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WHO Expert Committee on Specifications for Pharmaceutical Preparations

Fifty-first report

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Geneva, 17–21 October 2016

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Medicines Quality Assurance (EMP/RHT/TSN)
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[9] Unable to attend: Regional Office for the Americas; Regional Office for the Eastern Mediterranean; Regional Office for Europe; Regional Office for South-East Asia; Regional Office for the Western Pacific.

Declarations of interest

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

Professor E. Adams, Dr A. Sh. Alothmany, Dr M. Brits, Dr J. Gordon, Dr J. Gouws, Professor Jin S., Professor J. Hoogmartens, Dr A. Sitta Kijo, Ms G.N. Mahlangu, Dr J.A. Molzon, Mrs L. Paleshnuik, Dr L. Rägo, Dr J. Sabartova, Dr B. Santoso, Dr D. Sato, Dr G.N. Singh and Dr V. Dias Sousa reported no conflict of interest.

Professor S. Bawazir reported that he provides regular consultations to several pharmaceutical companies and is a board member of Astra Industrial Group. This disclosure does not constitute a conflict of interest as the topics of the meeting do not include any specific products manufactured by these companies.

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

Dr A.J. Van Zyl reported that he is a regulatory consultant and former auditor for the pharmaceutical industry. This disclosure does not constitute a conflict of interest as the topics of the meeting do not include any specific products manufactured by these companies.

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

Introduction

The World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 17 to 21 October 2016. Dr Marie-Paule Kieny, Assistant Director-General and Head of the WHO Health Systems and Innovation Cluster, welcomed the participants who had come from all six WHO regions, on behalf of the Director-General. She thanked the experts, technical advisers and teams at WHO collaborating centres for their major contributions to WHO's standard-setting work in the area of pharmaceuticals. She introduced Dr Suzanne Hill as the new Director of the Essential Medicines and Health Products (EMP) Department and informed the Committee that Ms Emer Cooke would take over as the new Head of Regulation of Medicines and other Health Technologies from 15 November 2016. Mr Deus Mubangizi was introduced as the new Coordinator of the Prequalification Team, which had extended its mandate to span a range of medical products including vector control tools.

Dr Kieny went on to highlight some high-priority issues that are relevant to the work of the Expert Committee. The topics of antimicrobial resistance, palliative care, medicine and vaccine shortages, children's medicines, hepatitis C and noncommunicable diseases had given rise to World Health Assembly (WHA) resolutions in 2016. Other issues that were high on the agendas of WHO and its Member States included innovation to support strategic local manufacturing, access to quality-assured products, further strengthening of regulatory systems and better monitoring for substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) products. For 2017, WHO was preparing for discussions on public health emergencies, the Global Action Plan on antimicrobial resistance, human resources for health, medicines shortages and other topics. As stakeholders' interest in pharmaceutical products increases, more public attention is being given to the Committee's standard-setting work. Stringent procedures for selection of experts and declarations of interest are therefore more important than ever. Dr Kieny gave an overview of the links of the Expert Committee with other WHO groups and activities and outlined the areas of discussion for its fifty-first meeting. Experts were reminded that they serve on the Committee in a personal capacity.

Dr Hill outlined the vision and directions for the Department. Access to quality-assured medical products for all is an important objective in achieving the health-related targets of the Sustainable Development Goals. WHO is continuing to respond to major challenges, such as SSFFC products and lack of access to biological products to treat chronic diseases. In addition to its standard-setting role, WHO will have a facilitating role in shaping future policies on pricing and use of medicines. The launch of the report of the Lancet Commission on Essential Medicines in November 2016 would provide

an opportunity to demonstrate the Department's impact. Dr Hill thanked the experts and advisers for their contribution to WHO's standard-setting work and wished them a successful meeting.

The Expert Committee elected Ms Gugu Mahlangu as Chairperson, Dr Daisaku Sato as Co-Chairperson and Dr Justina Molzon and Dr Jitka Sabartova as Rapporteurs. Ms Mahlangu then took the chair and welcomed the members, temporary advisers and observers to the open session of the Expert Committee.

Open session

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.

Dr Sabine Kopp, the Secretary of the Expert Committee, described the Committee's role in fulfilling WHO's constitutional mandate by setting standards for a wide range of health products and by responding to global emergencies. She explained the role and functions of WHO's Expert Committees, which are the highest advisory bodies to the Director-General. A set of strengthened rules and procedures govern the selection of members, technical advisers and observers and their participation in an Expert Committee. Strict rules are in place for declarations of interest.

The WHO Expert Committee on Specifications for Pharmaceutical Preparations maintains *The International Pharmacopoeia* and provides technical guidance on quality assurance for medicines, including radiopharmaceuticals, at all stages of the product life-cycle. In developing new guidance, the Committee responds to current needs and international trends and draws on recommendations from meetings such as the International Conference of Drug Regulatory Authorities (ICDRA). Draft guidelines are developed with input from experts and the working documents are published on the WHO website for public consultation. The report of each annual Expert Committee meeting is presented to the WHO Governing Bodies and published in the WHO Technical Report Series (TRS), with the adopted guidelines as annexes. More than 80 WHO guidelines and good practice documents on the development, manufacture, inspection, distribution and quality control of medicines as well as related regulatory guidance are currently available on the WHO website and on CD-ROM. In recent years, collaborative initiatives with other groups have been increasing. The importance of wide communication of the outcomes of this work was emphasized. The Secretary concluded by thanking all partners for their valuable contributions.

1. General policy

1.1 Cross-cutting pharmaceutical quality assurance issues

Expert Committee on the Selection and Use of Essential Medicines

Ms Bernadette Cappello of the WHO Policy, Access and Use team presented an oral update from the Expert Committee on the Selection and Use of Essential Medicines, which meets every two years to update the WHO Model List of Essential Medicines. Some ground-breaking changes had been made in 2015 with the inclusion of medicines for cancer and hepatitis C, some of which are extremely costly. The next meeting of the Expert Committee on the Selection and Use of Essential Medicines will be held from 27 to 31 March 2017. At that meeting the Committee will review the section on antibiotics, which has remained largely unchanged for several decades, in the context of antimicrobial resistance. A stepwise approach will be considered to optimize the use of these medicines and preserve their effectiveness. Other medicines to be evaluated are expected to include medicines for noncommunicable diseases, for example, insulin analogues and new oral treatments for diabetes and new oral anticoagulants for the prevention of cardiovascular events. Some of the medicines for cancer, hepatitis C, HIV and multidrug resistant tuberculosis will also be under review.

The Committee noted the report.

Member State Mechanism on SSFFC and SSFFC surveillance and monitoring

Mr Michael Deats provided an update on the Member State Mechanism on SSFFC medical products, an international collaboration from a public health perspective. This body is composed of two representatives from each of the six WHO regions and meets two to three times per year. An overview was given of the main activities, which are led by different Member States. A socioeconomic study of the public health impact of SSFFCs is expected to be published in 2017 and will motivate investments in supply chain integrity.

The global SSFFC surveillance and monitoring system has been rolled out to a total of 125 countries. Since 2012 more than 1300 suspect products have been reported from 90 countries, resulting in 17 WHO global drug alerts and a number of other warnings. WHO provided technical assistance in more than 100 cases. The most frequently affected product categories were antiparasitics and systemic anti-infectives; reports of falsified vaccines have also regularly been received. These are worrying findings in the context of antimalarial and antimicrobial resistance, at a time when confidence in vaccine programmes is critical to close the immunization gap. Most reports of suspect medicines came from Africa where the surveillance system was first implemented. It was introduced in

south-east Asia in late 2016 and WHO has engaged with Asia-Pacific Economic Cooperation to seek opportunities for collaboration. New technologies are being used to fight SSFFC products. A platform has been established for reporting by smartphone, and a portal on the WHO website allows searches to be made for products and batch numbers that have been reported as falsified.

The Committee noted the report.

Regulatory support

Mr Mike Ward presented an update about WHO's regulatory support activities. Regulatory systems strengthening started in 1997 as part of quality assurance for vaccine programmes. The benchmarking tool has also been adapted to be used for pharmaceuticals and will be extended to medical devices, which are not fully regulated in many Member States. The concept of functionality of a regulatory authority is evolving towards a system with maturity levels. A rapid assessment tool has been developed and will be tested in a group of African countries. Some indicators on SSFFCs have been added to the assessment tool with a view to identifying opportunities to strengthen supply chain systems and regulatory responses to incidents.

Efforts are ongoing to facilitate the registration of medicines, for example, through the collaborative registration procedure for WHO-prequalified products. In addition to systems and infrastructure, building human resources for regulation is critical. WHO supports regional networks, which have been established in many regions of the world to optimize the use of limited resources through information-sharing, work-sharing and reliance. The draft guidelines on good regulatory practices will provide a common framework to support these initiatives. Ongoing efforts include work on good reliance practices, quality management systems for regulatory authorities and a definition of medical products of assured quality. Regulatory best practice and collaboration would also be discussed at the ICDRA meeting in Cape Town on 29 November–2 December 2016. Mr Ward thanked the South African Medicines Control Council for hosting this important event.

Resourcing of WHO's regulatory support activities is becoming increasingly difficult. Furthermore, the increasing prevalence of other development organizations involved in regulatory strengthening efforts calls for a more coordinated approach. In response, a new business model has been launched, which aims to build a coalition of interested partners around a common institutional development plan, and to develop centres of excellence in different parts of the world to support WHA resolution 67.20.

The Committee noted the report.

Quality control of herbal medicines

Ms Yukiko Maruyama presented a document titled *Proposed WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines* to the Expert Committee. A proposal to develop WHO technical guidelines on analytical methods for herbal medicines was first presented to the WHO Expert Committee at its thirty-seventh meeting in October 2001. This initiative was supported by recommendations made at various international meetings and by the WHA resolution on traditional medicine (WHA56.31), which requested WHO to provide technical support to develop a methodology to monitor or ensure the quality, efficacy and safety of herbal products. The guidance was developed through the usual wide consultative process. The Expert Committee was updated on progress in 2004, 2005, 2010, 2011 and 2014 and responded with guidance and comments.

The document presented to the Expert Committee at its fifty-first meeting represents the third revised draft, which resulted from the discussion and consensus reached at the second WHO consultation on quality control of herbal medicines held in Hong Kong SAR, China, in November 2014. Ms Maruyama thanked the Government of Japan for its financial support for the development of this guidance, as well as Health Canada, the General Authority for Health Services for the Emirate of Abu Dhabi, and the Department of Health of Hong Kong SAR, China, for hosting relevant WHO meetings required in the process.

The Committee adopted the proposed guidelines, noting that they are in the form of a dynamic document which can be updated on an ongoing basis. Note was taken of a request for WHO to develop guidance on registration of herbal products by collecting best practices from other countries. The Committee agreed that the document would be published as Annex 1 to the WHO TRS and could also be issued as a separate publication to enable wider access.

Expert Committee on Biological Standardization

Dr David Wood gave an update on the strategic directions of the Expert Committee on Biological Standardization (ECBS). Established in 1947, the ECBS has provided more than 70 global written standards and more than 300 global measurement standards for biological products. Today, the key priorities of the ECBS are to respond to public health emergencies, increase access to affordable biotherapeutic products of assured quality and strengthen regulatory systems. The ECBS recently adopted guidance texts on the regulation of biotherapeutic products and biosimilars, and on regulation of recombinant DNA-derived products. Implementation workshops have been held with regulators in African and Asian countries. A topic of current interest is the value of WHO reference

preparations for bioassays in labelling, dosing and use of biological products. An update of the guidance on antivenoms is on the ECBS workplan.

The Committee noted the update.

1.2 International collaboration

United Nations Children's Fund (UNICEF)

Dr Peter Svarrer Jakobsen presented an update on UNICEF's work. UNICEF was established in 1946 to promote and protect children's rights. The UNICEF Supply Division in Copenhagen works with logistics staff in about 150 countries to bring good quality medicines and other supplies to children and their families. The Supply Division holds an Emergency Relief Authorization from the Danish Health and Medicines Agency and has a fully automated warehouse. In 2015, UNICEF provided supplies and services worth US$ 3.4 billion worldwide, including US$ 1.7 billion worth of vaccines, US$ 151 million worth of pharmaceuticals and US$ 58.7 million worth of bed nets and insecticides. All procurement is authorized by the head office in Denmark, to ensure that quality standards are adhered to. UNICEF applies the WHO model quality assurance system for procurement agencies (MQAS), and WHO guidelines on good distribution practices. UNICEF relies on WHO prequalification for vaccines, antiretrovirals, antimalarials and anti-TB products. For needed products that do not have stringent regulatory mechanisms for marketing approval in place, qualified UNICEF pharmacists conduct a prequalification process which involves evaluation of a product questionnaire as published in the MQAS guidelines and related documents, as well as inspection of manufacturing sites on a risk basis to verify compliance with WHO good manufacturing practice (GMP) guidelines. Since 2006 UNICEF has been a partner to the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

The Committee noted the report.

Global Fund to Fight AIDS, Tuberculosis and Malaria

Dr Alain Prat described the Global Fund's quality assurance policy for pharmaceuticals. As a non-technical agency, the Global Fund relies on stringent assessment of medicines by the WHO Prequalification Team and/or by a stringent regulatory authority for core products. The Global Fund welcomed the Expert Committee's intention to revisit the definition of "stringent regulatory authority" (see section 9.5).

For needed products that have not yet undergone a stringent review, the Expert Review Panel (ERP) performs a risk assessment and provides a time-limited opinion for decision-making by procurers. Examples of such products are kanamycin injection, paediatric first-line antituberculosis products and sofosbuvir tablets. After eight years of implementation the ERP process will

undergo a review, for which the Global Fund is seeking input from a wide range of stakeholders.

All products must be authorized in the country of use. Grant recipients, in collaboration with national regulatory authorities, are required to implement a risk-based plan for quality monitoring of pharmaceuticals at WHO-prequalified or International Organization for Standardization (ISO)-accredited laboratories. The use of analytical methods that are different from the methods approved during the authorization or prequalification process poses a challenge. Furthermore, grant recipients are strongly encouraged to monitor adverse drug reactions in line with WHO recommendations on pharmacovigilance.

The Committee noted the report.

Pharmacopoeial Discussion Group

Dr Andrea Lodi provided an update on the activities of the Pharmacopoeial Discussion Group (PDG), which consists of the European Pharmacopoeia, the Japanese Pharmacopoeia and the United States Pharmacopeia. The latest meeting of the PDG was hosted by the European Directorate for the Quality of Medicines & HealthCare (EDQM) in Strasbourg, France, from 26 to 27 May 2016. Dr Lodi outlined the PDG's stepwise working process and spoke about the main topics currently under discussion. These include harmonization of various general texts, including the chapter on chromatography, and identification of strategies for implementation of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q3D guideline on control of elemental impurities. An overview was also provided of the status of new and revised general texts and monographs. The next meeting of the PDG would take place in Tokyo, Japan in October 2016.

During the discussion that followed this update it was suggested that pharmacopoeias could approach the core group of PDG members to find out whether requests for observer status could be considered.

The Committee noted the report.

2. Quality control – specifications and tests

2.1 *The International Pharmacopoeia*

2.1.1 Updates

Dr Herbert Schmidt thanked the Committee for its work, which had resulted in some major achievements since the last meeting. The sixth edition of *The International Pharmacopoeia* had been made available on CD-ROM. The new edition includes 12 new and 16 revised texts, including new monographs on dextromethorphan hydrobromide and dextromethorphan oral solution and a new levomethorphan limit test for dextromethorphan-containing finished products. These new texts, together with a newly established International Chemical Reference Substance, enable testing of dextromethorphan active pharmaceutical ingredient (API) and dextromethorphan-containing finished products for contamination with levomethorphan. In 2013 and 2014, contaminated dextromethorphan cough syrup had led to two incidents causing numerous deaths and cases of intoxication.

Following a decision made by the Expert Committee at its fiftieth meeting, 18 outdated texts had been transferred to a publicly accessible archive section on the WHO website with a note on their terms of use. Also in line with a Committee decision, information had been published on the WHO website on reference substances established by other pharmacopoeias and found suitable to be used according to *The International Pharmacopoeia*. This will foster harmonization among pharmacopoeias and reduce duplication of work. Furthermore the Secretariat had set up a web community to facilitate communication and information exchange between the Secretariat and collaborating experts and laboratories. The pharmacopoeias were encouraged to include a link to the online version of *The International Pharmacopoeia* on their websites.

The Committee Secretary thanked all experts, colleagues, the custodian centre for International Chemical Reference Substances (ICRS), collaborating centres and laboratories, manufacturers and donors for their valuable contributions to *The International Pharmacopoeia*.

The Committee noted the report and congratulated the Secretariat on these achievements.

2.1.2 Workplan 2016–2017

Monographs proposed for elaboration or withdrawal

The Expert Committee was provided with a comprehensive data compilation which served as a basis to identify the need for elaboration, revision and withdrawal of monographs. Monographs for 17 pharmaceutical substances and 34 specific dosage forms were proposed for elaboration with high priority (Table 1). These monographs are on medicines that are included in the 19th

WHO Model List of Essential Medicines (EML) as well as in invitations for expression of interest for prequalification, and for which no monograph is included in the 2016 British Pharmacopoeia, the 16th edition of the Japanese Pharmacopoeia or the 39th edition of the United States Pharmacopeia. The workplan for *The International Pharmacopoeia* would also cover any APIs which would be needed to support the finished pharmaceutical product monograph and which are not yet available or would need to be revised.

Table 1
Monographs proposed for elaboration with high priority

Active pharmaceutical ingredients (APIs)	Finished dosage forms
	abacavir and lamivudine dispersible tablets
amphotericin B (sodium deoxycholate or liposomal complex)	amphotericin B liposomal complex for injection
	artemether and lumefantrine dispersible tablets
	amodiaquine and artesunate tablets
	artesunate and mefloquine tablets
	artesunate rectal capsules
	clofazimine capsules
daclatasvir hydrochloride	daclatasvir tablets
darunavir	darunavir tablets
dasabuvir	dasabuvir tablets
entecavir	entecavir oral solution
	estradiol cypionate and medroxyprogesterone acetate injection
ledipasvir	ledipasvir and sofosbuvir tablets
linezolid	linezolid powder for suspension
	linezolid tablets
mifepristone	mifepristone tablets
	morphine hydrochloride or sulfate oral solution/suspension
	morphine hydrochloride or sulfate tablets (slow-release)
	morphine sulfate granules (slow-release; to mix with water)

Table 1 *continued*

moxifloxacin hydrochloride	moxifloxacin capsules
	moxifloxacin tablets
	nevirapine dispersible tablets
	norethisterone enantate injection
ombitasvir paritaprevir	ombitasvir, paritaprevir and ritonavir tablets
oseltamivir	oseltamivir powder for oral suspension
p-aminosalicylic acid	*p*-aminosalicylic acid granules for oral solution
	protionamide capsules
	protionamide tablets
	pyrazinamide dispersible tablets
rifapentine	rifapentine tablets
simeprevir	simeprevir capsules
sofosbuvir	sofosbuvir capsules
terizidone	terizidone capsules
	terizidone tablets

In addition, 15 substances and 31 dosage forms were identified as being of medium priority for monograph development. Monographs for 73 substances and seven dosage forms were proposed to be withdrawn as they have been omitted from the EML, are not invited for prequalification and no specific reason exists to keep them. During development of the above workplan, 33 monographs were identified as requiring revision.

The Committee adopted the proposed workplan.

2.2 Specifications for medicines, including children's medicines and radiopharmaceuticals

2.2.1 Maternal, newborn, child and adolescent health medicines

Ceftriaxone sodium

Ceftriaxone for injection

Injectable ceftriaxone has been identified by the United Nations (UN) Commission for Life-Saving Commodities as a life-saving medicine for second-line treatment of neonatal sepsis. A first draft of the monographs was received

from the collaborating centre in March 2015. They were discussed at an informal consultation and circulated for public comment in 2015. The drafts were revised accordingly and discussed at an informal consultation held in May 2016. Revised drafts were posted for public consultation in July 2016. The draft monographs were further revised in line with comments received and presented to the Committee for discussion.

The Committee adopted the amended monographs. The possibility of adding a robust method to the alternatives for identity testing will be investigated.

Chlorhexidine digluconate solution

Chlorhexidine digluconate topical solution

Chlorhexidine digluconate solution and topical solution/gel for umbilical cord care are important low-cost products to reduce mortality of neonates. The topical solution was added to the EML for children in 2013. Draft monographs for these formulations were received from the collaborating centre in September 2015 and presented to the Committee at its fiftieth meeting for information. Public comments were sought and collated in 2016. Revised drafts were presented to the Committee for discussion at its fifty-first meeting.

The Committee adopted the amended monographs.

Medroxyprogesterone acetate

Medroxyprogesterone injection

Following information received from the custodian centre for ICRS, the EDQM, it was proposed to revise the monographs on medroxyprogesterone acetate and medroxyprogesterone acetate injection. Draft revisions were prepared in February 2016. The drafts were discussed at an informal consultation held in May 2016 and they were circulated for public consultation in June 2016. The drafts were further revised in line with comments received and were presented to the Committee for discussion at its fifty-first meeting.

The Committee adopted the two monographs and authorized the use of medroxyprogesterone acetate reference substance for system suitability, which was established by the European Pharmacopoeia, for use with the monographs. The addition of an alternative assay method will be investigated, and proposed for consideration by the Committee in a subsequent revision.

