India; Dr A. Rajan, Director, Celogen Lifescience & Technologies, Mumbai, India; Mr T.L. Rauber, Specialist in Health Surveillance, Agência Nacional de Vigilância Sanitária Agency, Brasilia, Brazil; Mr N. Raw, Inspection, Enforcement and Standards Division, Medicines and Healthcare Products Regulatory Agency, London, England; Mr N. Rech, Brazilian Pharmacopoeia, Brazilian Health Surveillance Agency, Brasilia, DF, Brazil; Dr J.-L. Robert, Luxembourg; Dr S. Rönningen, Global Quality Manager, F. Hoffmann-La Roche, Basel, Switzerland; Dr J. Isasi Rosas, CNCC, Chorrillos, Lima, Peru; Dr N. Ruangrittinon, Bureau of Drug and Narcotic Department for Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Dr J. Sabartova, Prague, Czech Republic; Dr L.A. Sotelo Ruiz, Comisión de Control Analítico y Ampliación de Cobertura, Tlalpan, Distrito Federal, Mexico; Rusan Pharma Ltd, Selaqui, Dehradun, India; Dr P.L. Sahu, Indian Pharmacopoeia Commission, Raj Nagar, Ghaziabad, Uttar Pradesh, India; Dr E.I. Sakanyan, Director, Centre of the Pharmacopoeia and International Collaboration, Federal State Budgetary Institution, Scientific Centre for Expert Evaluation of Medicinal Products, Moscow, Russian Federation; Dr C. Sánchez González, Adviser, Centre para el Control de Medicamentos, Equipos y Dispositivos Médicos, Havana, Cuba; Dr E. Moya Sánchez, Radiofarmaceutica-Evaluadora de Calidad, División de Química y Tecnología Farmacéutica, Departamento de Medicamentos de Uso Umano, Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain; Sanofi Aventis, Antony, France; Sanofi, Bridgewater, NJ, USA; Dr G. Mendes Lima Santos, Coordinator of Therapeutic Equivalence, Brazilian Health Surveillance Agency, Brasilia, DF, Brazil; Dr B. Santoso, Sleman, Yogyakarta, Indonesia; Dr T. Sasaki, Pharmaceutical and Medical Devices Agency, Tokyo, Japan; Dr J. Satanarayana, Matrix Laboratories, Secunderabad, India; Dr B. Schmauser, Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany; Dr A. Schuchmann, Brazil; Dr I. Seekkuarachchi, Project Manager, Takeda Pharmaceutical Co., Osaka, Japan; Dr A. Seiter, Member, United States Pharmacopeia International Health Expert Committee, Rockville, MD, USA; Ms K. Sempf, Teaching Assistant, Institut für Pharmazeutische Technologie, Biozentrum, Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany; Dr U. Shah, Formulation Research Fellow, Cheshire, Merseyside & North Wales LRN, Medicines for Children Research Network, Royal Liverpool Children’s NHS Trust, Liverpool, England; Dr R. Shaikh, Pakistan; Shasun Research Centre, Chennai, Tamil Nadu, India; Dr P.D. Sheth, Vice-President, International Pharmaceutical Federation, New Delhi, India; Ms R. Shimonovitz, Head of Inspectorates, Institute for Standardization and Control of Pharmaceuticals, Ministry of Health, Israel; Shin Poong Pharmaceutical Co. Ltd, Seoul, Republic of Korea; Dr P.G. Shrotriya, Ambli, Ahmedabad, India; Dr M. Sigonda, Director-General, Tanzania Food and
Acknowledgements

Drugs Authority, Dar-es-Salaam, United Republic of Tanzania; Dr G.L. Singal, Drugs Controller of Haryana, Department of Health Services, Civil Dispensary, Panchkula, Haryana, India; Dr A.K. Singh, Daman, India; Dr G.N. Singh, Secretary-cum-Scientific Director, Government of India, Central Indian Pharmacopoeia Laboratory, Ministry of Health and Family Welfare, Raj Nagar, Ghaziabad, India; Dr S. Singh, Professor and Head, Department of Pharmaceutical Analysis, National Institute of Pharmaceutical Education and Research, Nagar, Punjab, India; Ms K. Sinivuo, Senior Researcher and Secretary, National Agency for Medicines, Helsinki, Finland; Dr L. Slamet, Jakarta Selatan, Indonesia; Mr D. Smith, Faerie Glen, Pretoria, South Africa; Dr R. Smith, Wolfson Brain Imaging Centre, University of Cambridge, Cambridge, England; Dr N. Kumar Soam, Mankind Pharma Limited, Unit-II, Vill. Kishanpura, Paonta