2.2.2 Antituberculosis medicines

Moxifloxacin hydrochloride

Moxifloxacin tablets

New monographs on moxifloxacin hydrochloride and moxifloxacin tablets were drafted based on information found in other pharmacopoeias, information

received from the manufacturers, and laboratory investigations. The monograph on moxifloxacin tablets was developed in collaboration with the British Pharmacopoeia. Both monographs were discussed at an informal consultation on quality control laboratory tools and specifications for medicines in May 2016. They were presented to the Expert Committee for information and comment, pending completion of laboratory investigations and circulation of the monographs for public consultation.

The Committee took note of the update and provided comments on the monograph.

2.2.3 Antiviral medicines

Atazanavir

The Secretariat received information from a manufacturer that there had been a transcription error in the description of the test for optical rotation. The monograph had been corrected and published in the sixth edition of *The International Pharmacopoeia*.

The Committee took note of the correction to the monograph.

Ganciclovir

Ganciclovir for injection

Ganciclovir for injection is one of the HIV-related medicines invited for WHO prequalification. New monographs have been drafted by a collaborating centre. The monographs were discussed at an informal consultation on quality control laboratory tools and specifications for medicines held in May 2016. They were presented to the Expert Committee for information and discussion, pending their circulation for public comment.

The Committee noted the monographs and provided input on the drafts to be circulated.

2.2.4 Medicines for tropical diseases

Mebendazole

Mebendazole chewable tablets

Mebendazole tablets

A draft revision of the monograph on mebendazole was prepared in April 2016, taking into account relevant specifications and tests published in the European Pharmacopoeia. In parallel, new monographs were drafted on mebendazole tablets and mebendazole chewable tablets, based on information received from manufacturers and on laboratory investigations. The three monographs were discussed at an information consultation on quality control laboratory tools and specifications for medicines held in May 2016. The draft monographs on

mebendazole and mebendazole chewable tablets were sent out for public comment in July 2016, and were further revised taking into account comments received. The monograph on mebendazole tablets had yet to be sent out for public consultation, and additional samples would be requested from manufacturers. The three drafts were presented to the Committee for discussion at its fifty-first meeting.

The Committee adopted the monographs, pending their finalization by a small workgroup for inclusion in the 7th edition of *The International Pharmacopoeia*.

2.2.5 Other anti-infective medicines

Amoxicillin trihydrate

Potassium clavulanate

Amoxicillin and clavulanic acid tablets

Monographs on amoxicillin trihydrate and potassium clavulanate were drafted in July 2016. The drafts were presented to the Expert Committee for information and discussion, pending verification of the provisions and specifications in the monographs by a WHO collaborating centre and their circulation for public comment.

A draft monograph on amoxicillin and clavulanic acid tablets was developed by a WHO collaborating centre and discussed at an informal consultation on quality control laboratory tools and specifications for medicines held on 9–11 May 2016. Laboratory investigation is ongoing. The draft monograph was presented to the Committee for information and discussion, pending its circulation for public consultation.

The Committee noted the update.

Clindamycin palmitate hydrochloride

Clindamycin palmitate for oral suspension

Draft monographs were developed by a WHO collaborating centre from October 2015–January 2016 and were discussed at an informal consultation on quality control laboratory tools and specifications for medicines in May 2016. They were circulated for public comment in July 2016, further revised in consultation with the laboratory that had prepared the draft, and presented to the Committee. Work on the assay for clindamycin palmitate for oral suspension is ongoing. The monograph was presented to the Committee for information and discussion.

The Committee noted the report. It was decided that in this monograph and in the two monographs on amoxicillin oral suspension and artemether and lumefantrine oral suspension, the dosage form should be defined as "powder for oral suspension".

Clindamycin phosphate

Clindamycin phosphate injection

In 2015–2016 the monograph on clindamycin phosphate was revised, and a new monograph on clindamycin phosphate injection was drafted based on laboratory investigations. The draft texts were discussed at an informal consultation on quality control laboratory tools and specifications for medicines in May 2016, and further revised drafts were circulated for public comment in August 2016. Proposed revised drafts were prepared based on comments received, in consultation with the collaborating laboratory. The draft monographs were presented to the Committee for discussion.

The Committee adopted the monographs and authorized the use of the clindamycin phosphate reference substance for system suitability established by the custodian centre for use as proposed in *The International Pharmacopoeia*.

2.2.6 Other medicines

Methylthioninium chloride

Methylthioninium injection

The monograph on methylthioninium chloride was revised based on information from the manufacturer and laboratory investigations, and a new monograph on methylthioninium injection was drafted by a collaborating laboratory. The draft monographs were received in April 2016 and were discussed at an informal consultation on quality control laboratory tools and specifications for medicines in May 2016. They were sent out for public consultation in July 2016. The draft monographs were presented to the Committee for discussion.

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

2.2.7 Radiopharmaceuticals

On behalf of the International Atomic Energy Agency (IAEA), Dr Uday Bonsle reported on progress with updating monographs for radiopharmaceuticals. Owing to resource limitations in IAEA, the submission of the revised specifications had taken longer than expected. The situation had now improved and a new workplan was proposed. The monographs listed below have been updated in accordance with the official procedure for updating of radiopharmaceutical monographs.[10] The monographs were circulated for consultation, revised in line with comments received and finalized, subject to review by an expert:

[10] Updating mechanism for the section on radiopharmaceuticals in *The International Pharmacopoeia*. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 2 (WHO Technical Report Series, No. 992).

- fludeoxyglucose (^{18}F) injection
- gallium (^{67}Ga) citrate injection
- iobenguane (^{123}I) injection
- iobenguane (^{131}I) injection
- samarium (^{153}Sm) lexidronam complex injection
- sodium (^{125}I) iothalamate injection
- sodium iodide (^{131}I) capsules
- sodium pertechnetate (^{99}mTc) injection (fission)
- sodium pertechnetate (^{99}mTc) injection (non-fission)
- sodium phosphate (^{32}P) injection
- strontium (^{89}Sr) chloride injection
- technetium (^{99}mTc) bicisate complex injection
- technetium (^{99}mTc) colloidal sulfur injection
- technetium (^{99}mTc) colloidal tin injection
- technetium (^{99}mTc) mebrofenin complex injection
- technetium (^{99}mTc) medronate complex injection
- technetium (^{99}mTc) mertiatide complex injection
- technetium (^{99}mTc) pentetate complex injection
- technetium (^{99}mTc) sestamibi complex injection
- technetium (^{99}mTc) succimer complex injection
- technetium (^{99}mTc) tetrofosmin complex injection
- technetium (^{99}mTc) tin pyrophosphate complex injection
- yttrium (^{90}Y) silicate injection

The general monograph was also updated. It was reiterated that the above-mentioned monographs would be subject to the usual public consultation process prior to their adoption by the Expert Committee in line with the official procedure.

The Expert Committee noted the report. The Committee's Secretariat thanked the IAEA for this important revision.

2.3 General monographs for dosage forms and associated method texts

Proposed revision of the General Chapter 1.11 Colour of liquids

Chapter 1.11 Colour of liquids, prescribes the use of dichromate for the preparation of the four colour standard solutions. To avoid the use of chromium (VI) salts, it was proposed to gradually replace the current procedure with

that described in the European Pharmacopoeia. Permission to reproduce the procedure will be sought once the proposed text is adopted by the Expert Committee.

For the period of transition, both procedures will be kept: the current procedure in section 1.11.1, which will be referred to in existing monographs, and the new procedure in section 1.11.2, which will be referred to in new or revised monographs. It was further proposed to delete the definition of "colourless" in the General Notices section and instead to include it in the proposed section 1.11.2 ensuring that all existing monographs that refer to "colourless" solutions include a reference to the definition in section 1.11.1.

These revisions were first proposed by the Secretariat in September 2015 and were discussed at an informal consultation on quality control laboratory tools and specifications for medicines held in May 2016. A draft was sent out for public consultation in July 2016. The proposed chapter was presented to the Committee for discussion.

The Committee adopted the revised chapter and approved the inclusion of references in existing and new monographs as proposed.

Proposed revision of the General Chapter 2.6 Non-aqueous titration

As part of the activities to avoid the use of mercury salts and other toxic reagents in *The International Pharmacopoeia* (see section 2.4), notably the direct titration of the halide salts of weak bases with perchloric acid in anhydrous acetic acid and the titration of the halide salts of bases in alcoholic media with sodium hydroxide, it was proposed to revise Chapter 2.6 Non-aqueous titration. A revised draft was received from an expert in November 2015, discussed at an informal consultation on quality control laboratory tools and specifications for medicines held in May 2016, then further revised and sent out for public consultation in June 2016. The comments received and the draft chapter with additional revisions based on these comments were presented to the Committee for discussion.

The Committee adopted the revised chapter, subject to the amendments agreed.

2.4 General policy

Revised concepts and future perspectives

A proposed revision of the 2003 guidance on "The International Pharmacopoeia: *revised concepts and future perspectives*" was presented to the Committee for discussion. The updated draft reflects the current approaches to prioritization and development of monographs and other texts. Furthermore, it proposes that initiatives should be taken to promote and implement collaboration among pharmacopoeias to achieve harmonization as described in the guidance on good

pharmacopoeial practices (GPhP), and making use of existing forums, such as the PDG and the international meetings of world pharmacopoeias.

The Committee adopted the new guidance as an annex to the report of the fifty-first meeting of the Expert Committee (Annex 2).

Transition from microbiological to chromatographic assay of antibiotics: capreomycin

At its meeting in 2009, the Expert Committee had decided that microbiological assays in monographs for antibiotics should be replaced by chromatographic methods, where possible and appropriate. Significant progress was made subsequently in developing physicochemical assay methods for pharmaceutical products. At its fiftieth meeting the Committee had adopted a number of proposals to update monographs accordingly. While the transition from microbiological to physicochemical assays has been largely completed for single-component antibiotics, it remains challenging for multicomponent compounds.

Capreomycin consists of a mixture of four structurally related components with different activities in the microbiological assays. The monographs on capreomycin sulfate and capreomycin for injection published in *The International Pharmacopoeia* prescribe a chromatographic method. However, the content in mass units as determined by this method is currently not correlated with the activity of the substance as determined by microbiological methods.

The Committee agreed that the International Chemical Reference Substance (ICRS) should be released with the following note in the leaflet: "The International Chemical Reference Substance for capreomycin sulfate ICRS is intended to be used as described in *The International Pharmacopoeia* for assay by high-performance liquid chromatography (HPLC) according to the monographs for capreomycin sulfate and capreomycin for injection. The substance is suitable to serve as a reference for the quantitative determination of the content of capreomycins IA, IB, IIA and IIB from the declared content in capreomycin sulfate RS. **A correlation between the concentration of IA, IB, IIA and IIB and the activity of the substance, determined with microbiological methods, has not been established.**"

It was further agreed that information should be obtained from manufacturers of capreomycin API and powders for injection about the composition of the capreomycin sulfate manufactured or used in their products, methods used to determine the composition and information regarding a correlation between the mass concentration of the capreomycin components and the microbiological activity of their products. Furthermore an analytical comparison of pharmacopoeial microbiological standards should be conducted. The outcome of these surveys will determine whether the monograph should be further revised to revert to a microbiological assay.

Replacement of titration methods using mercury acetate in *The International Pharmacopoeia*

At its fiftieth meeting, the Expert Committee had endorsed the proposal by the Secretariat of *The International Pharmacopoeia* to replace the use of titrations using mercury salts by alternative methods to reduce the risk to analysts and the environment. The Committee had recommended giving preference to volumetric methods for assay over liquid chromatographic methods, as they are usually more precise and do not require the use of a reference standard. Based on a WHO-commissioned survey, the Secretariat identified suitable volumetric methods from other pharmacopoeias for use in 40 of the 47 monographs and determined that these assay methods can be considered validated and fit for purpose. For the monographs on gallamine triethiodide, tubocurarine hydrochloride, loperamide hydrochloride, procarbazine hydrochloride, quinine dihydrochloride, dehydroemetine dihydrochloride and thiamine hydrobromide, no suitable volumetric method was identified in the survey. The Secretariat proposed that volumetric titration methods should be developed through experimental laboratory studies and suggested that each of the monographs would need to describe a different titration method.

The Committee took note of the update. The proposals to replace the titration method in each of the monographs were discussed in connection with the proposed revision of the General Chapter 2.6 Non-aqueous titration (see point 2.3). The monographs that currently prescribe the use of mercuric acetate for titrations will be gradually revised using the new recommended procedures – method A(i) and A(ii) of the revised chapter.

Note for guidance on organic impurities in APIs and finished products

A note for guidance was drafted by the Secretariat of *The International Pharmacopoeia* in early 2015. The text is intended to replace the text titled "*Related substances in dosage form monographs*" in the Supplementary information section of *The International Pharmacopoeia*. The document was discussed at an informal consultation, underwent one round of public comments in 2015 and was then presented to the Expert Committee at its fiftieth meeting in October 2015. A subgroup had been formed during that meeting to address some issues raised in the discussions and had reported back to the Committee. It was concluded that work on the draft should continue. A revised draft was then prepared by an expert and circulated for comment among the members of the working group. The draft was further discussed at an informal consultation on quality control laboratory tools and specifications for medicines in May 2016 and was revised again before being sent out for a second round of public consultation. The draft was further revised in line with comments received and was presented to the Committee at its fifty-first meeting.

The Committee adopted the text with the agreed amendments.

General policy for drafting monographs

During the discussion of the individual monographs it became apparent that there was a need for a comprehensive document that provides guidance on the drafting of monographs for inclusion in *The International Pharmacopoeia*. This document should make clear that limits should be set in such a way that they are not more stringent than those stipulated in other well-established pharmacopoeias, unless justified. A policy for the naming of monographs and the design of identity tests should also be set out in this guidance document.

It was suggested that the Secretariat should develop such a document.

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

Dr Andrea Lodi presented a report on the activities of the EDQM, which is the custodian centre in charge of ICRS for use in tests and assays described in *The International Pharmacopoeia*. The work on establishment of ICRS in 2015 was reduced compared to 2014 owing to the departure of the Study Director. In 2015–2016 two ICRS were established: dextromethorphan for system suitability, which will enable the performance of the limit test for levomethorphan adopted by the Committee at its fiftieth meeting, and an ICRS for capreomycin sulfate. The latter was released during the discussions about points to consider when moving from microbiological to chromatographic assay methods for antibodies (see section 2.4).

EDQM informed the Committee that most of the ICRS leaflets had been revised to conform to a new institutional style and to include hazard pictograms as agreed by the ICRS Board. Potency statements were removed from the leaflets for five ICRS as agreed by the Expert Committee at its fiftieth meeting. EDQM continued to monitor ICRS in 2015 to ensure their continued fitness for purpose and no negative findings had been reported.

The Committee confirmed the release of the dextromethorphan for system suitability ICRS by the ICRS Board. The Committee adopted the release of capreomycin ICRS 1 following a discussion about the transition from microbiological to physicochemical methods for antibiotics (see section 2.4).

Following a request by the Committee, the Secretariat will conduct a survey on the number of available and missing ICRS for use with monographs in *The International Pharmacopoeia* and will inform the Committee of the findings.

The Committee and the Secretariat expressed their gratitude to EDQM and the ICRS Board for ensuring the preparation, establishment, storage, distribution and monitoring of ICRS for use as stipulated in *The International Pharmacopoeia*.

4. Quality control – national laboratories

4.1 External Quality Assurance Assessment Scheme (EQAAS)

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 (QCLs). Since 2000 it has been organized with technical assistance from EDQM.

An update was given on two EQAAS Phase 6 studies, using samples of cycloserine. The aim of the first of these studies was to assess the performance of QCLs in determining specific optical rotation using the method described in *The International Pharmacopoeia*. The second study served to assess the laboratories' performance in conducting the assay by titration on the same samples. For both studies possible sources of error were identified. Laboratories that failed to perform the tests successfully were advised to investigate their procedures in order to improve their performance.

Samples for EQAAS Phase 7 studies are being sent out. Participants will be asked to perform a dissolution test and assay by HPLC. As the common test sample, sulfadoxine and pyrimethamine tablets will be distributed. The results will be presented to the Expert Committee at its fifty-second meeting.

The Committee noted the report and emphasized the value of EQAAS for quality assurance of QCLs.

4.2 Guidance on testing of "suspect" substandard/spurious/falsely-labelled/falsified/counterfeit medicines

This general text on the testing of "suspect" SSFFC medicines was developed based on the outcomes of a survey among some 50 pharmaceutical QCLs. In October 2014, the Committee had endorsed a draft outline for this guidance, which included chapters on techniques and sampling. The guidance was discussed at the informal consultation on screening technology, sampling and specifications for medicines held in April 2015. A first draft was prepared in May 2015 based on the discussions during the consultation and additional input from experts. The draft was circulated for comment to QCLs in August and September 2015, and an update was provided to the Committee at its fiftieth meeting. The draft was further revised, and draft annexes were added giving an overview of technologies and an example of a standard operating procedure for the testing of suspect SSFFC medicines. Feedback was obtained from the laboratories that had participated in the 2014 survey, and the draft was discussed at an informal consultation on QCL tools and specifications for medicines in May 2016. The draft was once more circulated among relevant experts and then opened for public comment.

The Committee noted the update.

4.3 Recommendations from the meeting on regulatory guidance for multisource products

Proposal for revision of the model certificate of analysis

During an informal consultation on regulatory guidance held in July 2016, it was suggested that the WHO model certificate of analysis, published in 2002, should be revised and updated to align it with new trends and international developments. A proposal for revision was prepared by a consultant and presented to the Committee for discussion, pending its circulation for public comments.

The Committee endorsed the proposal to circulate this document for public consultation.

Proposal for an update of the guidance on considerations for requesting analysis of samples

An update of the 2002 WHO guidance document *Considerations for requesting analysis of drug samples* was proposed at an informal consultation on regulatory guidance held in July 2016. A draft revision was prepared by a consultant and was presented to the Committee for discussion, pending its circulation for public comments.

The Committee endorsed the proposal to circulate this document for public consultation.

5. Prequalification of quality control laboratories

5.1 Update on the prequalification of quality control laboratories

Mr Rutendo Kuwana presented an update on the procedure for prequalification of QCLs, which was established in 2004. Participation is voluntary and is open to both public and private QCLs. About 10 requests for prequalification are received each year. Of 83 QCLs that have shown interest in prequalification, 40 were WHO-prequalified laboratories as at October 2016. This included two laboratories affiliated to manufacturing companies. A third such laboratory withdrew its submission of an Expression of Interest due to a conflict of interest, as the company to which it is affiliated was pursuing prequalification of a pharmaceutical product.

Capacity-building activities were ongoing for laboratories seeking WHO prequalification, particularly national QCLs. A peer audit scheme was introduced in 2015 as a capacity-building measure. Seven peer audits had been conducted to date. An international seminar to which all 83 QCLs were invited was planned for 25–28 October 2016 in Shenzhen, China, in collaboration with the Shenzhen Institute of Drug Control. The QCLs of 50 countries had confirmed their participation. The objectives of the meeting were to provide training on selected elements of good practices for QCLs with the aims of achieving a common understanding of WHO norms and standards and facilitating networking between QCLs. A network of prequalified QCLs has been established and is coordinated by a South African laboratory, which is also a WHO collaborating centre.

The Committee noted the report.

5.2 Update on WHO quality monitoring projects

In 2015 and 2016 the Prequalification Team (PQT), in cooperation with the regulatory authorities of five African countries conducted a quality survey of antiretrovirals. A total of 126 samples were collected, of which 123 samples complied with the pharmacopoeial specifications set for the survey. Two of the three noncompliant samples were found to be compliant when they were re-tested according to the manufacturer's method. The remaining sample did not meet the manufacturer's specification for appearance due to contamination with co-packed drying agent.

A study focusing on artemisinin combination therapies will be organized, focusing on prequalified products. The study is to be performed in two phases. Phase I, which will start at the end of 2016, will serve to develop a spectral library for prequalified products to support the use of near infrared and Raman spectroscopy screening methods using samples of pivotal batches from manufacturers of prequalified products. In phase 2, market samples will

be collected and fully tested at two prequalified laboratories. In addition, the samples will be screened and compared using the technologies applied in phase I in order to evaluate the suitability of these screening methods.

Quality testing was also conducted in response to reports of suspected substandard products from Member States, following the publication of Notices of Concern by the WHO PQT–Inspections, and for the purposes of pre-purchase testing of products for neglected tropical diseases.

The Expert Committee noted the report.

5.3 Revision of the procedure for assessment of quality control laboratories

Participation in the prequalification procedure for QCLs is voluntary, open to any pharmaceutical QCL, and is currently free of charge. Given limited WHO resources for inspection and technical assistance, priority is given to assessing applications for prequalification received from laboratories that will serve the objectives of prequalification, i.e. quality control testing of pharmaceutical products for UN agencies, WHO partners and governments. Two manufacturers' laboratories are prequalified, but have shown no activity related to these objectives. Interest from manufacturers in prequalification of their laboratories has been increasing, and there is a need for a clear public and transparent policy on how these applications should be handled.

Revisions have been proposed to the procedure titled *Prequalification of quality control laboratories. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies* to address the above-mentioned issue. It is proposed to limit the eligibility or maintenance of prequalification processes for laboratories that have conflicts of interest or that fail to provide services to UN agencies or national authorities. A draft revision of the procedure was developed in early 2016 and circulated for comment. The draft and comments received were discussed at an informal consultation held in May 2016. A second round of public comment was sought in June 2016. Comments were compiled and the text was further revised with input from the WHO Office of the Legal Counsel. The revised text was presented to the Expert Committee.

The Committee discussed the text and proposed some changes. The text was reviewed and a revised version was presented to the Committee and further discussed. The Committee adopted the guidance with amendments as agreed (Annex 3).

6. Quality assurance – collaboration initiatives

6.1 International meetings of world pharmacopoeias

Convergence of pharmacopoeial standards would help to reduce the costs arising from differences between standards used in the production and testing of medicines, thus making good quality medicines accessible to more people. International meetings of world pharmacopoeias have been co-hosted regularly since 2012 by a pharmacopoeia and WHO. These meetings have served as a platform for convergence and collaboration, including the development of common guidance on GPhP.

The seventh WHO international meeting of world pharmacopoeias was held in Tokyo, Japan, from 13 to 15 September 2016. The meeting was co-hosted by WHO and Japan's Ministry of Health, Labour and Welfare/Pharmaceuticals and Medical Devices Agency. A total of 50 national pharmacopoeial authorities were represented in their own capacity or through the European Pharmacopoeia. The participants agreed on the way forward to finalize additional texts to the GPhP guidance (see point 6.2) and discussed actions and proposals for the eighth international meeting of world pharmacopoeias. Participants also agreed that a subgroup of pharmacopoeial representatives should draft a proposal for future meeting topics, and that a survey should be conducted before the next international meeting to evaluate the impact and value of the GPhP guidance.

The representative of the Japanese Pharmacopoeia thanked all contributors for the support received in co-hosting the seventh meeting.

The Expert Committee noted the report and expressed its gratitude to Japan as the host of the seventh international meeting of world pharmacopoeias.

The eighth meeting will be co-hosted by the Brazilian Pharmacopoeia in June or July 2017. Dr Varley Dias Sousa, the representative of the Brazilian Pharmacopoeia, thanked WHO for the confidence placed in his organization in co-hosting the eighth meeting. He noted that participation of Latin American regulatory and pharmacopoeial authorities would strengthen the representativeness of the outcomes, and that Brazil is working on a national document on implementing GPhP principles in national laws.

6.2 Good pharmacopoeial practices

The primary objective of GPhP is to define approaches and policies for establishing pharmacopoeial standards, with the ultimate goal of harmonization. Development of GPhP guidance started in 2012 and continued at successive meetings of world pharmacopoeias (see 6.1). The main text of the GPhP guidance, which describes general principles for the design, development and maintenance of pharmacopoeial standards, had been adopted by the Committee at its fiftieth meeting.

The Committee was briefed on the status of work on drafting additional chapters of the GPhP text and on developing a technical annex with details on GPhP. A GPhP glossary had been developed by the Japanese Pharmacopoeia Secretariat with input from the WHO Secretariat and the British Pharmacopoeia, and was circulated to the other pharmacopoeias in July 2016 for comments. During the seventh international meeting of world pharmacopoeias held in Tokyo, Japan from 13 to 14 September 2016, participants discussed feedback received on the draft glossary as well as additional working documents on compounded preparations and on herbal medicines. The glossary was close to completion. The texts of the documents on compounded preparations and on herbal medicines were in preparation and were expected to be circulated to all pharmacopoeias for comment by the end of 2016. Participants at the Tokyo meeting agreed that, after their finalization and adoption, the additional GPhP texts should be published as separate annexes to the WHO Technical Report Series.

The Committee noted the report and thanked all individuals and groups that had contributed to this important work.

6.3 Inspection guidelines and good practices

The Expert Committee was given an update about collaborative initiatives in the area of inspections. In line with a Committee recommendation, WHO had engaged with PIC/S to share information and to work towards convergence of guidance. Former PIC/S Chairperson (2014–2015), Dr Joey Gouws, informed the Committee that a partnership agreement was signed by WHO and PIC/S in February 2016 providing for information-sharing, sharing of guidance documents for comments and collaboration in the areas of inspections, training and publication of rapid alerts. Dr Ian Thrussell of PQT–Inspections emphasized the importance of collaboration in the context of limited regulatory resources globally. He highlighted the value of information-sharing opportunities with PIC/S, which has evolved into a truly global organization, and thanked PIC/S for their support in prequalification inspections.

The Committee noted the update.

7. Quality assurance – good manufacturing practices

7.1 Update of WHO good manufacturing practices: validation

Work on updating the published guidance on validation and its appendices was triggered by a suggestion from the Prequalification of Medicines Programme in 2013 that this guidance, originally issued in 2006, should be aligned with current trends in validation. In October 2014, the Committee adopted the revised Appendix 7, *Non-sterile process validation*. The need for updates to the validation guidelines and to Appendices 1–6 had been discussed at an informal consultation on data management, bioequivalence, GMP and medicines' inspection held from 29 June to 1 July 2015. A draft proposal for revision of the main text and several appendices was prepared by specialists in collaboration with the WHO Medicines Quality Assurance Group and PQT–Inspections, based on the feedback received during the meeting and from PQT–Inspections. At its fiftieth meeting in October 2015 the Committee was briefed on the progress of the revision process.

The revised draft texts were further discussed at an informal consultation held in April 2016. At that consultation it was proposed to replace Appendices 1 and 2 by cross-references to the respective WHO guidelines on these topics, one of which is currently under revision (see section 7.2), to maintain Appendix 3, and to proceed with revising Appendices 4, 5 and 6. Draft revisions of the main text and Appendices 4, 5 and 6 were prepared and posted on the WHO website in May and June 2016 for public consultation. The four working documents were further revised in line with feedback received and were circulated to the Committee in advance of its fifty-first meeting.

The Committee adopted the revised main text of the guidelines with amendments as agreed during the meeting. Publication is pending finalization of the revisions of Appendices 4, 5 and 6. In addition, the Committee agreed to replace the content of Appendix 1 by a cross-reference to the WHO guidelines on that topic (currently under revision, see 7.2 below), to proceed in the same way with Appendix 2, and to republish Appendices 3 and 7. This will enable adoption and publication of the complete guidance package on validation, including all appendices and cross-references as outlined above.

7.2 Heating, ventilation and air-conditioning (HVAC)

The Committee was updated on progress with revising the guidance on HVAC in line with current trends in engineering and experience gained during implementation of the guidance at inspections. This guidance had been revised in 2015 and circulated for public comment in September 2015. An update was presented to the Expert Committee at its fiftieth meeting. The revised draft and comments were further discussed at a technical consultation held in April 2016,

revised in line with input received and circulated for public comment in May 2016. As in 2015, a large number of comments had been received. The working document and the comments were presented to the Expert Committee for information and discussion.

The Committee noted the progress made with updating these guidelines. Given the large number of comments received and the difficulty of maintaining specialized technical examples, the Committee agreed that the guidance should be revised to reflect the main principles, including details on validation, for presentation to the Committee at its fifty-second meeting. The design and implementation examples will be published separately in a questions-and-answers document.

7.3 Update and recommendations from the inspectors' meeting

Concept paper on the preparation of new guidance on good practices for desk review

On-site inspections of manufacturing sites, testing sites and clinical trials are resource-intensive for regulatory authorities and stakeholders. Good regulatory practices call for risk-based prioritization of regulatory inspections, making the best possible use of available resources and existing information on compliance of sites with relevant good practices (GXP) by relying, where appropriate, on desk review of inspectional information from reliable and trusted sources rather than conducting on-site inspections. Such reliance is currently practised, for example, by PQT–Inspections and the Therapeutic Goods Administration of Australia.

There is no general guidance on best practices in conducting desk reviews. During a WHO training symposium on collaborative registration procedures in Kenya in September 2016, participants recommended that WHO, together with regulatory authorities, should draft such guidance.

A concept paper on the preparation of new guidance on good practices for desk review, including a proposed outline for this guidance was prepared by PQT–Inspections and stakeholders and presented to the Committee for discussion.

The Committee recommended proceeding with the development of guidelines on good practices for desk review for use by regulatory authorities and PQT.

8. Regulatory frameworks

8.1 Local manufacturing of essential medicines

Discussions on manufacture of medicines in low- and middle-income countries (LMICs) often focus on classes of pharmaceuticals needed to treat certain conditions and on general capacity-building aspects. However, the technical level of what is to be produced in conjunction with the risk associated with the product itself is often not adequately addressed.

To fill this gap, a tool for the risk-based selection of non-biological essential medicines for manufacture in start-up situations was developed in 2015 under the leadership of the WHO Public Health, Innovation and Intellectual Property (PHI) unit, as part of the local production project "Improving access to medical products in developing countries through building capacity for local production and related technology transfer" supported by the European Commission. Based on that tool, a concept paper was drafted and subsequently published in *WHO Drug Information* on 24 March 2016 with an invitation for comments. The paper and feedback received were discussed during an informal consultation held from 8 to 9 July 2016 with experts from relevant groups. Based on these discussions a revised draft was prepared and posted on the WHO website in August 2016 for public consultation, and was presented to the Expert Committee as a possible new guidance text on risk-based identification of candidate products for local manufacturing in countries with relatively limited pharmaceutical manufacturing capability and experience.

At the informal consultation it had been suggested that the paper could either be part of WHO's "Notes to consider" guidance on pharmaceutical development aspects, or form part of a larger framework on local manufacturing. This larger framework could include an approach developed by the United Nations Industrial Development Organization (UNIDO), proposing a tailored, phased approach towards achieving compliance with WHO's GMP in LMICs. Staff from UNIDO introduced this approach to the Committee.

During the discussions emphasis was laid on the need to provide a broader perspective to adequately address the criteria involved when setting up local manufacturing.

The Committee noted the draft guidance text and recommended that its content should be further clarified based on the input and discussions during the Expert Committee meeting and the feedback received during the consultation phase, for possible presentation of the text to the Committee after the usual consultative process.

8.2 WHO Global Model Regulatory Framework for Medical Devices

Resolution WHA 67.20 on regulatory system strengthening for medical products urges Member States to strengthen national regulatory systems and requests WHO to prioritize support to target the least regulated areas, such as medical devices. This product group is growing and is increasingly important for public health, yet is not fully regulated in all Member States, particularly in low-resource settings. There is significant scope for collaboration across regulatory authorities to promote common standards for medical devices. To support Member States in this regard, WHO initiated the development of a model regulatory framework for medical devices. At its fiftieth meeting the Expert Committee agreed to oversee this project and suggested that a subgroup of suitably qualified experts should be created to perform the work. ECBS agreed to receive the WHO Global Model Framework document for information.

The project plan was approved in April 2015. A working group was formed consisting of professionals involved in medical device regulation and WHO staff. A draft of the Model was developed by a drafting group and reviewed by the working group during 2015 and 2016. The draft underwent two rounds of public consultation in May and July 2016 and was then revised based on comments received from a wide range of stakeholders. The document proposes a framework for medical devices, based on the principles developed by the Global Harmonization Task Force, and its successor, the International Medical Device Regulators Forum. It proposes a stepwise approach to implementation of regulatory controls and their enforcement. The draft WHO Global Regulatory Model for Medical Devices, including in vitro diagnostic medical devices, was presented to the Committee for discussion.

The Expert Committee adopted the document and commended the working group for its excellent work in developing this much-needed guidance (Annex 4). The Committee took note of plans to organize regional training workshops to promote the implementation of this guidance.

9. Regulatory guidance

9.1 Biowaiver list based on the WHO List of Essential Medicines

Dr Gabriela Zenhäusern presented an update on the WHO biowaiver list. Following the forty-eighth meeting of the Expert Committee in 2013, the Secretariat had made contact with the WHO Collaborating Centre in Germany to discuss the additional studies needed for the update of the currently published biowaiver list, involving additional laboratories. A new concept was proposed, namely, to move from a literature-based approach towards making available a list of APIs eligible for biowaivers, based on verified laboratory data. The intention is to maintain this list as a living document to be revised continuously, based on the latest available data, in close collaboration with experts from PQT's assessment group.

The Committee noted the update.

9.2 International Comparator Products List for equivalence assessment of interchangeable multisource (generic) products

The first list of international comparator products for equivalence assessment of generic products was published in 2002. Efforts had been made to revise this list over the years. In 2014 the Expert Committee adopted the revised *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* and agreed that the actual comparator list should be maintained as a living document separately from the general guidance text on the selection of comparator products.

In November 2014 the list itself and possible collaboration in this area were discussed with the International Generic Drug Regulators Programme Steering Committee. The draft list of comparator products was further updated with the support of external experts, and was presented to the Expert Committee at its fiftieth meeting, together with revised explanatory notes on the selection of comparator products. In line with the Committee's recommendations, both the list and the explanatory guidance were revised further to ensure consistency and applicability. The two documents were circulated for consultation to all interested parties in February 2016. Feedback was compiled and addressed. Both documents underwent another round of public consultation in June 2016. They were then discussed at an informal consultation in July 2016, revised accordingly and reposted on the WHO website in August 2016. A maintenance process was proposed to keep the list up to date. The background document and the list were presented to the Committee for discussion.

The Committee adopted the background document as an annex to its report (Annex 5). The Committee also adopted the list of comparator products

for publication on the WHO website as a living document to be updated on an ongoing basis according to information received from manufacturers and other stakeholders.

9.3 Good regulatory practices

WHA 67.20 requests WHO and its Member States to strengthen regulatory systems. Good governance principles and legal frameworks for health product regulation are vital in Member States. The importance of developing guidance on good regulatory practices was reflected in the outcomes of the 14th ICDRA in 2010. A project was subsequently initiated to develop WHO guidelines on good regulatory practices (GRP). A concept paper was drafted in October 2013, and guideline development was advanced in two subsequent workshops with the participation of WHO Member States and public health stakeholder organizations. At its fiftieth meeting the Expert Committee was informed of progress and expressed its support for the plans to continue developing this important guidance.

The outcome of the drafting process was an outline of a high-level guideline for GRP for medical products, drawing upon documents from multilateral bodies and national regulatory guidelines. The draft document was sent out for public consultation in October 2016, inviting submission of comments by 15 December 2016. The feedback will be considered by both the ECBS and the Expert Committee on the Selection of Pharmaceutical Products. An overview of the draft document was presented to the Committee for information at its fifty-first meeting, pending further revision based on the comments received.

The Expert Committee noted the update and emphasized the need for this guidance as well as the positive feedback received from regulatory authorities in response to the circulation of the working draft for public consultation.

9.4 Collaborative procedure for stringent regulatory authority-approved medicines

Dr Milan Smid presented an oral update about the pilot procedure for collaborative registration of pharmaceutical products approved by a stringent regulatory authority (SRA). This pilot scheme was initiated in 2013, based on experience gained with the collaborative registration procedure for WHO-prequalified products as adopted by the Expert Committee in 2012 and revised in 2015.

Like the existing procedure for prequalified products, the pilot procedure is voluntary for all stakeholders. It provides a mechanism for confidential sharing of detailed assessment information with regulatory authorities to

whom registration applications are submitted, together with evidence that the product to be offered in the target country will be technically the same as that approved by the SRA, or that any differences are well-defined, both pre- and post-registration. The application process follows national guidelines and regulations, and the regulatory authority commits to reaching its independent regulatory decision within a target period of 90 days. After achieving national registration, the national authority will be able to benefit from SRA-approved variations in applying simplified procedures.

Unlike the existing procedure for WHO-prequalified products, the SRA pilot procedure is applicable to any SRA-approved product in any target country, provided that the necessary agreements among the relevant regulators and applicants have been concluded. The SRA information is submitted to the regulatory authority by the applicant; the SRA will provide authentication on request. The information may include a bridging report relating to the use of the product in the target country, as opposed to its use in the country of the SRA.

The WHO Secretariat proposed that WHO guidelines for collaborative registration of SRA-approved products should be developed. The use of such a procedure can shorten the time to registration for pharmaceutical products, promote collaboration and support regulatory convergence and capacity-building. WHO would facilitate applications only for products needed in public treatment programmes of interest to WHO.

The Committee discussed some of the concepts put forward for this type of collaboration, and endorsed the proposal to develop WHO guidelines for collaborative registration of SRA-approved products. The Committee expected that such guidance may be used as a model to guide collaborative registration procedures more generally through reliance on information shared by any trusted reference authority.

9.5 Recommendations from the meeting on regulatory guidance for multisource products

Revision of WHO stability guidelines

The 2009 update of the *WHO guidelines on stability testing of active pharmaceutical ingredients and finished pharmaceutical products* was prepared in close consultation with regulatory parties, and included cross-references to various related guidelines produced by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), formerly the International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, and WHO. At that time it was noted that these guidelines should be applied to all products on the market and should allow for the assessment of conformance to stability

requirements upon reregistration or re-evaluation. Also, several regulatory authorities revised their own stability testing guidelines to require up to 30 °C/75% relative humidity as the long-term storage conditions for hot and humid climates. Furthermore, discussions held during the 12th ICDRA meeting in 2006 led the ICH Steering Committee to withdraw its ICH Q1F guideline on storage conditions in climatic zones III and IV and to leave their definition to the respective national or regional authorities and WHO guidelines. The 2009 WHO guidelines include a separate Appendix 1 titled *Long-term stability testing conditions as identified by WHO Member States*, which is updated continuously upon receipt of relevant information from national regulatory authorities.

Following some recent queries, an analysis was commissioned identifying the areas in need of revision. The analysis was discussed during an informal consultation on regulatory guidance held in July 2016. Participants endorsed the findings of the analysis and confirmed the need for revision of the stability guidelines.

A proposal was submitted to the Expert Committee to revise the 2009 WHO guidelines on stability to reflect recent developments and current standards for stability testing, and the findings of the commissioned analysis were presented.

The Committee endorsed the proposal for revision of the stability guidelines.

Definition of stringent regulatory authority

The WHO prequalification procedure and several other WHO guidance documents provide for mechanisms to rely on SRAs, defining an SRA as a regulatory authority which is a member or an observer of ICH, or is associated with an ICH member through a legally-binding mutual recognition agreement. The definition originated from the Global Fund and it is reflected in the quality assurance policies of most major international organizations involved in procuring medicines.

ICH has undergone structural changes and has expanded its reach to include organizations and associations at the global level. In view of these developments the WHO Secretariat proposed an interim definition of an SRA. The interim definition of an SRA will include the same elements as the current definition, each qualified by the wording "as before 23 October 2015", as follows:

A regulatory authority which is:

a. a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented

by the Pharmaceuticals and Medical Devices Agency ***(as before 23 October 2015)****; or*

b. an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada ***(as before 23 October 2015)****; or*

c. a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway ***(as before 23 October 2015)****.*

The Expert Committee adopted the interim definition and noted the work being done towards developing a new approach to the assessment of national regulatory authorities, based on the various existing systems currently in place such as that used by the Pan American Health Organization and that applied by WHO with respect to vaccines. The Committee requested that an update on this work be provided at its fifty-second meeting.

Assessing the solubility of APIs according to the Biopharmaceutics Classification System

At its forty-ninth meeting the Expert Committee had adopted revised *guidelines on registration requirements to establish interchangeability of multisource (generic) pharmaceutical products*. The guidance includes regulatory requirements for in vitro equivalence testing in the context of the Biopharmaceutics Classification System (BCS) and granting of biowaivers based on the BCS.

After publication of the revised guidance, it was suggested that an appendix on assessing the solubility of APIs would be useful. A proposed appendix, titled *Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the Biopharmaceutics Classification System*, was drafted with the support of an external regulatory expert. The document was introduced and discussed during an informal consultation held in July 2016 and was posted for public comment in August 2016. Most comments received asked for more details to be included. The working document was presented to the Committee for discussion.

Dr Sousa mentioned that a general chapter on equilibrium solubility measurements had recently been adopted for inclusion in the Brazilian Pharmacopoeia.

The Committee adopted the document as an appendix to *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 992, 2015) (Annex 6), subject to amendments agreed. It was also recommended that a general chapter on this topic should be developed for inclusion in *The International Pharmacopoeia*.

Proposal to consider the need for updating guidelines

During an informal consultation on regulatory guidance for multisource products held in July 2016, participants considered that the following guidance texts, which have been published as annexes to the WHO TRS, need updating:

- General regulatory guidance:
  Guiding principles for small national drug regulatory authorities (Annex 6, WHO TRS, No. 790, 1990)
- Guidance related to inspectorates and inspections:
  Inspection of pharmaceutical manufacturers (Annex 2, WHO TRS, No. 823, 1992)

  Guidelines on import procedures for pharmaceutical products (Annex 12, WHO TRS, No. 863, 1996)
- *Inspection of drug distribution channels* (Annex 6, WHO TRS, No. 885, 1999)

  Pre-approval inspections (Annex 7, WHO TRS, No. 902, 2002)

  Quality system requirements for national GMP inspectorates (Annex 8, WHO TRS, No. 902, 2002)

  Specific regulatory guidance:

  Guidelines on packaging for pharmaceutical products (Annex 9, WHO TRS, No. 902, 2002)
- *Guidelines for registration of fixed-dose combination medicinal products* (Annex 5, WHO TRS, No. 929, 2005)

The Expert Committee confirmed the need to update the guidance texts listed above, and recommended that the Secretariat should prepare a database of WHO guidance documents and guidance from partner organizations as a tool for change control.