Sahib, Distt. Sirmour, India; Dr M. Da Luz Carvalho Soares, Expert Health Regulation, Brazilian Health Surveillance Agency, Brasilia, Brazil; Dr C. Sokhan, Deputy Director, Department of Drug and Food, Phnom Penh, Cambodia; Dr A. Spreitzhofer, AGES PharmMed, Vienna, Austria; Mr K. Srinivas, Group Legal Counsel, Trimulgherry, Secunderabad, Andhra Pradesh, India; State Regulatory Agency for Medical Activities, Ministry of Labour, Health and Social Affairs, Tbilisi, Georgia; Dr J.A. Steichen, Manager, Regulatory and Quality Compliance Services, Safis Solutions, LLC, Indianapolis, IN, USA; Dr Y. Stewart, Scientific, Technical and Regulatory Affairs, European Federation of Pharmaceutical Industries and Associations, Brussels, Belgium; Dr L. Stoppa, Inspections & Certifications Department, Manufacturing Authorisation Office, Italian Medicines Agency, Rome, Italy; Dr R.W. Stringham, Scientific Director, Drug Access Team, Clinton Health Access Initiative, Boston, MA, USA; Dr N. Sullivan, Director, Sensapharm, Sunderland, England; Mr Philip Sumner, Pfizer Global Engineering, New York, NY, USA; Dr Sun Cuilain D., Senior Analytical Scientist, Pharmaceutical Laboratory, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; Dr V. Suvarna, Medical Director, Boehringer Ingelheim India Private Limited, India; Dr E. Swanepoel, Head, Operations, Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa; Professor M. Sznitowska, Department of Pharmaceutical Technology, Medical University of Gdansk, Gdansk, Poland; Dr K. Tadano, Committee of the Japanese Pharmacopoeia, Tokyo, Japan; Dr K. Takahashi, Senior Policy Advisor, Division of Regulations, Guidance and Standards, Office of Policy for Pharmaceutical Quality, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA; Tanzania Food and Drugs Authority, Dar-es-Salaam, United Republic of Tanzania; Dr D. Teitz, Manager, Bristol-Myers Squibb Company, New Brunswick, NJ, USA; Teva API Division, Petah Tiqva, Israel; Dr N. Thao, National Institute of Drug Quality Control, Hanoi, Viet Nam; Dr B.B. Thapa, Chief Drug Administrator, Department of Drug Administration, Ministry of Health and Population, Kathmandu, Nepal;
The Danish Medicines Agency, Denmark; Dr R. Torano, Pharmacopoeial Technical Expert, GlaxoSmithKline, Co. Durham, England; Dr P. Travis, Team Leader – Compendial Affairs Group, Pfizer Inc., Parsippany, NJ, USA; Ms M. Treebamroong, Senior Pharmacist, Drug Quality and Safety, Department of Medical Sciences, Bureau of Drug and Narcotic, Ministry of Public Health, Nonthaburi, Thailand; Mr R. Tribe, Holder, ACT, Australia; Associate Professor Trinh Van Lau, Director, National Institute of Drug Quality Control, Hanoi, Viet Nam; Professor Tu Guoshi, National Institute for the Control of Pharmaceutical and Biological Products, Ministry of Public Health, Beijing, People’s Republic of China; Dr C. Tuleu, Senior Lecturer and Deputy Director, Department of Pharmaceutics and Centre for Paediatric Pharmacy Research, School of Pharmacy, University of London, London, England; Dr Richard Turner, British Pharmacopoeia Commission, Medicines and Healthcare Products Regulatory Agency, London, England; United States of America Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD, USA; United States of America Food and Drug Administration, Office of Pediatric Therapeutics, Office of the Commissioner, Rockville, MD, USA; Ms E. Uramis, GMP Advisor, Oficina Central Polo Científico, Havana, Cuba; Dr A.R.T. Utami, National Agency for Drugs and Food Control, Jakarta Pusat, Indonesia; Dr R. Vaillancourt, International Pharmaceutical Federation, The Hague, Netherlands; Validation and Qualification Department, Pharmaceutical Laboratory, Esteve, Spain; Mrs M. Vallender, Editor-in-Chief, British Pharmacopoeia Commission Secretariat, London, England; Mr M. van Bruggen, EU Liaison – Regulatory