10. Prequalification of priority essential medicines and active pharmaceutical ingredients

10.1 Update on the prequalification of medicines

Mr Deus Mubangizi gave an update on behalf of PQT. He thanked the Expert Committee for its work in reviewing and adopting the norms and standards that underlie prequalification and pointed out that PQT provides important feedback on its experience with implementation of the guidance. The common standards developed in this way are promoting harmonization across WHO regions in the area of pharmaceutical quality management. Mr Mubangizi gave some examples of the specific tools and procedures used in prequalification, which have had positive spin-offs in regulatory capacity-building, promotion of unified standards and awareness of quality by all stakeholders. He highlighted that the wide consultative approach used in developing these guidelines promotes ownership. This enables the results of prequalification to have equally wide applicability.

Prequalification encompasses vaccines, medicines and in vitro diagnostic products. A work stream on vector control products will be added starting in 2017. In response to public health emergencies, PQT has developed a set of emergency use assessment and listing procedures to expedite access to needed products. Mr Mubangizi noted that prequalification is not intended to replace the regulatory responsibility in Member States either for locally used or for exported products.

The Committee noted the report and expressed its sincere appreciation of this team, and its hope that its continuation will be assured.

10.2 Update on the prequalification of APIs

Ms Helena Martin-Ballestero Zaldivar presented an update about prequalification of APIs, which is performed according to a number of guidance documents, including the guidelines adopted by the Expert Committee. The assessment team is composed of regulatory experts from 12 different countries. Among the four options that can be used to demonstrate API quality in prequalification of finished products, the API master file procedure and prequalification of the API in its own right remain the most popular choices. Over the past six years a shift towards the latter has been observed. To date, a total of 94 APIs has been prequalified and 64 API master files have been accepted. The selection of the starting materials has been a challenge for regulators and industry. The ICH Q11 Questions and Answers document, to which PQT had contributed as an observer to the interim working group, is expected to promote convergence over this matter. Furthermore, ways are being explored to incorporate the new ICH Q3D approach on the control of elemental impurities into the API assessment, as the

elemental impurity content of finished products is often influenced significantly by the APIs. At the financial level, recent changes to the fee structure have increased the costs of API prequalification for manufacturers. PQT is monitoring whether this increase is a barrier to participation.

The Committee noted the report.

11. Nomenclature, terminology and databases

11.1 Quality assurance terminology

The Committee was informed that the Secretariat had updated the collection of terms and definitions included in the guidance documents published in the TRS, up to and including TRS, No. 996 published in 2016.

The Committee noted the report.

11.2 International Nonproprietary Names (INN) for pharmaceutical substances

The Expert Committee heard an update on current INN-related activities. Established in 1953, the INN Programme assigns unique names to new pharmaceutical substances. The names are protected under a World Health Assembly resolution and cannot be registered as trade names. A record number of 119 names was included in the 115th list of proposed INNs, published in June 2016.

Since 2002, regular WHO meetings have been held to address general and specific aspects of nomenclature of biologicals. The rules that are followed to name substances of different classes are becoming more complex with the growing number of biological substances. Biologicals accounted for more than half of all INN applications in 2016 and of the names on the 115th list of proposed INNs. A review on INNs for biological and biotechnological substances was published in 2016. This inventory of the policy decisions taken by the INN Expert Group over the years and the names assigned to biological and biotechnological substances is intended as a living document that will be updated regularly on the website of the INN Programme.

Roughly half of the biological products are monoclonal antibodies. With current naming policies the Programme will run out of possible unique names for these products. A working group has been formed to consider alternative approaches for naming monoclonal antibodies. The nomenclature of advanced therapies will be aligned with existing nomenclature for gene and cell therapies. Naming of vaccine-like substances is also being considered.

The Expert Committee noted the report.

11.3 Revision of guidance on representation of graphic formulae

Guidance on the representation of graphic formulae was adopted many years ago and needs to be updated in line with current conventions. Dr Raymond Boudet-Dalbin of the University of Paris, France, presented some examples of graphic representation of formulae for biological products. He demonstrated that different approaches are used by different pharmacopoeias, resulting in a risk of

confusion and mistakes. There is a need to identify a harmonized approach that can be recommended for use by all organizations.

The Committee thanked Dr Boudet-Dalbin for his presentation and confirmed that harmonization of names and graphical representations of pharmaceutical substances in monographs would be useful. The Expert Committee expressed its support for ongoing work in this regard, which will enable an update of WHO guidance on representation of graphic formulae.

12. Closing remarks

The Chair thanked the Committee members for their active participation and constructive discussions. The Secretary of the Expert Committee added her own thanks to the Chair, the Co-Chairperson and the rapporteurs for their support in holding an efficient meeting, and expressed her appreciation of the participants' tremendous contributions to WHO's standard-setting work.

The Chair closed the meeting and wished the participants a safe journey.

13. Summary and recommendations

The WHO Expert Committee on Specifications for Pharmaceutical Preparations advises the Director-General of WHO in the area of medicines quality assurance. The Expert Committee is composed of members and temporary advisers who are appointed according to a strict selection process, and meets once a year.

The Committee oversees the maintenance of *The International Pharmacopoeia* and provides independent expert recommendations and guidance for use by regulatory authorities in WHO Member States to ensure that medicines meet unified standards of quality, safety and efficacy. The Committee's guidance documents are developed through a broad consensus-building process, which includes a public consultation phase. Representatives from international organizations, non-state actors, pharmacopoeias and relevant WHO departments are invited to the annual meetings to provide updates and input to the Committee's discussions.

At its fifty-first meeting held from 17 to 21 October 2016 in Geneva, the Expert Committee heard updates from the WHO Expert Committee on the Selection and Use of Essential Medicines, the WHO Expert Committee on Biological Standardization, the WHO Member State Mechanism on Substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products, the WHO International Nonproprietary Names (INN) Programme, and the WHO Regulatory Systems Strengthening (RSS) unit. Updates were also presented by representatives from UNICEF, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the Pharmacopoeial Discussion Group (PDG).

Progress updates were presented by the European Directorate for the Quality of Medicines & HealthCare (EDQM) as the custodian centre in charge of International Chemical Reference Substances (ICRS) for use with monographs of *The International Pharmacopoeia*, and by the International Atomic Energy Agency (IAEA) on the development of radiopharmaceutical monographs for *The International Pharmacopoeia*. The Committee was also briefed on the outcomes of the seventh international meeting of world pharmacopoeias, which was co-hosted by WHO and Japan's Ministry of Health, Labour and Welfare/Pharmaceuticals and Medical Devices Agency, and on the results of proficiency testing studies conducted in Phase 6 of the WHO EQAAS. Further progress updates were provided on prequalification of medicines and active pharmaceutical ingredients (APIs), as well as on the prequalification of quality control laboratories (QCLs) and on completed and planned surveys to monitor the quality of medicines circulating on the markets of WHO Member States.

The Expert Committee reviewed new and revised specifications and general texts for quality control testing of medicines for inclusion in *The*

International Pharmacopoeia. The Committee adopted five guidance texts, two appendices to existing guidance texts, one revised definition and 17 pharmacopoeial texts as listed below. The Committee also adopted four new ICRS established by the custodian centre.

The decisions and recommendations made by the Expert Committee at its fifty-first meeting are listed below.

The following guidelines were adopted and recommended for use:

- WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines (Annex 1)
- *The International Pharmacopoeia*: revised concepts and future perspectives (Annex 2) (update)
- Prequalification of quality control laboratories. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies (Annex 3) (update)
- Guidelines on qualification and validation (for publication once Appendices 4, 5 and 6 to this text and the WHO guidance text on heating, ventilation and air-conditioning systems – cross-referenced in lieu of Appendix 1 – have been revised and adopted)
- WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices (Annex 4)
- General background notes on the list of international comparator pharmaceutical products (Annex 5).

Furthermore the Expert Committee adopted the following texts:

- an updated list of international comparator products for equivalence assessment of interchangeable (generic) products for publication on the WHO website as a living document, to be updated on an ongoing basis with new information received;
- guidance on equilibrium solubility experiments for the purpose of classification of APIs according to the Biopharmaceutics Classification System, as an appendix to the WHO guidelines on *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (Annex 7, WHO Technical Report Series, No. 992, 2015) (Annex 6);
- a revised interim definition of the term "stringent regulatory authority".

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

For maternal, newborn, child and adolescent health medicines

- ceftriaxone sodium
- ceftriaxone for injection
- chlorhexidine digluconate solution
- chlorhexidine digluconate topical solution
- medroxyprogesterone acetate (revision)
- medroxyprogesterone injection (revision)

For medicines for tropical diseases

- mebendazole (revision)
- mebendazole chewable tablets
- mebendazole tablets

For other anti-infective medicines

- clindamycin phosphate (revision)
- clindamycin phosphate injection

For other medicines

- methylthioninium chloride (revision)
- methylthioninium injection (revision)

General monographs for dosage forms and associated method texts

- General Chapter 1.11 Colour of liquids (revision)
- General Chapter 2.6 Non-aqueous titration (revision)

General policy

- Note for guidance on organic impurities in APIs and finished products (to replace the note for guidance on *Related substances in dosage form monographs* in the Supplementary information section of *The International Pharmacopoeia*)

The Committee further adopted the workplan for new monographs to be included in *The International Pharmacopoeia*.

International Chemical Reference Substances (ICRS)

The Committee adopted the following two ICRS newly characterized by the custodian centre:

- capreomycin sulfate ICRS 1, with the following note in the leaflet: "The International Chemical Reference Substance for capreomycin sulfate ICRS is intended to be used as described in *The International Pharmacopoeia* for assay by HPLC according to the monographs for capreomycin sulfate and capreomycin for injection. The substance is suitable to serve as a reference for the quantitative determination of the content of capreomycins IA, IB, IIA and IIB from the declared content in capreomycin sulfate RS. **A correlation between the concentration of IA, IB, IIA and IIB and the activity of the substance, determined with microbiological methods, has not been established.**"
- dextromethorphan for system suitability ICRS 1.

The Committee also authorized the clindamycin phosphate for system suitability reference substance established by the EDQM and the medroxyprogesterone acetate for system suitability reference substance established by the EDQM for use with the respective monographs adopted at the meeting.

Recommendations

The Expert Committee made the recommendations listed below in the various quality assurance-related areas.

The International Pharmacopoeia

The Committee recommended that the Secretariat, in collaboration with experts as appropriate, should:

- obtain relevant information from manufacturers of capreomycin API and powders for injection, and conduct a comparison of pharmacopoeial microbiological standards to determine whether the monographs on capreomycin sulfate and capreomycin for injection should be further revised to revert to a microbiological assay;
- conduct a survey on the number of available and missing ICRS for use with monographs of *The International Pharmacopoeia*;
- develop a general chapter on equilibrium solubility measurements for inclusion in *The International Pharmacopoeia*;

- continue development of monographs, general methods and texts and general supplementary information, including radiopharmaceutical monographs developed by IAEA, in accordance with the workplan and as decided at the meeting;
- develop a guidance text on general policies for drafting of monographs, including but not limited to, naming of monographs, designing identity tests and setting of limits in analytical methods.

Quality control – national laboratories

- Circulate the draft revised *WHO model certificate of analysis* for public consultation.
- Circulate the revised *Considerations for requesting analysis of medicines samples* for public consultation.
- Circulate the revised version of the WHO *Draft guidance on testing of "suspect" spurious/falsely-labelled/falsified/counterfeit medicines*

Quality assurance – good manufacturing practices

- Proceed with revising appendices 4 (*Analytical method validation*), 5 (*Validation of computerized systems*) and 6 (*Qualification of systems and equipment*) of the guidelines on validation, as well as the guidelines on heating, ventilation and air-conditioning (HVAC) mentioned below, which are cross-referenced in the validation guidelines in replacement of Appendix 1, to enable adoption of the complete validation guidance package, including all appendices and cross-references.
- Proceed with the revision of the *Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms*, excluding the design and implementation examples and reflecting only the main principles.
- Publish the design and implementation examples from the above-mentioned HVAC guidelines in a separate questions-and-answers document, to be updated as the need arises.
- Proceed with the development of new guidance on good practices for desk review of inspection information, for use by regulatory authorities and the WHO Prequalification Team.

Regulatory frameworks

- Clarify the content of the proposed guidance text on risk-based identification of essential medicines for local manufacturing, including the options to propose that it appears either as "Notes to consider" guidance on pharmaceutical predevelopment aspects or as part of a larger framework on local manufacturing, and circulate the draft text for public consultation with a view to its possible presentation to the Expert Committee.

Regulatory guidance

- Proceed with developing new guidance on a collaborative procedure for the assessment and accelerated national registration of pharmaceutical products approved by stringent regulatory authorities.
- Proceed with the revision of the guidelines on *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products*.
- Proceed with updating one general regulatory guidance text, five guidance texts related to inspectorates and inspections and two specific regulatory guidance texts that were identified as outdated during an informal consultation on regulatory guidance held in July 2016.
- Continue the work on the revision of the "biowaiver" guidance document, including examples of medicines, based on the WHO Model List of Essential Medicines, for which in vivo bioequivalence studies can be waived.
- Maintain the international list of comparator products for equivalence assessment of interchangeable (generic) products.

Nomenclature, terminology and databases

- Find a viable definition of the term "stringent regulatory authority" to replace the interim definition agreed at the fifty-first meeting.
- Continue working towards an update of WHO guidance on representation of graphic formulae.
- Prepare a database of WHO guidance documents and guidance from partner organizations as a tool for change control of guidance texts.

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Annex 1

WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines

1. Introduction

1.1 Background

With the constant increase in the use of herbal medicines worldwide and the rapid expansion of the global market for them, the safety and quality of herbal materials and finished herbal products has become a major concern for health authorities, pharmaceutical industries and the public. The safety and efficacy of herbal medicines largely depend on their quality. Requirements and methods for quality control of finished herbal products, particularly for mixture herbal products, are far more complex than for chemical medicines. The quality of finished herbal products is also influenced by the quality of the raw materials used.

The World Health Assembly resolution on traditional medicine (WHA56.31), adopted in May 2003, requested WHO to provide technical support to develop methodology to monitor or ensure the quality, efficacy and safety of herbal products.

The International Conference of Drug Regulatory Authorities (ICDRA) in 2002 and 2004, as well as the Meetings of National Centres Participating in the WHO Programme of International Drug Monitoring (in 2000, 2001, 2002 and 2003) requested WHO to develop and continuously update the technical guidelines on quality, safety and efficacy of herbal medicines. One of the challenges in analysing the cause of adverse events reported in connection with use of herbal medicines is the lack of expertise in identifying and testing ingredients and constituents of suspect herbal products at the national pharmacovigilance centres, and/or national quality control laboratories.

To reduce the proportion of adverse events attributable to poor quality of herbal medicines, WHO has committed to developing new guidelines on quality assurance and control of herbal medicines, as well as to updating existing ones.

As a follow-up to the WHO Informal Meeting on Methodologies for Quality Control of Finished Herbal Products, held in Ottawa, Canada in July 2001, WHO decided to develop four new documents to provide technical guidance at the key stages where quality control is required in production of herbal medicines:

(1) *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants* (published in 2003) (*1*);

(2) *WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues* (published in 2007) (*2*);

(3) *Good processing practices for herbal materials* (in preparation); and

(4) *Analytical methods for chemical identification of ingredients/ constituents for quality control of herbal medicines* (originally proposed title).

In 2006, WHO revised the *Good manufacturing practices (GMP) supplementary guidelines for manufacture of herbal medicines* (*3*) to take into account the recent update of the WHO core GMP and the fact that many Member States were considering establishing specific GMP for herbal medicines. Subsequently the WHO guidelines on *Good manufacturing practices (GMP) for herbal medicines* were published in 2007 (*4*).

WHO also revised the *Quality control methods for medicinal plant materials* (*5*) updating several chapters relating to determination of major contaminants and residues (e.g. microbial contaminants, toxic heavy metals and pesticide residues) and published it under the title *Quality control methods for herbal materials* (*6*).

1.1.1 Preparation of the document

The original title suggested for these guidelines was *Analytical methods for chemical identification of ingredients/constituents for quality control of herbal medicines*, as mentioned above. In February 2004, WHO convened a working group meeting on quality control of herbal medicines with financial support from Health Canada, in Vancouver, Canada. During this meeting, a brainstorming session was held on how to approach the issue of marker substances in quality assurance and control of herbal medicines. Subsequently, a WHO Consultation on quality control of herbal medicines, held in Abu Dhabi, United Arab Emirates, in July 2005, provided the forum to discuss the working draft of these guidelines. After wide global reviews of subsequent versions of the draft guidelines, the final draft guidelines were reviewed and discussed at the 2nd WHO Consultation on quality control of herbal medicines held in Hong Kong SAR, China, in November 2014. In October 2016, the finalized guidelines were submitted to the fifty-first meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations; the Committee endorsed and adopted the guidelines for publication as an annex to the report of the fifty-first meeting and as an independent WHO publication.

1.2 Objectives

The objectives of this document are to:

1) provide selection criteria for marker substances of herbal origin for quality control of herbal medicines;

2) identify methods and techniques for the identification and assay of these substances;
3) provide examples of selected marker substances in selected herbal materials;
4) contribute to the technical guidance on methodologies for quality control of herbal materials, herbal preparations and finished herbal products, in order to meet the quality control requirements;
5) promote the safety and efficacy of herbal medicines by contributing to consistent and reproducible quality.

1.3 Glossary

The terms used in this document are defined below. Additional terms that may be used in pharmaceutical texts referring to herbal medicines are also included. These terms and their definitions have been selected and adapted from other WHO documents and guidelines that are widely used by the WHO Member States. The citation numbers in parentheses following a term refer to the publication, as listed in the reference list, from which the term has been derived.

These definitions may differ from those included in national regulations, and are therefore provided for reference only.

1.3.1 Terms related to herbal medicines

Medicinal plants are plants (wild or cultivated) used for medicinal purposes (*1*, *3*, *4*).

Medicinal plant materials: see *Herbal materials*

Herbal medicines include ***herbs*** and/or ***herbal materials*** and/or ***herbal preparations*** and/or ***finished herbal products*** in a form suitable for administration to patients (Box A1.1).

Note: In some countries herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (e.g. animal and mineral materials).

Box A1.1
Definition of herbs, herbal materials, herbal preparations and finished herbal products

Herbs are crude plant material which may be entire, fragmented or powdered. Herbs include, e.g. the entire aerial part, leaves, flowers, fruits, seeds, roots, bark (stems) of trees, tubers, rhizomes or other plant parts.

Box A1.1 *continued*

Herbal materials include, in addition to herbs, other crude plant materials. Examples of these other plant materials include gums, resins, balsams and exudates.

Herbal preparations are produced from herbal materials by physical or biological processes.

These processes may be extraction (with water, alcohol, supercritical carbon dioxide (CO_2)), fractionation, purification, concentration, fermentation and other processes. They also include processing herbal materials with a natural vehicle or steeping or heating them in alcoholic beverages and/or honey, or in other materials.

The resulting herbal preparations include, among others, simply comminuted (fragmented) or powdered herbal materials as well as extracts, tinctures, fatty (fixed) or essential oils, expressed plant juices, decoctions, cold and hot infusions.

Finished herbal products consist of one or more herbal preparations made from one or more herbs (i.e. from different herbal preparations made of the same plant as well as herbal preparations from different plants. Products containing different plant materials are called "mixture herbal products").

Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be "herbal".

Substitute is a herbal material or herbal preparation that is replaced by another, appropriately labelled herbal material, or herbal preparation consistent with the national pharmacopoeia, or traditional (or complementary and alternative) medicine practice.

Adulterant is herbal material, a herbal constituent or other substance that is either deliberately or non-intentionally (through cross-contamination or contamination) added to a herbal material, herbal preparation, or finished herbal product.

1.3.2 Terms related to constituents of herbal medicines

Constituents are chemically defined substances or group(s) of substances found in a herbal material or herbal preparations.

Therapeutic activity refers to the successful prevention, diagnosis and treatment of physical and mental illnesses. Treatment includes beneficial alteration or regulation of the physical and mental status of the body and development of a sense of general well-being as well as improvement of symptoms.

Active ingredients refer to constituents with known therapeutic activity, when they have been identified. Where it is not possible to identify the active ingredients, the whole herbal medicine may be considered as one active ingredient.

Constituents with known therapeutic activity are substances or group(s) of substances which are chemically defined and known to contribute to the therapeutic activity of the herbal material or of a preparation (*3*, *4*).

Constituents with recognized pharmacological (biological) activities are characteristic constituents (substances or group(s) of substances) which are chemically defined and where the relevance of the pharmacological (biological) activities for the therapeutic or toxicological effects of the herbal material or herbal preparation has not yet been fully established.

Characteristic constituents are chemically defined substances or group(s) of substances that are specific for one medicinal plant or for certain plant species, families or genera.

Toxic constituents are substances or group(s) of substances that are chemically defined and their toxic property is predominant, although they may contribute to the therapeutic activities of the herbal material or herbal preparation.

1.3.3 Terms related to standardization and quality control of herbal materials and herbal preparations

Reference substances are chemically defined molecular entities (appropriate for intended uses in standardization or quality control of herbs and herbal materials).

Markers (marker substances) are reference substances that are chemically defined constituents of a herbal material. They may or may not contribute to the therapeutic activity. However, even when they contribute to the therapeutic activity, evidence that they are solely responsible for the clinical efficacy may not be available.

Primary chemical reference substances are substances that are widely acknowledged to have the appropriate qualities within a specified context, and whose assigned content when used as a (mostly as an assay) standard is accepted without requiring comparison to another chemical substance (*7*).

Secondary chemical reference substances (also called *working standards*) are substances whose characteristics are assigned and/or calibrated by comparison with a primary chemical reference substance.

The extent of characterization and testing of a secondary chemical reference substance may be less than for a primary chemical reference substance (*7*).

International Chemical Reference Substances (ICRS) are primary chemical reference substances established on the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

They are supplied primarily for use in physical and chemical tests and assays described in the specifications for quality control of medicines published in *The International Pharmacopoeia* or proposed in draft monographs. The ICRS may be used to calibrate secondary standards (*7*).

Certified reference substances are primary reference substances certified by regulatory bodies.

Pharmacopoeial reference substances (standards) are primary reference substances established and distributed by pharmacopoeial authorities following the general principles of the *ISO Guide 34* (*8*).

Note: a different approach is used by the pharmacopoeial authorities to give the user the information provided by certificate of analysis and expiration dates (*7*).

Reference materials refer to materials other than substances appropriate for intended uses in standardization or quality control of herbs and herbal materials. Reference materials include, among others, herbarium samples, authentic specimens of herbal materials (such as extracts and their fractions), herbal reference preparations and authentic spectra or fingerprints.

2. Selection criteria for substances of herbal origin relevant for standardization and quality control of herbal medicines

2.1 General considerations in the standardization and quality control of herbal materials, herbal preparations and herbal medicines

Herbal materials, herbal preparations and finished herbal products are very complex. This can make the identification and quantification of herbal medicines very difficult and the detection of adulteration is very challenging.

It should be emphasized that the identification of herbal medicines using markers, and quantification of marker substances in herbal medicines are not in themselves sufficient to guarantee the quality of herbal medicines. Quality control must cover all steps of their production and must be complemented by good agricultural and collection practices (GACP) and good manufacturing practices (GMP) (such as those described in references *1* and *4*), as appropriate.

Criteria for the selection of reference substances and quality control of herbal medicines should take into account that various ingredients may have different levels of influence on the final quality, safety and efficacy. For this reason, the order of selection of the substances for identification and quantification should follow the rules presented below.

1) If **constituents with known therapeutic activity (activities)** have been identified, they should be used as markers.
2) If 1. is not the case, but **constituent(s) with recognized pharmacological activity (activities) is (are) known**, they should be used as markers.
3) If the above cases are not applicable, the identity and quantity of herbal materials, preparations and medicines may be established by the production process and by analysing marker substance(s) containing other characteristic constituent(s).

Note that identification of herbal materials, and also to some extent herbal preparations and finished herbal products, may be be done or may be complemented by microscopic, macroscopic or DNA analytical methods using appropriate reference materials and descriptions.

2.2 Purpose and expected functions of relevant marker substances

Markers used as chemical reference substances should be international chemical or pharmacopoeial reference substances. If others are used, markers for quantitative determination should be of high purity as required by national regulations, determined by validated analytical methods, including physical and chemical ones. These analyatical methods may be different from those employed for quantifying herbal materials. For markers used for identification, lower purity may be suitable.

The general requirements for markers are:

- identity, specificity and selectivity using the specified analytical method(s);
- should be present in traceable quantity for identification or sufficient quantity for assay;
- should be easily obtained,[1] stable under specified storage conditions;
- should be easily detected and quantified analytically.[1]

[1] This does not apply to substances described under 2.2.4.

2.2.1 Marker substances of constituents with known therapeutic activity[2]

PURPOSE AND FUNCTION

Markers of constituents with known therapeutic activity should serve their appropriate purpose (identification or quantification).

SELECTION CRITERIA

The criteria for selection of a marker substance of constituents with known therapeutic activity are as follows:

- The marker must be readily available (for example, as an international or pharmacopoeial reference substance). New markers may only be selected if no such reference substance is available. In that case, detailed documentation should be provided on the identity and properties of the selected markers.
- It should be relatively easy to separate or distinguish the marker analytically from other structurally similar herbal constituents.
- Markers should be detectable and quantifiable with available analytical instrumental methods (such as thin-layer chromatography (TLC), high-performance thin-layer chromatography (HPTLC), gas chromatography (GC) or high-performance liquid chromatography (HPLC).
- Different marker substances may be selected for the same herbal medicines depending on the analytical instrumental methods available.

Notes

- Derivatives of the naturally occurring markers may be used where the latter are not easy to detect, are not stable or are not easily obtained.
- Different marker substances may be selected for the same herbal materials depending on the different forms of herbal preparations or finished herbal products.
- A group of markers may be selected if a single marker is not sufficient to identify and evaluate the herbal materials or finished herbal products.

[2] They could also be named "reference substances". However, taking the complex nature of all kinds of herbal medicines into account, it is unlikely that one single compound would be solely responsible for the therapeutic action. Thus, substances of constituents with known therapeutic activity are generally also called "markers".

2.2.2 Marker substances of constituents with recognized pharmacological activities

PURPOSE and FUNCTION

Markers of constituents with recognized pharmacological activities should serve as qualitative and quantitative measures in herbal medicines.

SELECTION CRITERIA

The criteria for selection of a marker substance of constituents with recognized pharmacological activities are as follows:

- They occur naturally in sufficient quantities in herbal materials.
- *Markers for quantification*: should be representative of the main therapeutic or pharmacological profiles of the herbal materials and finished products.
- *Markers for identification*: should be specific for one plant or for certain plant species and genera. If not, other marker(s) should be selected for specific identification.
- They should be detectable and quantifiable by available instrumental analytical methods (such as TLC, HPTLC, HPLC, GC) or by another relevant analytical method.
- Different substances may be selected for the same herbal materials depending on the different forms of the herbal preparations (including different, e.g. aqueous and alcoholic extracts) or different therapeutic indications.
- A group of substances may be selected if a single one is not sufficient to evaluate the herbal material or finished herbal product.

2.2.3 Marker substances of characteristic constituents

PURPOSE and FUNCTION

The main purpose of markers of characteristic constituents is identification and quantification of herbal materials in herbal preparations and finished herbal products.

SPECIFIC REQUIREMENTS

Markers for identification:

- The marker should be specific for one plant. If not, the marker should be specific for a certain plant species, genus and family.

  Note: a plant family may contain many classes of biologically diverse species and chemically diverse ingredients, but the plants in the

same genus are normally genetically close and contain structurally similar secondary metabolite constituents.

- If not specific for one plant, the marker should be specific at least for one herbal material or preparation in a mixture herbal preparation or herbal medicines.
- The marker should consist of one substance or group of substances, or characteristic pattern of substances.

  Note: A pattern of substances characteristic for a specific herb may replace a single substance.

Markers for quantification:

- The marker for quantification should be available in sufficient quantity for assay.

SELECTION CRITERIA
The criteria for selection marker substances of characteristic constituents are as follows:

- They should occur naturally in sufficient quantities in herbal materials.
- An authentic reference should be available.
- Spectral data on the substance should be recorded in an available library or database.
- TLC chromatogram pattern or other analytical identification should be illustrated in an available source.
- A simple identification and quantification test should be described for the substance or its chemical class.
- There should be adequate experimental evidence that the substance or group of substances is characteristic of the given herbal medicine.

2.2.4 Marker substances for toxic constituents

PURPOSES AND FUNCTION
Marker substances for toxic constituents are used to define maximum acceptable concentrations of toxic constituents in herbal materials, herbal preparations or finished herbal products.

REQUIREMENTS

- As a consequence of the composition of the herbal material or product, such a limit test is needed.

- There should be a defined upper tolerable limit for the mode of application and posology intended (e.g. oral, topical, inhalation, short-term, subchronic or chronic application).
- A toxicological evaluation is required, but experience with traditional use should be taken into account.
- Genotoxicity, mutagenicity and carcinogenicity should also be considered when establishing toxicity criteria.
- An analytical detection procedure for the established tolerable limits should be available.
- These requirements should always be met by the finished herbal product destined for human use, since processing and conservation may alter toxicity.

SELECTION CRITERIA

- An appropriate reference substance should be available.
- For identity, specificity and selectivity are important characteristics.
- Limit of detection and limit of quantitation values for the target herbal medicines should be specified.
- Highly sensitive instrumental analytical methods (such as TLC, HPTLC, GC, HPLC, GC/mass spectrometry (MS), liquid chromatography (LC)/MS) should be available for detection of toxic substances.
- Simple identification tests for groups of toxic substances, such as alkaloids or terpenoids should be available.

Note: The criteria used for selecting marker substances for toxic constituents apply to detection of a toxic substance specific to a particular herbal material. To ensure its safety for human consumption, the toxic constituents of a herbal material, its herbal preparation or its finished herbal product should be identified accurately.

The toxicity may assessed for control by the absence of a constituent or by establishing and testing allowable tolerable limit(s) for the toxic constituents using selected marker(s) and analytical methods. For example, the absence of thiaminase enzyme activity in horsetail (*Equisetum arvense*) as well as a method for the detection of kavalactone (a hepatotoxic agent) in kava kava (*Piper methysticum*) should be required.

If it is not possible to exclude the toxic effect, e.g. because there is no appropriate marker constituent or because of the lack of an analytical method or specific method of preparation, the herbal material or its herbal preparation should not be used in finished herbal products.

2.3 Use of reference materials

Various types of herbal reference materials are used as complements to analytical methods that were performed using markers and especially when no reference substances for the above-mentioned markers are available. They may also be used when markers are available, but are not adequate for identification of the herbal materials, preparations or finished products.

For example, herbal medicines may contain a group of specified constituents or constituents with recognized pharmacological activities, such as flavonoids, alkaloids and saponins. There are also cases (e.g. well-identified extracts) when the reference material might be more stable than single ingredients with a high degree of purity (primary or secondary reference standards).

PURPOSE AND FUNCTION

Identification and quantification of herbs, herbal materials and herbal medicines.

REQUIREMENTS

- Botanical reference materials and/or herbal preparations should be described by national pharmacopoeias or materia medica (e.g. those of China, Indonesia and Japan).
- Herbarium samples and authentic herbal material for microscopic and macroscopic comparison should be developed in cooperation with botanists for systematic authentication.
- If herbal preparations are used as the reference standard, full documentation on the preparation needs to be submitted to allow full traceability.
- Reference materials should be prepared following methods described in guidelines on validation.

SELECTION CRITERIA

- Herbal reference extracts should be prepared in accordance with standard operating procedures and the characteristic and/or active constituents should be well demonstrated on chromatograms (obtained by instrumental analytical methods such as TLC, high-performance thin-layer chromatography (HPTLC), HPLC, GC) and spectra (such as nuclear magnetic resonance (NMR) or MS) under specified conditions.
- The herbal reference extracts or herbal reference preparations and their main constituents should be stable and identifiable using available analytical instruments and analytical methods.

- There should be predetermined in-house criteria on how to use herbal reference preparations for identification of specified finished herbal products produced by manufacturers.

3. Analytical methods for substances of herbal origin in herbal medicines

This section describes testing methods employed for quality control.

3.1 General considerations regarding the test methods to be employed

Analytical methods used for quality control of herbal materials, herbal preparations and finished herbal products are generally based on:

a) chemical reactions;
b) chromatographic procedures (such as TLC, HPTLC, GC and HPLC), including fingerprinting;
c) spectroscopic and spectrometric methods;
d) a combination of b) and c); and
e) others.

Test methods should be specific and selective for the selected substances in the herbal materials, herbal preparations or finished herbal products. Test methods must be validated. It might be necessary to revalidate the method if the substance is tested at different stages of the production process (e.g. herbal preparations such as extracts and finished herbal products) because other substances, e.g. excipients may influence the analytical procedures.

Test methods, if applicable, should be able to detect substitutes or adulterants that are likely to be present in the sample.

- *Herbal materials, herbal preparations or finished herbal products with constituents with known therapeutic activity*

  The analytical methods used for quality control should be capable of detecting and quantifying the constituents with known therapeutic activity. The use of reference substances for the therapeutically important constituents in the analysis is recommended.

- *Herbal materials, herbal preparations or finished herbal products with constituents with recognized pharmacological activities*

  The analytical methods used for quality control should be capable of detecting and quantifying the constituents with recognized

pharmacological activities. The use of reference substances for the therapeutically important constituents in the analysis is recommended.

- *Herbal materials, herbal preparations or finished herbal products with characteristic constituents (whose pharmacologically or therapeutically active constituents are unknown)*

  When the pharmacological and the therapeutically active constituents are unknown, the identification and assay procedures should be based on characteristic constituents (markers) and fingerprint chromatograms, or on characteristic microscopic or macroscopic features of the herbal materials, herbal preparations or finished herbal products. Reference samples should be used in the analysis, where available.

Where the local laboratory has limited capacity, the use of dependable but simple basic technical and testing methods is recommended. However, the producer should not be discouraged from developing and applying more sophisticated methods for testing products intended for export.

3.2 Monographs

It is recommended that pharmacopoeial monographs prepared by national or regional authorities should incorporate substances and constituents for quality control of herbal materials, herbal preparations or finished herbal products.

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Annex 2

The International Pharmacopoeia: revised concepts and future perspectives

General context and overview

WHO Constitution and World Health Assembly

The quality of pharmaceuticals has been a concern of the World Health Organization (WHO) since its inception. The setting of global standards is requested in Article 2 of the WHO Constitution, which cites as one of the Organization's functions that it should "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products". The World Health Assembly has adopted many resolutions requesting the Organization to develop international standards, recommendations and instruments to assure the quality of medicines, whether produced and traded nationally or internationally. In addition, many national governments financially support the activities of WHO collaborating centres.

Expert Committee and activities related to *The International Pharmacopoeia*

In response to the World Health Assembly resolutions, the WHO Expert Committee on Specifications for Pharmaceutical Preparations, which was originally established to prepare *The International Pharmacopoeia* (Ph.Int.), has made numerous recommendations relevant to quality assurance and quality control of medicines.[1]

The activities related to Ph.Int. are an essential element in overall quality control of pharmaceuticals, contributing to the safety and efficacy of medicines. In contrast to other pharmacopoeias, priority has been given for many years to medicines included in the WHO Model List of Essential Medicines, to those important for WHO health programmes and to those that are not included in other pharmacopoeias, e.g. new antimalarials. Since the inception of the WHO Prequalification of Medicines Team (PQT) in 2001 the Ph.Int. workplans also focus on medicines that are included in the PQT's invitations to submit an Expression of Interest for product evaluation. These first focused on

[1] See, for example, *Quality assurance of pharmaceuticals: WHO guidelines, good practices, related regulatory guidance and GXP training materials*, 2016 (CD-ROM, regularly updated).

antiretrovirals and medicines used in the treatment of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis (TB) and malaria, and were later expanded to other groups of products.

The quality control specifications published in the Ph.Int. are developed independently in accordance with an international consultative procedure. The official procedure for the development of monographs and other texts for *The International Pharmacopoeia* was developed and adopted by the Expert Committee on Specifications for Pharmaceutical Preparations and is updated regularly. The policy is to use state-of-the-art analytical procedures. However, the needs of developing countries are taken into account and, whenever possible, simpler, appropriate alternative methods are also included.

The Ph.Int. undoubtedly strengthens the scientific credibility of WHO.

Revised concepts and future perspectives

The first volume of the first edition of the Ph.Int. was published in 1951 with the aim of harmonizing quality requirements for pharmaceutical substances worldwide. After 65 years of existence, and in the light of new international efforts towards pharmacopoeial harmonization and synergy, it would seem appropriate to propose revised concepts and perspectives for the Ph.Int. This will be realized through WHO's observer status to the Pharmacopoeial Discussion Group (PDG) and the initiation of regular international meetings of world pharmacopoeias with the objectives of preparing guidelines on good pharmacopoeial practices and convergence of methodology and specifications. A more global approach and exploitation of new opportunities for synergies in the area of quality control of pharmaceuticals will contribute to the reduction of costs and thus increase the access to affordable quality medicines worldwide.

Targets and priorities

The ultimate goals are the promotion of good quality pharmaceutical products and the development of quality control methods so as to assure the safety and efficacy of medical treatments worldwide. The Ph.Int. thus supports programmes for the eradication or control of WHO priority diseases, e.g. HIV/AIDS, malaria and TB, by development of appropriate monographs. In addition, monographs for newly developed antimicrobials will be needed to help combat microbial resistance.

The Ph.Int. provides international standards for the identification, content, purity and quality of active ingredients, pharmaceutical products and excipients moving in international commerce. Each monograph must be interpreted in accordance with all the general requirements and testing methods, texts or notices pertaining to it. A product is not of pharmacopoeial quality unless it complies with all the applicable requirements. Moreover, the

underlying principle of a pharmacopoeia is that pharmaceutical substances and products intended for medical use should be manufactured according to good manufacturing practices since quality cannot be tested into a product. The development of monographs in the context of WHO's prequalification activities is a priority. Priority will also be given to those active pharmaceutical ingredients and finished pharmaceutical products that are not covered by any other pharmacopoeia.

Implementation of the guidance on good pharmacopoeial practices and further collaboration with other pharmacopoeias are targeted, for example, through:

- adoption or adaptation of existing standards (with due reference to the source of the text);
- development of a new standard through coordinated consideration (prospective harmonization);
- revision or creation of a standard between two or more pharmacopoeias (bilateral or multilateral harmonization), e.g. through a harmonization initiative of the PDG.

Monographs in the Ph.Int. together with related general methods and notices have an added value as discussed above and can also be used as references in the development of national quality standards as well as for the assessment of registration dossiers.

Setting of specifications and validation of methods

The independence of WHO in setting specifications is of fundamental importance.

Validation of analytical methods is a prerequisite for the publication of monographs and WHO is actively assisted in this task by numerous WHO collaborating centres worldwide.

International Chemical Reference Substances

The establishment of International Chemical Reference Substances (ICRS) is an essential part of quality control. This major task is performed by the custodian centre located in the Council of Europe. This work must be fully supported to ensure the supply of ICRS and thus the success of WHO programmes.

List of priorities

In the context of medicines quality control, the priorities are as follows:

- continuation of the development of international standards for testing pharmaceuticals;

- promotion of global synergy and harmonization in the quality control of pharmaceuticals by strengthening cooperation with world pharmacopoeias, e.g. PDG, agreements, and making use of the opportunities provided by their international meetings;
- increasing the availability of documents and information on WHO activities in quality assurance;
- providing advice to WHO priority programmes on quality assurance matters;
- providing information to WHO Member States on the harmonization process and on collaboration;
- promotion of external quality assurance assessment schemes to improve the performance and recognition of laboratories.

Annex 3

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

Introduction

This document provides an update of the procedure originally published as Annex 12 in World Health Organization (WHO) Technical Report Series, No. 961, 2011. WHO provides United Nations (UN) agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States, on request, with advice on the acceptability, in principle, of quality control laboratories (QCLs) that are found to meet WHO-recommended quality standards for such laboratories. These standards are set out in *Good practices for pharmaceutical quality control laboratories* (GPCL) (*1*), and include, where applicable, good practices for pharmaceutical microbiology laboratories (*2*) and the relevant parts of good manufacturing practices (GMP) (*3*). This is done through a standardized quality assessment procedure. The purpose of the quality assessment procedure is to evaluate whether the QCLs to be used for the quality control of pharmaceutical products meet the requirements recommended by WHO for such laboratories.

Participation in the prequalification procedure is voluntary and any pharmaceutical QCL (governmental or private) providing quality control services for pharmaceutical products to UN agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States is eligible.

Accreditation, such as ISO (in terms of ISO/IEC17025), is encouraged and will also be considered in the prequalification procedure. Laboratories are recommended to work towards obtaining accreditation.

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

- evidence that the laboratory provides or is committed to offering quality control services for pharmaceutical products to UN agencies and their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States;
- a general understanding of the documented quality assurance management and quality control testing activities of the laboratory;
- evaluation of information submitted by the laboratory;
- assessment of compliance with WHO-recommended quality standards for QCLs, i.e. GPCL (*1*), including, where applicable, good practices for pharmaceutical microbiology laboratories (*2*) and the relevant parts of GMP (*3*);
- monitoring of performance of prequalified laboratories.

WHO invites the national medicines regulatory authority (NMRA), having regulatory oversight over a laboratory participating in the prequalification procedure, to join as an observer in the inspection of the laboratory's compliance with WHO-recommended standards for QCLs. WHO recommends that laboratories expressing an interest in participating in the prequalification procedure inform the regulatory authority of the country in which they are established as well as relevant networks (e.g. the official medicines control laboratories network) of their submission for prequalification.

This procedure is to be followed for prequalification of QCLs for use by UN agencies and their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States.

1. Steps of the procedure

WHO requires information related to the activities of, and quality control of pharmaceutical products in, laboratories interested in being assessed under this procedure. Interested QCLs should submit the information about their activities as requested by WHO (see point 1.2 below). In addition to the evaluation of the information submitted, a site inspection (or inspections) may be performed.