Intelligence, F. Hoffmann-La Roche, Basel, Switzerland; Mr F. Vandendriessche, Merck, Sharp and Dohme Europe, Brussels, Belgium; Mr P. van der Hoeven, APIC, Brussels, Belgium; Dr J.E. van Oudtshoorn, Pretoria, South Africa; Dr A.J. van Zyl, Sea Point, Cape Town, South Africa; Dr G. Vedoya, CABA, Instituto Nacional de Medicamentos (INAME/ANMAT), Argentina; Mr S. Akbaralli Veljee, Director, Food and Drugs Administration, Directorate of Food and Drugs Administration, Government of Goa, Dhanwantari, Bambolim, Goa, India; Dr A. Kumar Velumury, Cipla Ltd, New Delhi, India; Mr A. Vezali Montai, Specialist in Regulation and GMP, Agência Nacional de Vigilância, Brasília, Brazil; Mrs L. Vignoli, Regulatory Affairs, Pharmaceuticals and Cosmetics, Roquette Cie, Lestren, France; Dr O. del Rosario Villalva Rojas, Executive Director, Quality Control Laboratories, National Quality Control Center, National Institute of Health, Lima, Peru; Mr L. Viorney, Agence nationale de sécurité du médicament et des produits de santé, Saint Denis, France; Dr L. Virgili, USA; Mr J. Wang, Deputy Commissioner, Dalian Food and Drug Administration, Dalian, Liaoning, People’s Republic of China; Mr P. Wang, Deputy Secretary-General, Chinese Pharmacopoeia Commission, Beijing, People’s Republic of China; Mrs T. Wang, Deputy Director, Shenzhen Municipal Institute for Drug Control, Shenzhen, People’s Republic of China;
Dr G. Wang’ang’a, Head, Microbiological and Medical Devices Units, National Quality Control Laboratory, Nairobi, Kenya; Dr A. Ward, Regulatory Affairs, Avecia Vaccines, Billingham, England; Dr D. Waters, Acting Scientific Operations Advisor, Office of Laboratories and Scientific Services, Therapeutic Goods Administration, Woden, ACT, Australia; Dr W. Watson, Associate Manager, CMC Regulatory Affairs, Gilead Sciences International, Cambridge, England; Dr J. Welink, Medicines Evaluation Board, Utrecht, Netherlands; Ms Wei N., Associate Researcher, Division of Chemical Drugs, National Institutes for Food and Drug Control, Beijing, China; Professor W. Wieniawski, Polish Pharmaceutical Society, Warsaw, Poland; Mr J. Wilkinson, Director, Devices, Medicines and Healthcare products Regulatory Agency, London, England; Dr J. Skutnik Wilkinson, Biogen, Oneco, CT, USA; Dr M. Jiwo Winanti, Senior GMP Inspector, National Authority for Food and Drug Control, Indonesia; Dr S. Wolfgang, US Food and Drug Administration, Silver Spring, MD, USA; Mr E. Wondemagegnehu Biwota, Addis Ababa, Ethiopia; World Self-Medication Industry, Ferney-Voltaire, France; Dr B. Wright, Group Manager, GMP/GDP, North East Region, Medicines Inspectorate, Medicines and Healthcare Products Regulatory Agency, York, England; Professor Z.-Y. Yang, Guangzhou Municipal Institute for Drug Control, Guangzhou, People’s Republic of China; Professor Z.-Y. Yang, Member, United States Pharmacopeia International Health Expert Committee, Rockville, MD, USA; Ms C. Munyimba-Yeta, Director Operations (Plant), NRB Pharma Zambia Limited, Lusaka South Multi Facility Economic Zone, Lusaka, Zambia; Dr D. Yi, Scientist, US Pharmacopeia, Rockville, MD, USA; Dr H. Yusufu, National Agency for Food and Drug Administration and Control, Abuja, Nigeria; Dr M. Zahn, Keltern, Germany; Dr H. Zhang, GMP Department Head, Center for Certification & Evaluation, Shanghai Food and Drug Administration, Shanghai, People’s Republic of China; Dr G. Zenhäusern, Senior Case Manager, Sector Authorisation, Swissmedic, Berne, Switzerland; Professor (Mrs) Zhang M., Deputy Director, Institutes for Food and Drug Control, and Vice Chairman, Antiobiotic Subcommittee, Chinese Pharmacopoeia Commission, China; Dr T. Zimmer, CD Safety, Quality & Environmental Protection, Boehringer Ingelheim, Ingelheim, Germany; Dr N. Zvolinska, Deputy Director, Pharmaceutical Department, State Pharmacological Centre, Ministry of Health, Kiev, Ukraine.