If, due to insufficient resources and time constraints, WHO has to set priorities in the assessment of interested laboratories, then priority will be given to QCLs in areas where UN agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States identify the need for testing of the quality of pharmaceutical products.

Applications from laboratories that belong to or are affiliated with a manufacturer of pharmaceutical products, particularly those that have an interest in having one or more of their products prequalified by WHO or whose product(s) is/are already prequalified by WHO, may be given lower priority or may not be evaluated at all.

WHO reserves the right to terminate the quality assessment of a laboratory when the laboratory is not able to provide, or fails to provide, the required information, when the information supplied is inadequate to complete the quality assessment effectively, and when the laboratory fails to collaborate in inspections required by WHO and/or is unable to implement corrective actions that WHO may require within a specified time period.

1.1 Publication of invitation for Expressions of Interest

WHO will publish an invitation to QCLs to submit an Expression of Interest (EOI) to participate in the prequalification procedure. Such an invitation will specify the scope of quality control testing which is subject to prequalification

and will be published widely, i.e. on the WHO website and possibly also through other media, such as the international press. The invitation will be open and transparent, inviting all interested QCLs to submit an EOI for prequalification.

1.2 Submission of EOIs and laboratory information

Each interested laboratory should provide the WHO focal point indicated in the invitation for EOIs with:

- a cover letter expressing interest in participating in the prequalification procedure;
- evidence that the laboratory provides, or is committed to offering, quality control services for pharmaceutical products to UN agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States; and
- the relevant laboratory information.

WHO will record the receipt of the EOI from each laboratory in a register. If the laboratory has documented its quality system as a quality manual, this can be submitted, provided that it is supplemented with the information required for the laboratory information file (LIF) (see below) that is not provided in the quality manual.

The information should be submitted as described in the document *Guidelines for preparing a laboratory information file* (*4*) and cover the areas listed below:

- general information on the laboratory, including activities proposed for prequalification;
- quality management system implemented, and inspections and external audits performed in the laboratory;
- participation in proficiency testing schemes and/or collaborative trials;
- internal audits;
- control of documentation and records;
- personnel;
- premises;
- equipment;
- reagents, reference substances and reference materials;
- subcontracting of testing (where applicable);
- handling of samples;

- validation and/or verification of analytical procedures;
- investigation of out-of-specification (OOS) results;
- stability testing (where applicable);
- microbiological testing (where applicable).

Guidelines for the submission of EOIs and for the preparation and submission of the relevant information are available on the WHO website at http://apps.who.int/prequal/ and will be sent to interested laboratories upon request.

1.3 Screening of submitted laboratory information

The *Guidelines for preparing a laboratory information file* (*4*) will be used in an initial screening of the information supplied. The information will not be evaluated if it is not complete. In such cases the laboratory will be requested to provide additional information within a specified time. If the additional information is not received by the deadline, the application will be rejected.

1.4 Evaluation of the laboratory information

Laboratory information that complies with the requirements set out in section 1.2 will be evaluated in accordance with a standard operating procedure (SOP) established by WHO to ensure uniformity in evaluation of the information. The information will be evaluated against the WHO-recommended quality standards for QCLs, i.e. GPCL (*1*), including, where applicable, good practices for pharmaceutical microbiology laboratories (*2*) and the relevant parts of GMP (*3*), and the laboratory will be considered for a possible site inspection.

A laboratory may submit the report of the inspection or audit performed by a regulatory authority applying standards at least equivalent to WHO-recommended quality standards for QCLs, i.e. GPCL (*1*), including, where applicable, good practices for pharmaceutical microbiology laboratories (*2*) and the relevant parts of GMP (*3*), and the response of the laboratory to the observations made by the authority during inspection or audit.

Based on an SOP established by WHO for review of external inspections and audits, if the laboratory is considered to be operating at an acceptable level of compliance with WHO-recommended standards, WHO may decide that it is not necessary to conduct a site inspection.

1.5 Site inspection

Depending on the outcome of the evaluation of the laboratory information, WHO may plan and coordinate inspections of the laboratory to assess compliance with WHO-recommended quality standards for such laboratories,

i.e. GPCL (*1*), including where applicable good practices for pharmaceutical microbiology laboratories (*2*) and the relevant parts of GMP (*3*).[1] The inspection will be performed by an inspector, or a team of inspectors, having the relevant qualifications and experience in the field of quality control of pharmaceutical products.

External inspectors will be appointed in accordance with an SOP established by WHO and will act as temporary advisers to WHO. The external inspectors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure. A WHO staff member will coordinate the team. The inspector or inspection team will perform the inspections and report on the findings in accordance with SOPs established by WHO to ensure a standard harmonized approach.

A representative or representatives of the NMRA having regulatory oversight over a laboratory participating in the prequalification procedure will be invited to accompany the team as an observer.

With a view to coordinating inspection activities, avoiding duplication and promoting information sharing without prejudice to the protection of any confidential and proprietary information of the laboratory in accordance with the terms of this procedure, WHO may disclose inspection-related information to regulatory authorities of WHO Member States, UN agencies and to the European Directorate for the Quality of Medicines & HealthCare.

1.6 Report and outcome of inspection

The inspector or inspection team will finalize a report describing the findings according to the established WHO SOP and format. The report will be communicated by WHO to the laboratory and a copy will be sent to the NMRA having regulatory oversight over the laboratory.

If any additional information is required, or if a corrective action has to be taken by the laboratory, WHO will postpone its decision on the acceptability of the laboratory concerned until the additional information has been evaluated, or the corrective action has been taken, and found satisfactory. If the decision cannot be made based on the information received, a follow-up inspection will be performed.

In the event of any disagreement between a laboratory and WHO, an SOP for the handling of such disagreements will be followed to discuss and resolve the issue.

As WHO is responsible for the quality assessment procedure, the ownership of the reports lies with WHO (without prejudice, however, to any

[1] Training modules can be found on the WHO Prequalification website (http://apps.who.int/prequal/).

confidential and proprietary information of the laboratory contained in this report). Thus, WHO shall be entitled to use and publish such reports subject always, however, to the protection of any confidential and proprietary information of the laboratory. "Confidential information" in this context means:

- confidential intellectual property, "know-how" and trade secrets (including, e.g. programmes, processes or methods, unpublished aspects of trademarks and patents);
- commercial confidences (e.g. structures and development plans).

Provisions of confidentiality will be contained in the letters exchanged between WHO and the laboratory, to be agreed upon before the evaluation of the information and site inspection.

Notwithstanding the foregoing, WHO reserves the right to share the full reports with the relevant authorities of any interested Member State of the Organization and interested UN agencies.

1.7 Results of assessment

Once WHO is satisfied that the quality assessment process for the laboratory is complete, and that the laboratory is acceptable in principle for use by UN agencies and their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States (i.e. it has been found to meet the WHO-recommended quality standards for QCLs), the laboratory at the specified site will be included in a list referred to as "List of prequalified quality control laboratories".

Laboratories on the list will be considered to be able to test products in compliance with WHO-recommended quality standards for QCLs. Inclusion in the list does not, however, imply any approval by WHO of the laboratories (which is the sole prerogative of national authorities).

Before publication of its name on the list of prequalified laboratories, each laboratory will receive a letter from WHO informing it of the outcome of the quality assessment process for that particular laboratory.

A copy of this letter will be sent to the NMRA of the country where the laboratory is located. The list of prequalified laboratories will be published on the WHO website and will specify the areas of expertise assessed and considered prequalified. The list will be updated whenever new relevant information is obtained.

In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, WHO will – subject to the protection of any confidential and proprietary information – publish WHO Public Inspection Reports on the laboratories considered to meet WHO-recommended quality standards for QCLs. These reports will be published on the WHO website.

1.8 Monitoring of prequalified QCLs

Once the laboratory is included in the list of prequalified QCLs, it should inform WHO without delay about the implementation of any changes that may have an impact on the prequalification of the laboratory (such as changes to facility, equipment or key personnel) and should submit an updated LIF.

Each prequalified QCL will be re-evaluated at regular intervals (annually) or earlier, when information indicating the necessity for re-evaluation is obtained by WHO.

To enable WHO to carry out re-evaluation, all prequalified laboratories are requested to submit a brief annual report on their activities. The report should cover all activities related to quality control of pharmaceutical products within the preceding three years and should be submitted by the end of March of the subsequent year. The following items should be included in the report:

- a summary of services provided to UN agencies and their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States;
- a summary of number of samples analysed, differentiating between compliant and noncompliant samples including any OOS/out-of-trend investigations;
- a list of analytical methods used;
- a summary of complaints received from customers concerning results of analyses performed by the laboratory;
- brief details of participation in proficiency testing schemes (organizing party, methods involved, outcomes and, if appropriate, corrective measures adopted);
- listing of inspections and audits performed by external parties, identifying the party and the scope of the inspection and audit;
- in the case that changes have been implemented, which have an impact on the content of the LIF, a summary of these changes should be included in the report and an updated LIF should be attached.

WHO will conduct re-inspections of prequalified laboratories in accordance with SOPs established by WHO. The frequency of such re-inspections depends on WHO's assessment of the quality risk management factors described below. Normally, however, such re-inspections will take place at least once every three years. The following factors will be taken into account when planning inspections:

- major changes, e.g. to premises, equipment or key personnel;

- the results of previous inspection(s)/audit(s) by WHO or another external party, and history of compliance of the laboratory with WHO-recommended quality standards;
- the outcomes of participation of the laboratory in proficiency testing schemes;
- number and significance of complaints made known to the QCL by customers;
- laboratory experience with testing of pharmaceutical products;
- WHO experience with testing services provided by the laboratory.

WHO reserves the right to proceed with the re-inspection of a prequalified laboratory at any time this is considered necessary based on information or complaints received by WHO. The NMRA that has regulatory oversight over the laboratory will be invited to participate in the re-inspection as an observer.

WHO may suspend or withdraw a prequalified QCL from the list of prequalified QCLs when there is evidence of noncompliance with the WHO-recommended quality standards for such laboratories and/or this procedure.

The re-evaluation of the prequalification status of a QCL may not be prioritized if the laboratory has not, for a continuous period of more than three years, provided quality control services for pharmaceutical products to UN agencies, their partners, procurement agencies serving national authorities and UN agencies and/or national authorities of WHO Member States. In such cases, WHO will request the QCL to provide evidence that such services had been offered to, or commitments made to continue to offer such services, to UN agencies, their partners, procurement agencies serving national authorities and/or national authorities.

1.9 Monitoring of complaints

Complaints concerning the results of analysis of pharmaceutical products performed by the prequalified laboratory or concerning the service provided by the prequalified laboratory, which are communicated to WHO, will be investigated in accordance with an SOP established by WHO. The NMRA that has regulatory oversight over the laboratory will be invited to participate in the investigation of the complaint.

After conducting its investigation, WHO will provide a written report of the problem, which may, where appropriate, include recommendations for action to the laboratory under investigation and to the NMRA having the regulatory oversight over the laboratory.

1.10 Cost recovery

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

1.11 Confidentiality undertaking

WHO will require any external inspectors (acting as temporary advisers to WHO) to treat all information to which they gain access during the inspections of the laboratory, or otherwise in connection with the discharge of their responsibilities in regard to the prequalification procedure, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set out below.

Such inspectors will be required to take all reasonable measures to ensure that confidential information:

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

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

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

1.12 Conflict of interest

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

of interest is correct and complete, and that he/she will immediately notify WHO of any change in this information.

All external inspectors furthermore agree that, at the laboratory's request, WHO will advise the laboratory in advance of the identity of each inspector and the composition of the team performing the site inspection and provide curricula vitae of the external inspectors. The laboratory then has the opportunity to express possible concerns regarding any of the external inspectors to WHO prior to the visit. If such concerns cannot be resolved in consultation with WHO, the laboratory may object to an external inspector's participation in the site visit. Such an objection must be made known to WHO by the laboratory within 10 days of being notified of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel its agreement with the inspector in question and the activities to be undertaken by that inspector, in whole or in part.

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Annex 4

WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices

Acronyms and abbreviations

AHWP	Asian Harmonization Working Party
ASEAN	Association of Southeast Asian Nations
ATMP	advanced therapy medicinal products
CAB	conformity assessment body
CLSI	Clinical and Laboratory Standards Institute
FSCA	field safety corrective action
GDP	good distribution practice
GHTF	Global Harmonization Task Force
GMDN	Global Medical Device Nomenclature
IEC	International Electrotechnical Commission
IMDRF	International Medical Device Regulators Forum
ISO	International Organization for Standardization
IVD	in vitro diagnostic medical device
NRA	national regulatory authority
QMS	quality management system
SF[1]	substandard and falsified medical products
SUMD	single-use medical device
UN	United Nations
UNFPA	United Nations Population Fund
US FDA	United States Food and Drug Administration
WHO	World Health Organization
WHA	World Health Assembly

[1] The Member State mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products has recommended the World Health Assembly to adopt a simplified terminology for substandard and falsified (SF) medical products (EB140/23, Annex, Appendix 3 (dated 10 January 2017)).

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[2] Secretary-General, Council for International Organizations of Medical Sciences (CIOMS), Geneva, Switzerland from 18 April 2016.

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1. Introduction

Medical devices contribute to the attainment of the highest standards of health for individuals. Without medical devices, common medical procedures – from bandaging a sprained ankle, to diagnosing HIV/AIDS, implanting an artificial hip or any surgical intervention – would not be possible. Medical devices are used in many diverse settings, for example, by laypersons at home, by paramedical staff and clinicians in remote clinics, by opticians and dentists and by health-care professionals in advanced medical facilities, for prevention and screening and in palliative care. Such health technologies are used to diagnose illness, to monitor treatments, to assist disabled people and to intervene and treat illnesses, both acute and chronic. Today there are an estimated 2 million different kinds of medical devices on the world market, categorized into more than 22 000 generic devices groups.[3]

In May 2007, the first resolution on health technologies was adopted by the World Health Organization (WHO) World Health Assembly (WHA) (WHA 60.29), which set out the framework for an unprecedented focus on health technologies, but more specifically on medical devices. In 2014, the WHA adopted a resolution regarding regulatory system strengthening for medical products (WHA 67.20). The Resolution states "effective regulatory systems are an essential component of health system strengthening and contribute to better health outcomes".

In the context of Resolution 67.20, the growing interest in medical devices in the global health community and the lack of regulatory systems for medical devices in many countries, WHO decided to develop this document. It is intended to provide guidance and support to WHO Member States that have yet to develop and implement regulatory controls relating to medical devices, as well as to jurisdictions that are continuing to improve their regulatory frameworks as they take steps to ensure the quality and safety of medical devices available in their countries. This WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices (IVDs) (hereafter referred to as the Model) will provide a basis for such work.

[3] The Global Medical Device Nomenclature Agency has listed more than 22 000 generic device groups for medical devices (*Source*: GMDN Agency).

Many countries have neither the financial resources nor the technical expertise to transition successfully from an unregulated market to a comprehensive medical devices law in a single programme. Instead, the Model recommends a progressive, or stepwise, approach to regulating the quality, safety and performance of medical devices. It provides guidance for a staged development of the regulatory system. This starts from basic-level controls – such as the publication of the law and resourcing the regulatory authority to undertake enforcement actions – then progresses to expanded-level controls – such as inspection of registered establishments and oversight of clinical investigations.

The resources – people, funds, technology and facilities – available in any country for regulatory control of medical devices are, and probably always will be, limited. Generally, such resources will be allocated to support overall government policy objectives and priorities but will also reflect the characteristics of the national market for medical devices: public health needs and burden of disease; demographic trends; economic development; size of the country; sources of supply (e.g. primarily imported versus domestic sources); and nature of devices on the market.

More broadly, it should be understood that regulation of medical devices does not take place in isolation, but should be coordinated with regulation of other medical products (e.g. medicines and vaccines) and wider government policy objectives.

1.1 The WHO Global Model Regulatory Framework for Medical Devices including IVDs

The Model recommends guiding principles, harmonized definitions and specifies the attributes of effective and efficient regulation, to be embodied within binding and enforceable law. Its main elements refer to international harmonization guidance documents developed by the Global Harmonization Task Force (GHTF) and its successor, the International Medical Device Regulators Forum (IMDRF).

The Model is particularly relevant for WHO Member States with little or no regulation for medical devices currently in place but with the ambition to improve this situation. It foresees that such countries will progress from basic regulatory controls towards an expanded level to the extent that their resources allow. The Model is written for the legislative, executive and regulatory branches of government as they develop and establish a system of medical devices regulation. It describes the role and responsibilities of a country's regulatory authority for implementing and enforcing the regulations. Also, it describes circumstances in which a regulatory authority may either "rely on", or "recognize" the work products from trusted regulatory sources (such as scientific assessments, audit and inspection reports) or from the WHO Prequalification Team.

Section 2 of this document recommends definitions of the terms "medical devices" and IVDs. It describes how they may be grouped according to their potential for harm to the patient or user and specifies principles of safety and performance that the device manufacturer must adhere to. It explains how the manufacturer must demonstrate to a regulatory authority that its medical device has been designed and manufactured to be safe and to perform as intended during its lifetime.

Section 3 presents the principles of good regulatory practice and enabling conditions for effectively regulating medical devices. It then introduces essential tools for regulation, explaining the function of the regulatory entity and the resources required.

Section 4 presents a stepwise approach to implementing and enforcing regulatory controls for medical devices, as the regulation progresses from a basic to an expanded level. It describes elements from which a country may choose according to national priorities and challenges. Also, it provides information on when the techniques of reliance and recognition may be considered and on the importance of international convergence of regulatory practice.

Section 5 provides a list of additional topics to be considered when developing and implementing regulations for medical devices. It explains the relevance of these topics and provides guidance for regulatory authorities to ensure they are addressed appropriately.

1.2 Limitations of the WHO Global Model Regulatory Framework for Medical Devices including IVDs

The Model outlines a general approach but cannot provide country-specific guidance on implementation. While it does not offer detailed guidance on regulatory topics it contains references to relevant documents where further information may be found. It does not detail responsibilities of other stakeholders such as manufacturers, distributors, procurement agencies and health-care professionals, all of whom have roles in assuring the quality, safety and performance of medical devices.

2. Definition, classification, essential principles and conformity assessment of medical devices

2.1 Definition of medical device and IVD

The GHTF developed a definition of the terms medical device and IVD. Major jurisdictions have accepted the principles of this definition. In the interest of international regulatory convergence it is recommended to promote its widespread use.

Medical device[4,5] means any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury;
- investigation, replacement, modification or support of the anatomy or of a physiological process;
- supporting or sustaining life;
- control of conception;
- disinfection of medical devices;
- providing information by means of in vitro examination of specimens derived from the human body,

and which does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means (*1*).

IVD[6] means a medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes (*1*).[7]

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[4] Note from GHTF definition (http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n071-2012-definition-of-terms-120516.pdf#search): Some jurisdictions include "accessories to a medical device" and "accessories to an IVD medical device" within their definitions of "medical device" or "IVD medical device", respectively. Other jurisdictions do not adopt this approach but still subject an accessory to the regulatory controls (e.g. classification, conformity assessment, quality management system requirements, etc.) that apply to medical devices or IVD medical devices.

[5] Spare parts, supplied for the replacement of existing components of a medical device that has already been registered, are not usually considered to be medical devices unless they are likely to significantly change the characteristics or performance of the finished device. If this is the case then such spare parts are likely to be considered medical devices in their own right and therefore may require regulatory control.

[6] Tests that provide information on the predisposition to a medical condition or a disease (e.g. genetic tests) and tests that provide information to predict treatment response or reactions (e.g. companion diagnostics) are IVDs.

[7] Note 1 from GHTF definition (http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n071-2012-definition-of-terms-120516.pdf#search): "IVD medical devices include reagents, calibrators, control materials, specimen receptacles, software and related instruments or apparatus or other articles and are used, for example, for the following test purposes: diagnosis; aid to diagnosis; screening; monitoring; predisposition; prognosis; prediction; determination of physiological status." Note 2: In some jurisdictions, certain IVDs may be covered by other regulations.

There may also be products on the market that are similar to medical devices in function and risk that do not fit within these definitions. For reasons of protecting public health they are regulated as if they were medical devices. Examples include: impregnated bed nets to protect against malaria-bearing mosquitoes; personal protective devices to avoid cross-infection; lead aprons to protect against radiation; some medical gases; and implantable or other invasive products for a cosmetic rather than a medical purpose (see section 5).

2.1.1 Glossary

For the purposes of this document, the following definitions and descriptions apply. They may have different meanings in other contexts.

accessory to an IVD medical device. An article intended specifically by its manufacturer to be used together with a particular IVD medical device to enable or assist that device to be used in accordance with its intended use (*1*).

accessory to a medical device. An article intended specifically by its manufacturer to be used together with a particular medical device to enable or assist that device to be used in accordance with its intended use (*1*).

accreditation. The term applied to third party attestation related to a conformity assessment body conveying formal demonstration of its competence to carry out specific conformity assessment tasks (*2*).

adverse event. Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device (*3*).

analytical performance. The ability of an IVD medical device to detect or measure a particular analyte (*4*).

assessment. A systematic, independent and documented process for obtaining assessment evidence and evaluating it objectively to determine the extent to which assessment criteria are fulfilled.

audit. A systematic, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled (*5*).

authorized representative. Any natural or legal person established within a country or jurisdiction who has received a written mandate from the manufacturer to act on his or her behalf for specified tasks, with regard to the latter's obligations under that country or jurisdiction's legislation (*6*).

certification. The term applied to third party attestation related to products, processes, systems or persons (*2*).

clinical evaluation. The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer (*7*).

clinical investigation. Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device (*7*).

clinical performance. The ability of an IVD medical device to yield results that are correlated with a particular clinical condition/physiological state in accordance with target population and intended user (*4*).

conformity assessment. The systematic examination of evidence generated, and procedures undertaken, by the manufacturer, under requirements established by the regulatory authority, to determine that a medical device is safe and performs as intended by the manufacturer and, therefore conforms to the Essential principles of safety and performance for medical devices (*32*).

conformity assessment body (CAB). A body, other than a regulatory authority, engaged in determining whether the relevant requirements in technical regulations or standards are fulfilled (*32*).

convergence (regulatory). Represents a process whereby the regulatory requirements across countries or regions become more similar or "aligned" over time as a result of the gradual adoption of internationally-recognized technical guidance documents, standards and scientific principles, common or similar practices and procedures, or adaptation of regulatory mechanisms, that might be specific to a local legal context but that align with shared principles to achieve a common public health goal. It does not necessarily represent the harmonization of laws and regulations, which is not a prerequisite for allowing the alignment of technical requirements and greater regulatory cooperation (*9*).

corrective action. Action to eliminate the cause of a detected nonconformity or other undesirable situation (*10*).

declaration of conformity. The manufacturer's written attestation that it has correctly applied the conformity assessment elements relevant to the classification of the device (*32*).

distribution chain. A collective term for local manufacturers, authorized representatives, importers and distributors established within the jurisdiction.

distributor. Any natural or legal person in the supply chain who, on their own behalf, furthers the availability of a medical device to the end-user (*6*).

enforcement. Action taken by an authority to protect the public from products of suspect quality, safety and effectiveness or to assure that products are manufactured in compliance with appropriate laws, regulations, standards and commitments made as part of the approval to market a product (*11*).

field safety corrective action (FSCA). An action taken by a manufacturer to reduce or remove a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market (*12*).

generic device group. Aset of devices having the same or similar intended purposes or commonality of technology allowing them to be classified in a generic manner not reflecting specific characteristics (*13*).

governance. Refers to the different ways that organizations, institutions, businesses and governments manage their affairs. Governance is the act of governing and thus involves the application of laws and regulations, but also of customs, ethical standards and norms. Good governance means that affairs are managed well, not that the laws, regulations or norms are themselves necessarily "good" (*14*).

guidelines/guidance documents. Non-statutory advisory publications intended to assist those parties affected by legislation to interpret requirements.

harm. A physical injury or damage to the health of people or damage to property or the environment (*15*).

harmonization (regulatory). The process by which technical guidelines are developed to be uniform across participating authorities (*9*).

hazard. A potential source of harm (*15*).

health-care facility. Any party within the country providing health-care services.

health technologies. Refers to the application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures and systems developed to solve a health problem and improve quality of lives (*16*).

importer. Any natural or legal person in the supply chain who is the first in a supply chain to make a medical device, manufactured in another country or jurisdiction, available in the country or jurisdiction where it is to be marketed (*6*).

inspection. An on-site evaluation by a regulatory authority of a manufacturing facility to determine whether such manufacturing facility is operating in compliance with regulatory requirements and or commitments made as part of the approval to market a product (*11*).

instructions for use. Information provided by the manufacturer to inform the device user of the medical device's intended purpose and proper use and of any precautions to be taken (*17*).

intended use/purpose. The objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer (*18*).

in vitro diagnostic (IVD) medical device. A medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes (*1*).

IVD for self-testing. Any IVD medical device intended by the manufacturer for use by laypersons (*19*).

label. Written, printed or graphic information either appearing on the medical device itself, or on the packaging of each unit, or on the packaging of multiple devices (*17*).

labelling. The label, instructions for use and any other information that is related to identification, technical description, intended purpose and proper use of the medical device, but excluding shipping documents (*17*).

law. Binding and enforceable legislation passed by a legislative body.

layperson. Individual who does not have formal training in a specific field or discipline (*17*).

life cycle. All phases in the life of a medical device, from the initial conception to final decommissioning and disposal.

listing. The process whereby a party submits information to the regulatory authority in a jurisdiction, regarding the identification of a medical device(s) that is or will be supplied to the market in that jurisdiction (*20*).

manufacturer. Any natural or legal person with responsibility for design and/or manufacture of a medical device with the intention of making the medical device available for use, under its name; whether or not such a medical device is designed and/or manufactured by that person himself or herself or on his or her behalf by another person(s) (*6*).

Note: This "natural or legal person" has ultimate legal responsibility for ensuring compliance with all applicable regulatory requirements for the medical devices in the countries or jurisdictions where it is intended to be made available or sold, unless this responsibility is specifically imposed on another person by the regulatory authority within that jurisdiction.

market surveillance. The activities carried out and measures taken by public authorities to ensure that products comply with the requirements set out in legislation and do not endanger health, safety or any other aspect of public interest protection (based on EU Council Directive EC No 756/2008 of 9 July 2008 concerning the requirements for accreditation and market surveillance relating to the marketing of products and repealing Regulation (EEC) No 339/93) (*21*).

medical device. Any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury;

- investigation, replacement, modification or support of the anatomy or of a physiological process;
- supporting or sustaining life;
- control of conception;
- disinfection of medical devices;
- providing information by means of in vitro examination of specimens derived from the human body,

and which does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means (*1*).

medical products. A term that includes medicines, vaccines, diagnostics and medical devices (*22*).

placing on the market. All controls applied by the regulatory authority to the manufacturer and/or authorized representative at the stage of, and as a condition of, making available an individual medical device with a view to its distribution and/or use within the jurisdiction.

postmarket controls. All controls applied by the regulatory authority to the manufacturer and/or authorized representative after a manufacturer's medical device has been placed on the market or put into service.

postmarket surveillance. The activities carried out and measures taken by a regulatory authority to ensure that medical devices placed on the market comply with regulations and do not endanger health, safety or any other aspect of public health (based on EU Council Directive 93/42/EEC of 14 JUNE 1993 concerning medical devices) (*23*).

premarket controls. All controls applied by the regulatory authority to the manufacturer and/or the authorized representative before the manufacturer's medical device may be placed on the market or put into service.

primary legislation. A form of law, created by a legislative branch of government, consisting of statutes that set out broad outlines and principles and may delegate authority to an executive branch of government to issue secondary legislation.

quality management system. The organizational structure, responsibilities, procedures, processes and resources for implementing quality management. For the purpose of these guidelines "implementing quality management" is taken to include both the establishment and maintenance of the system (*24*).

recall. Any measure aimed at achieving the return of a product that has already been made available to the end-user (based on EU Council Directive EC No 756/2008 of 9 JULY 2008 concerning the requirements for accreditation and market surveillance relating to the marketing of products and repealing Regulation (EEC) No 339/93) (*21*).

recognition. The routine acceptance by the regulatory authority in one jurisdiction of the regulatory decision of another regulatory authority or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B. Recognition may be unilateral or multilateral, and may be the subject of a mutual recognition agreement (*25*).

refurbishing. A systematic process of rebuilding or restoring that ensures safety and effectiveness of the medical equipment without significantly changing the equipment's or system's performance safety specifications and/or changing intended use as in its original registration (*26*).

registration. The process by which a party submits information to the regulatory authority in a jurisdiction, regarding the identification and establishment location(s) of the manufacturer and other parties, responsible for supplying a medical device(s) to the market in that jurisdiction (*20*).

regulation. A written instrument containing rules having the force of law.

regulatory authority. A government body or other entity that exercises a legal right to control the use or sale of medical devices within its jurisdiction, and that may take enforcement action to ensure that medical products marketed within its jurisdiction comply with legal requirements (*8*).

reliance. The act whereby the regulatory authority in one jurisdiction may take into account and give significant weight to – i.e. totally or partially rely upon – evaluations performed by another regulatory authority or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others (*25*).

reprocessing. The process carried out on a used medical device in order to allow its safe reuse including, where appropriate, cleaning, disinfection, sterilization and related procedures, repackaging, relabelling, as well as testing and restoration of the technical and functional safety of the used device based on proposal for amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 of 26 September 2012 concerning medical devices (*27*).

risk. The combination of the probability of occurrence of harm and the severity of that harm (*15*).

secondary legislation. A form of law, issued by an executive branch of government, specifying substantive regulations and procedures for implementing them. The power to pass delegated legislation is defined and limited by the primary legislation that delegated those powers.

serious adverse event. Adverse event that:

a) led to a death;

b) led to a serious deterioration in the health of the subject that either
   1) resulted in a life-threatening illness or injury;
   2) resulted in a permanent impairment of a body structure or a body function;
   3) required inpatient hospitalization or prolongation of existing hospitalization;
   4) resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function;
c) led to fetal distress, fetal death or a congenital abnormality or birth defect (*3*).

serious injury (also known as serious deterioration in state of health) is either:

- life-threatening illness or injury;
- permanent impairment of a body function or permanent damage to a body;
- a condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure (*28*).

single-use medical device. A medical device intended by the manufacturer to be used on an individual patient during a single procedure and then disposed of (*17*).

standard. A document, established by consensus and approved by a recognized body, that provides, for common and repeated use, rules, guidelines or characteristics for activities or their results, aimed at the achievement of the optimum degree of order in a given context (*29*).

substandard/spurious/falsely-labelled/falsified/counterfeit medical products. There is currently no universally agreed definition of what used to be widely known as "counterfeit medicine". Pending negotiation among Member States, WHO will continue to use the term substandard/spurious/falsely-labelled/falsified/counterfeit medical products (*30*).

technical documentation. The documented evidence, normally an output of the quality management system that demonstrates the medical device complies with the relevant principles of safety, performance and labelling specified through legislation (*32*).

user. The person, either professional or lay, who uses a medical device. The patient may be the user (*17*).

vigilance. A process whereby a manufacturer records and investigates any adverse event report it receives, taking field safety corrective action where necessary, and informing the regulatory authority of those that meet criteria specified through legislation. The regulatory authority may monitor the investigation.

World Health Assembly. The forum through which the World Health Organization is governed by its 194 Member States.

2.2 Medical devices classification and classification rules

The universe of medical devices is diverse with wide variations in potential severity of harm to the patient or user. This Model recommends that the regulatory authority allocates its resources and imposes controls proportional to the potential for harm associated with medical devices.

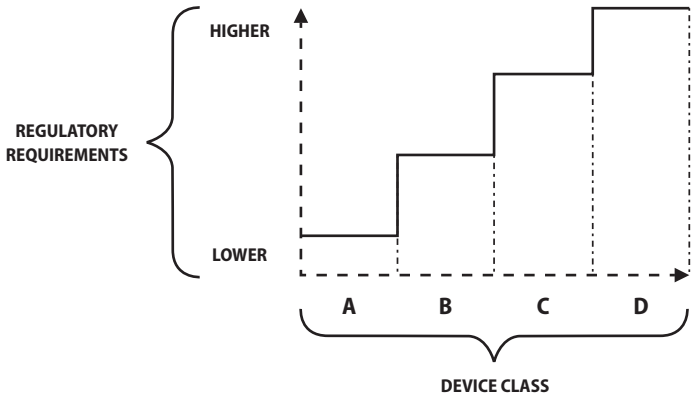
The regulation specifies the manner in which a manufacturer should demonstrate conformity with safety, performance and quality requirements. The regulatory oversight by the authority should increase in line with the potential of a medical device to cause harm to a patient or user (i.e. the hazard it presents). The risk class of a medical device is determined by factors such as the level of invasiveness and the duration of use in the body. In some jurisdictions, products such as viral inactivation devices used in the manufacture of medicinal or biological products are deemed to be higher risk medical devices and are regulated accordingly. The risk class of an IVD is determined primarily by the impact of an incorrect result, either on the health of the individual or on public health. A classification system for medical devices and IVDs guides the regulatory controls to be implemented for each device class.

It is widely accepted that medical devices are separable into groups or classes, typically four, A, B, C and D, by applying a set of classification rules (*18*), and specifying separately the different conformity assessment procedures that should apply to each group of devices (Figure A4.1).

The classification rules for medical devices other than IVDs depend on the features of the device, such as whether it:

- is life supporting or sustaining;
- is invasive and if so, to what extent and for how long;
- incorporates medicinal products;
- incorporates human or animal tissues or cells;
- is an active medical device;
- delivers medicinal products, energy or radiation;
- could modify blood or other body fluids;
- is used in combination with another medical device.

Figure A4.1
Impact of device classification on regulatory scrutiny



Note: As the regulatory requirements increase, so does the scrutiny by the regulatory authority.
Source: Reproduced from *Principles of medical devices classification* (*18*).

Classification also takes into account the technical, scientific and medical expertise of the intended user (layperson or health-care professional).

For IVDs, the risk classification depends both on the risk for the individual and for public health, taking into consideration:

- the intended use (including what is detected, the IVD function, the specific disorder, condition or risk factor of interest that the IVD is intended to detect, define or differentiate, and the testing population);
- the intended user;
- the importance of the information to the diagnosis, screening, monitoring or staging of disease (sole determinant or one of several);
- the impact of the test result on the individual and/or on public health.

The GHTF has published documents on the classification of medical devices and IVDs that use the principles above to establish classification rules (*18*, *19*). Additionally, the regulatory authority may develop explanatory guidance to help a manufacturer apply the rules (*31*). While the manufacturer has the primary obligation to classify its medical device, its decision may be challenged by the regulatory authority.

Table A4.1 shows examples of medical devices according to their risk class.

Table A4.1
Examples of medical devices by risk class[a]

Class	Risk	Examples
A	Low	Syringes, examination gloves, patient hoists, stethoscopes, wheelchairs, IVD instruments, microbiological culture media
B	Low–moderate	Surgical gloves, infusion sets, pregnancy tests
C	Moderate–high	Condoms (unless with spermicide (class D)), infusion pumps, neonatal incubators, therapeutic and diagnostic X-ray, lung ventilators, haemodialysers, anaesthesia equipment, self-test glucose strips, IVDs for the diagnosis of *Neisseria gonorrhoea*
D	High	Implantable cardioverter defibrillators, pacemakers, breast implants, angioplasty balloon catheters, spinal needle, IVDs for the diagnosis of HIV, hepatitis C or hepatitis B

[a] The actual classification of each device depends on the claims made by the manufacturer for its intended use and the technology or technologies it utilizes. As an aid to interpreting the purpose of each rule, illustrative examples of medical devices that should conform to the rule have been provided in the table above. However, it must be emphasized that a manufacturer of such a device should not rely on it appearing as an example but should instead make an independent decision on classification taking account of its particular design and intended use.

2.3 Essential Principles of safety and performance

Regulations should specify that a medical device should be safe and perform as intended when placed on the market. GHTF has established a list of Essential Principles of safety and performance for medical devices including IVDs (*8*). These requirements have been widely adopted. Manufacturers must be able to demonstrate to the regulatory authority that their product complies with the Essential Principles and has been designed and manufactured to be safe and perform as intended during its lifetime, when used according to the manufacturer's stated intended purpose. The general Essential Principles apply to all medical devices and are supplemented by those principles specific to particular medical device types (e.g. implants or electrically powered devices).

The general Essential Principles of safety and performance for medical devices include the following.

- The processes for the design and production should ensure that a medical device when used according to the intended purpose and meeting the conditions of technical knowledge and training of the

user is safe and does not compromise the clinical condition of the patient or the health of the user.

- The manufacturer should perform a risk assessment to identify known and foreseeable risks and to mitigate these risks in the design, production and use of the medical device.
- Medical devices should perform as the manufacturer intended when used under normal conditions.
- Performance and safety should not be affected during the lifetime of a medical device in such a way that it affects the safety of the patient or the user.
- Performance and safety should not be affected by transport or packaging and storage, provided the instructions for packaging, transport and storage are followed.
- Known and foreseeable risks should be weighed against the benefits of the intended purpose.

Ensuring that a medical device conforms to all relevant Essential Principles (*8*) is the responsibility of the manufacturer. However, the manufacturer's evidence of conformity, recorded in its technical documentation, may be subject to review by the regulatory authority, either before or after market introduction. The medical device regulation shall specify the extent of the regulatory authority's involvement with different classes of device (*31*). While retaining responsibility for the decisions it makes, the regulatory authority may appoint one or more conformity assessment bodies (CABs)[8] to assist it in this task (see section 4).

2.3.1 Clinical evidence for non-IVDs

One of the requirements of the Essential Principles is that "the device will perform as intended by the manufacturer and not compromise the clinical condition or the safety of patients". Clinical evidence is important to demonstrate these requirements. It is a component of the technical documentation of a medical device, which together with other design verification and validation documentation, device description, labelling, risk analysis and manufacturing

[8] Certain technical elements of the regulatory framework may be delegated to "designated" or "recognized" CABs. For example, they may be approved to perform initial certification and surveillance audits of a device manufacturer's quality management system (QMS) and/or premarketing evaluation of device conformity with the Essential Principles. Satisfactory compliance with requirements is typically confirmed by the CAB issuing a design examination or QMS audit certificate. Based on the CAB's evaluation the regulatory authority may make final decisions on compliance. The CAB performs its evaluation under the oversight of the regulatory authority and may be subject to periodic assessments by that authority.

information, is needed to allow a manufacturer to demonstrate conformity with the Essential Principles. In deciding whether to authorize a medical device, the regulatory authority may consider the acceptance of data from clinical investigations conducted outside its jurisdiction, provided that the applicant has demonstrated that the data are adequate and were obtained in accordance with applicable global standards.

Some technologies have been available for many years and their clinical safety and performance have been well characterized. Many devices, however, utilize new technology that has had little prior application in the diagnosis or treatment of humans and for which safety and clinical performance have not yet been established.

For long-established technologies, clinical investigation data that might be required for novel technologies may not be necessary. The available clinical data in the form of literature, reports of clinical experience, postmarket reports and adverse event data for previous versions of the device may, in principle, be adequate to establish the safety and performance of the device, provided that new risks have not been identified, and that the intended use(s)/purpose(s) has/have not changed. The manufacturer should perform a documented comprehensive evaluation of all the available clinical evidence under the control of its quality management system (QMS). That clinical evaluation report becomes part of the technical documentation for the device and may serve as the basis for determining whether a new clinical investigation is appropriate (*32*). A widely used international standard for the practice of clinical investigation is ISO 14155:2011 – *Clinical investigation of medical devices for human subjects – Good clinical practice* (*34*).

2.3.2 Assessing conformity to the Essential Principles

To a large extent the quality, safety and performance of a medical device are determined by systematic controls applied by the manufacturer to its design, development, testing, manufacture and distribution over the device's life cycle. In general, the manufacturer does this through implementation of a QMS. The degree of assessment of the QMS by the regulatory authority or CAB depends on the medical device risk class (*31*) (see section 4) (Table A4.2).

Table A4.2
Conformity assessment processes as determined by device class

Conformity assessment element	Class A	Class B	Class C	Class D
Quality management system (QMS)	Regulatory audit normally not required, except where assurance of sterility or accuracy of the measuring function is required.	The regulatory authority should have confidence that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to marketing authorization.	The regulatory authority should have confidence that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to marketing authorization.	The regulatory authority should have confidence that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to marketing authorization.
Technical documentation[a]	Premarket submission normally not requested.	Not normally reviewed premarket. The regulatory authority may request and conduct a premarket or postmarketing review sufficient to determine conformity with Essential Principles.	The regulatory authority will undertake a review sufficient to determine conformity with Essential Principles prior to the device being placed on the market.	The regulatory authority will undertake an in-depth review to determine conformity with Essential Principles, prior to the device being placed on the market.
Declaration of conformity	Submission normally not requested.	Review and verify compliance with requirements by the regulatory authority (see footnote to Table A4.1).	Review and verify compliance with requirements by the regulatory authority (see footnote to Table A4.1).	Review and verify compliance with requirements by the regulatory authority (see footnote to Table A4.1).

[a] There are many terms used to describe a product's technical documentation. The terms include technical file, standard technical documentation, design dossier, product design dossier, product summary file and product master file.

Depending on the class of the medical device, the evidence of conformity may be subject to regulatory assessment by the regulatory authority or CAB.

Class A medical devices, except those that are sterile or have a measuring function, are usually notified by the manufacturer to the regulatory authority by listing before being placed on the market and are generally not subject to premarket on-site QMS audits. Class A medical devices do not require premarket submission of technical documentation, but the manufacturer is required to maintain technical documentation demonstrating conformity with the Essential Principles. The regulatory authority may, at its discretion, require submission of a summary of the technical documentation and/or other evidence of conformity with the regulatory requirements.

For medical devices in all classes, the regulatory authority or CAB should have sufficient evidence to demonstrate the conformity of the manufacturing site(s) with the QMS requirements. For Class A devices, this would generally be on the basis of the manufacturer's declaration of conformity. For devices in Classes B and C, the regulatory authority can generally rely upon assessments and audits conducted by other recognized regulatory authorities or a CAB, when such audits have been done. For Class D devices, the regulatory authority or CAB may supplement such reliance with its own QMS audits. In all cases, the regulatory authority or CAB should retain the enforcement power and discretion to conduct its own QMS audits.

For medical devices in Classes C and D, the premarket assessment usually includes a review of the summary technical documentation. This would typically comprise a device description, the Essential Principles checklist, the risk management report, information on design and manufacturing, clinical evidence, product verification and validation and labelling. The regulatory authority should specify whether summarized or detailed information should be submitted; typically for Class D devices detailed information would be needed, while Class C devices may require only summary information. The regulatory authority could rely upon or recognize the work of another regulatory authority but the final responsibility lies with the national regulatory authority (NRA). For all classes of devices the manufacturer should prepare, hold and be prepared to submit as required a declaration of conformity that the device complies fully with all regulatory requirements (*32*).

2.4 Special considerations for regulation of IVDs

According to the Model, IVDs must comply with regulatory requirements similar to those for other medical devices. However, there are some differences that require consideration. This section discusses those differences and proposes steps to address them.

2.4.1 Classification of IVDs

As for other medical devices, risk-based classification provides a basis for allocating and prioritizing resources in assessment of the IVDs supplied in a particular market. There are a large number and variety of IVDs available, with varying impact on the diagnosis and treatment of patients. The higher the risk associated with an IVD, the more stringent the assessment should be. Unlike other medical devices, the risk associated with an IVD is indirect and is related to the risk of an incorrect diagnosis, to both the patient being examined and the population in general. For instance, an undiagnosed patient with a serious infectious disease can put a whole community at risk.

Because of the different risk profile, the classification rules developed for other medical devices on the basis of interaction with the body are not suitable for IVDs. The GHTF has published a document that provides a classification scheme for IVDs, based on risk to the individual and to public health (*19*). The highest risk IVDs are those that may impact on public health, in terms of detection of infectious disease, or in determining the safety of blood or blood products for transfusion or tissue for transplantation. The IVD classes in ascending order of risk are:

- A – low individual risk;
- B – low public health risk and/or moderate individual risk;
- C – moderate public health risk, but high individual risk;
- D – high individual risk and high public health risk.

The importance of the result of the IVD in making a diagnosis is also a factor; a higher risk class is assigned where the IVD is the sole determinant in making a diagnosis.

2.4.2 Essential Principles of safety and performance for IVDs

The GHTF has developed additional Essential Principles that apply to IVDs (*8*). While the Essential Principles are similar in nature for each product type, the different conditions of use of IVDs require more specific wording in some cases and more detailed explanation in others. Values assigned to calibrators and controls of IVDs need to be traceable to available reference measurement procedures and/or available reference materials of a higher order (ISO 17511:2003).

The main differences are that the Essential Principles for IVDs:

- do not cover incorporation of substances considered to be a medicine as even if these substances are present, there is no effect on the human body;

- place less emphasis on the need for veterinary controls on animals used as the source of biological material, as the risk of transmissible spongiform encephalopathy infection is reduced due to the mode of use of IVDs;
- include a requirement for the design to ensure that performance characteristics support the intended use;
- do not include requirements in relation to protection against ionizing radiation, since this is not a function of IVDs;
- have more limited requirements in relation to electrical safety and supply of energy, since IVDs do not connect to, or supply energy to the patient;
- include requirements for IVDs for self-testing;
- include requirements for performance evaluation of the IVD (whereas clinical evaluation is appropriate for non-IVD medical devices).

In developing and implementing a regulatory system, jurisdictions are advised to adopt the GHTF Essential Principles specific to IVDs, in addition to those for other medical devices.

2.4.3 Clinical evidence for IVDs

Clinical evidence for an IVD is all the information that supports the scientific validity and performance for its use as intended by the manufacturer. It is an important component of the technical documentation of an IVD, which together with other design verification and validation documentation, device description, labelling, risk analysis and manufacturing information, is needed to allow a manufacturer to demonstrate conformity with the Essential Principles. Clinical evidence includes analytical performance, clinical performance and clinical validity data.

In relation to collection of clinical data for IVDs, a considerable amount of information on performance is gained from analytical performance studies carried out using human specimens. This changes the risk profile of a clinical study as compared to clinical investigations for medical devices to be used on human patients. The application of ISO 14155:2011 – *Clinical investigation of medical devices for human subjects – Good clinical practice* (*34*) is therefore not suited to IVDs. A standard specific to IVDs is being developed by the ISO Technical Committee 212 (*35*).

2.4.4 Lot verification testing of IVDs

Some countries that have yet to implement effective regulation for medical devices but need to import high-risk (Class D) IVDs, may implement a system of lot verification of such IVDs before they are put into service. The objective of lot

verification testing is to verify that each lot supplied meets its safety, quality and performance requirements and that transport and/or storage conditions have been well controlled so as not to affect the performance of the IVD. The need for lot verification testing depends upon the other controls in place in the importing country and the extent of premarket evaluation conducted. Where there are stringent controls on transport and storage, and the receiving laboratory has in place an effective quality control programme that will detect problems in the performance of a new batch on arrival, lot verification testing may not be needed.

The regulatory authority may designate a national reference laboratory or other recognized laboratory that is assigned the overall responsibility for coordinating and conducting lot verification testing on its behalf.

3. Enabling conditions for effective regulation of medical devices

Public confidence in medical devices requires effective and efficient regulation built upon a sound legal and policy foundation, as well as good regulatory practices. WHO is developing *Good regulatory practices: guidelines for national regulatory authorities for medical products* (*25*). The general principles therein should be applied when establishing a new, or revising an existing, system of regulating medical devices and IVDs. They include:

- a foundation in law;
- consistency;
- effectiveness;
- efficiency;
- impartiality;
- clarity;
- transparency;
- flexibility.[9]

3.1 Legal requirements

Medical device regulation must have a sound basis in law. There is no single approach to the legal foundation of such a regulatory framework since it depends on the national constitution and existing general national legal and administrative systems within the country.

[9] Regulations should not be prescriptive; they should allow flexibility in responding to a changing regulatory environment and different or unforeseen circumstances.

The law should define the products within its scope and identify the entities subject to regulation. It should create a general requirement that only medical devices that are safe, perform as intended, and are of appropriate quality, may be marketed or made available for use in the jurisdiction. The law should delineate the responsibilities of the regulatory authority and establish its enforcement powers to include removing products from the market as well as imposing penalties. It should establish mechanisms for the accountability of the executive, judicial and legislative branches of government. It should address coordination with other bodies such as the justice ministry and the police and customs authorities. In countries with decentralized systems the respective powers and coordinating roles of the central regulatory authority and authorities in the political subunits will have to be defined.

The law should establish the responsibilities of manufacturers, importers, distributors and authorized representatives. Where a regulatory authority is delegated to an independent administrative agency there should be clear lines of political oversight and accountability, e.g. through the ministry of health. The legal framework should also provide scope for administrative and enforcement discretion that allows the regulatory authority to apply the principles of "reliance" and "recognition" (see also section 4), taking into account assessments and decisions by authorities in other jurisdictions when taking its own regulatory actions. The law should accommodate a transition from basic to expanded regulatory controls to the extent that resources allow as experience is gained. It should also allow the regulatory authority to respond to public health emergencies in an appropriate and timely manner.

The authority should adhere to good regulatory practices such as creating opportunities to obtain and review meaningful public comment on proposals, assessing regulatory impacts, allowing reasonable transition periods and adopting requirements that are proportionate and offer the least burdensome ways of achieving policy goals. The provisions of laws, regulations and guidelines should be as transparent, predictable and internally consistent as possible. Measures should be non-discriminatory, so that all similarly situated parties are treated in the same way and that decisions are taken without regard to national origin of a medical device or to the source of financing or the sector of the health-care system where it is used (e.g. whether primary, secondary, tertiary or emergency health care; whether delivered through a public, private or military facility).

3.2 Gap analysis of existing controls

It is important at an early stage to evaluate any existing regulatory controls that apply to medical devices. This will allow the policy-maker to understand both the steps and resources needed to achieve national public health goals and to develop regulatory capacity. A gap analysis is helpful in assessing the degree

to which national regulations are aligned with international guidance and best practices.

The authority should conduct a gap analysis and seek the views of interested parties, including patient representatives. The results of that assessment will aid in setting priorities for implementation. For example, in a country with little or no domestic production, it may be appropriate to focus first on import controls, rather than on manufacturing controls; in a country with a high prevalence of sexually transmitted diseases, it may be prudent to give priority to regulatory controls for medical devices used in the prevention, diagnosis and treatment of those diseases. Box A4.1 lists elements to be considered in a gap analysis.

Box A4.1

Non-exhaustive list of elements to be considered in the gap analysis for medical device regulation

- Are medical devices regulated at all?
- Are they currently regulated as medicines or some other product category?
- Is there a specific and sound legal foundation for regulation of medical devices?
- What is the public health risk in the country, associated with medical devices?
- Is there a clear definition of the term "medical device" and does it match with the definition recommended by this Model?
- Is there a NRA with clear powers and responsibilities for medical devices?
- Do the regulators have the proper competencies required for effective implementation and enforcement?
- Where there is a published regulation, is it enforced and does the regulatory authority have sufficient resources, expertise and funding to perform its duties?
- What proportion of medical devices are imported and from where?
- Are there local manufacturers of medical devices? If so, are their activities regulated and how?
- Are all relevant stakeholders adequately represented?
- Are distributors and importers subject to appropriate controls?
- Is there evidence that SF[a] medical devices have been placed on the market?
- Do existing laws and regulations comply with international good practices and treaty obligations?

[a] The Member State mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products has recommended the World Health Assembly adopt a simplified terminology for substandard and falsified (SF) medical products (EB140/23, Annex, Appendix 3 (dated 10 January 2017)).

3.3 Implementation plan

Once national legislation on medical devices has been adopted, the appointed regulatory authority should adopt and publish a plan for its implementation. The plan will be driven by public health priorities and needs and by the availability of resources, including trained competent staff to implement legislation.

The plan should include time for promoting awareness, drafting proposals for implementing regulations and seeking feedback from the public and other affected parties. Appropriate transition periods should be defined to allow industry to comply with new or amended requirements. The plan should also address how medical devices already in the market, in the distribution chain, or in use will be handled, e.g. allowing well-defined exemptions and transition provisions. The regulatory authority should hold meetings and publish guidance to ensure that medical device manufacturers, importers, distributors and purchasers are aware of their responsibilities, thereby avoiding disruption in the supply of medical devices during the transition period.

3.4 Monitoring implementation

At the time of development of the regulatory implementation plan, goals and performance indicators should be established to allow progress of implementation to be assessed against a baseline that represents the current status of medical devices regulation. Progress towards those goals should be reported to the legislature, parliament and the public. Such reports will contribute to transparency and political accountability. They may also be used to evaluate adequacy and use of resources. Progress made may be used to help determine the timing of future steps in implementing the regulatory framework. If expanded-level controls are established it may be appropriate to include performance measures such as timely response by the authority in monitoring the manufacturer's response to quality defects and serious injury associated with the use of medical devices. Other, more general, performance assessments may include periodic consultations with interested parties such as medical device users, patient representative groups and industry. Ultimately, the public and parliament or legislature will want to see that their confidence in the regulatory authority and its use of resources is justified.

3.5 Regulatory authority

Implementation of the medical device law will require the appointment of a NRA, with the ability to exercise independent decision-making within the regulatory framework. That regulatory body may be either within an existing government department such as the ministry of health, or an independent administrative agency accountable to a ministry. The governance of the authority should be defined, together with appropriate checks and balances and a requirement to publish periodic public reports on performance. In countries

where the law (or decree) consists of statutes setting out broad outlines and principles only, it must delegate power to the regulatory authority to issue secondary legislation (also known as statutory instruments or implementing acts), specifying substantive requirements and procedural regulations for implementing them. It should also provide the necessary enforcement powers.

While retaining in full the responsibilities placed upon it by the law, the regulatory authority may designate CABs to assist it in carrying out some of its duties. In this situation the legislation will include requirements for appointing a CAB, setting the scope of its responsibilities and monitoring performance. Although the CAB may perform some evaluation functions, the final decisions and enforcement powers remain with the regulatory authority.

3.6 Funding the regulatory system

Implementation of the regulatory system will require trained staff, infrastructure, facilities and information technology (IT). Resources allocated should be consistent with activities mandated in the law, with a legal provision enabling them to be increased as the regulatory system moves from the basic level to expanded-level controls. The pre-implementation gap analysis should include an assessment of the financial resources required. Consistent with its financial policies and legislative intent, a country may choose to fund all regulatory activities from public funds, or from a mixture of public funds and fees collected from the regulated industry. If user fees are imposed, they should be predictable, transparent, non-discriminatory, reasonable in relation to the services rendered and subject to periodic review. One way for the regulatory authority to increase efficiency and thereby reduce costs is to take into account the outputs (e.g. reports) and decisions of regulatory authorities in other jurisdictions in reaching its own decisions, i.e. reliance or recognition, as appropriate. Permission for the regulatory authority to impose fees for selected activities should be established through the medical devices law.

Costs of doing business, both direct (e.g. through paying user fees) and indirect (e.g. the regulatory burden of compliance with local requirements), may have an influence on whether medical devices are introduced to a particular market. If the costs of compliance appear disproportionately high compared with the potential of a market, or if regulatory requirements are not harmonized with those of other countries, manufacturers and importers may be discouraged from offering their products and that may impede achievement of national public health goals.

3.7 Conflict of interest and impartiality

Public confidence in the integrity of the regulatory authority and its actions is essential. The authority and its staff, advisory committees and third parties

should be seen to act consistently, impartially and transparently. Actual or perceived lack of impartiality of regulatory decisions can lead to unfair and unjust competitive advantages for parties in the medical device sector as well as a lack of confidence in medical devices supplied to the market. This can be prevented by the adoption and consistent adherence to a code of conduct by all members of staff. This code should provide a framework for decisions and actions and allow for public and legislative scrutiny of the authority. Staff must avoid situations where there may be a conflict, real or perceived, between their private interests and the public good. Leaders in the organization must set the tone by good example in their own conduct.

3.8 Regulatory competencies and resources

The practice of regulating medical devices effectively and efficiently requires appropriate individual expertise, reinforced by the institutional capacity of the regulatory authority, to act according to good regulatory practices. General competencies for regulatory professionals include an understanding of public health principles, analytical and communication skills, information handling and skills in effective intervention and crisis management (*36*). These competencies are needed even where the regulatory authority relies on or recognizes regulatory decisions of other jurisdictions. Additional specific competencies include essential knowledge of the regulatory system for medical devices, the responsibilities of the regulator, the concepts of international standards and harmonization, and an understanding of a range of different device technologies and their application (*37*).

For each stage of implementing the regulatory system a sufficient transition period should be established: this allows the regulatory authority to ensure it has sufficient qualified and trained staff, appropriate resources and adequate information systems for the increased responsibilities and functions. The regulatory authority requires legal support to interpret its responsibilities under the law, particularly in respect of monitoring, enforcement and safeguarding activities. In addition IT and administrative resources are required.

The basic-level regulatory controls would require general technical expertise on medical devices, whereas the expanded-level controls would require some regulatory staff to have more specific technical expertise. As the regulatory system and its implementation become more comprehensive, additional resources will be required.

In view of the importance of the manufacturer's QMS, the authority should recruit and train staff members with experience in that field. Such staff may inspect or audit manufacturers, authorized representatives, importers and distributors. These skills should allow the regulatory authority to provide appropriate oversight and control throughout the life cycle of the medical device. When elements of the regulatory framework are delegated to designated

or recognized third-party organizations (generally known as CABs (see section 4.3.1.2)), authorities should have competent regulatory staff to assess compliance by the CAB with the relevant requirements (*38*).

Given the diverse nature of medical devices, the regulatory authority should, according to the priorities in regulating specific medical devices, over time, recruit technical staff members with a variety of appropriate expertise (*39*). A career path, professional development and recognition of the value of regulating medical devices as a profession, may be important in recruiting and retaining staff.

Even advanced or well-resourced regulatory authorities find it impractical to have all their experts in-house. Instead they create advisory committee(s), consisting of independent experts in a variety of fields to advise in specific technical areas. The process of nominating advisers and creating an advisory board should be transparent and open to the public. Particular attention must be paid to the impartiality of members and the exchange of confidential information. The regulatory authority remains responsible for the decision based on the advice. Performing a basic-level assessment of the authority's current regulatory competencies and capacities gives insight into the identified gaps in regulatory systems and related functions. Guidance can be sought from the WHO global benchmarking tool for national regulatory authorities (under development), the *Global competency self-assessment* of the Regulatory Affairs Professionals Society (RAPS) (*40*), and the IMDRF *Good regulatory review practices – competence, training, and conduct requirements for regulatory reviewers* (under development). According to the gap analysis, initial and continuing training of medical devices regulators according to a training plan should be implemented.

4. Establishing a stepwise approach to regulating medical devices

4.1 Stepwise approach

This Model recommends establishing a regulatory system for medical devices taking a staged or stepwise approach – from basic to expanded controls. The regulatory framework must be sustainable, expandable and accommodate advances in clinical practices, public health needs and evolving technologies. The basic controls will form the foundation for the expanded controls. In order to promote international regulatory convergence and harmonization, this Model encourages countries to adopt the principles recommended in internationally harmonized technical guidance into their legislation (*41*).

Basic regulatory controls fall into three broad groups:

- those applied before a medical device is placed on the market;

- those applied when placing the device on the market;
- those applied after the device has been placed on the market.

The stepwise approach will allow the regulatory authority to respond to national public health priorities and to progressively develop the capacity, knowledge and experience required. This approach helps the regulatory authority determine the resources needed for further implementation. Without effective implementation of basic controls, the elements of expanded controls will be of limited value and difficult to manage effectively.

The regulatory authority has the opportunity to reduce the demands on its own staff by either relying upon or recognizing the work or decisions made by another medical devices regulatory authority. Resources may then be targeted to postmarket controls, which are the responsibility of the NRA. Furthermore, the regulatory authority will indirectly gain knowledge of the regulatory status in other jurisdictions of devices placed on its national market. As a regulatory authority subsequently implements expanded-level controls, emphasis will shift to premarket controls such as authorizing devices to be placed on the market, while continuing to rely upon or recognize the work of other jurisdictions, where appropriate.

4.1.1 Reliance and recognition

The law should establish to what extent the regulatory authority may reasonably use the work of regulatory authorities in other jurisdictions in assessing evidence that a device conforms to national requirements. The two main examples of these techniques are:

- *Reliance*. This is the process whereby a regulatory authority may take into account and give significant weight to (i.e. rely upon) assessments[10] performed by another regulatory authority or other trusted institution in reaching its own decision. For example, another regulatory authority authorizes a medical device to be placed on its own market and the NRA uses this information, possibly supplemented with information from the manufacturer, to reach its own decision.
- *Recognition*. This is the routine acceptance by the regulatory authority of an importing country of the regulatory *decision* of another regulatory authority or other trusted institution that evidence of conformity with the regulatory requirements of that

[10] In this document "assessment" is used in relation to medical devices in the same sense as "evaluation" is used for some other medical products.

country is sufficient evidence of conformity with the regulatory requirements of the importing country. For example, a regulatory authority or CAB audits a manufacturer and issues it with a QMS certificate. The NRA of the importing country accepts certificates issued by another authority as proof of compliance with its own QMS requirements.

In order for the regulatory authority to decide whether to use either the reliance or recognition option, it must have a clear understanding of the regulatory system that applies within the country where the medical device is manufactured. For example, medical device regulations in some jurisdictions permit a manufacturer to specify some devices as "export only" and only subject these to minimal controls rather than evaluating conformity of such a medical device with its own regulatory requirements. This places responsibility on the regulatory authority of the importing country and may make reliance and recognition inappropriate. Reliance and recognition are not appropriate for the assessment of specific requirements, such as language of labelling and electrical supply that do not apply in the exporting country.

Note that sometimes devices may have different configurations (regulatory versions) for different markets; these may vary in aspects such as the intended use, site of manufacture, power supply, labelling language and applied quality control, among others. It is therefore important to ensure that when relying on assessment outcomes by entities in other jurisdictions, the regulatory version is not substantially different from the product version that is proposed for placing on the market. Specifically for IVDs, the use of reliance or recognition as mechanisms for marketing authorization is complex. This is because of the wide variance in classification of IVDs in existing regulatory systems (which determines the level of regulatory scrutiny). For instance, the current European system requires independent assessment for the high-risk IVDs (Annex II of the EU Directive 98/79/EC on in vitro diagnostic medical devices, lists A and B) (*42*). This means that most IVDs bearing a CE mark are self-assessed by the manufacturer and have not been subject to scrutiny by a European CAB (known as a notified body). This is another example where knowledge of the regulatory system upon which reliance or recognition is based is important.[11]

In general, where a regulatory authority seeks to rely upon information from a counterpart in another jurisdiction, it must first establish confidence in the counterpart authority and reach agreement on the exchange of confidential

[11] All regulations are subject to occasional revision and this could affect the application of the reliance or recognition procedure. Importing countries must be alert to any such plans of the exporting jurisdiction and take them into account when relying upon or recognizing a regulatory decision of that jurisdiction.

information (*43*). The same considerations apply to the outsourcing of any activities, for example to CABs and third-party experts (locally or internationally based).

4.1.1.1 National responsibilities

There are certain regulatory activities that, by their nature, are inherently only within the competence of the national authority. Examples include import controls; registration of domestic manufacturers, importers, distributors and authorized representatives; handling reports of adverse events, including vigilance reports; market surveillance activities; and communication and monitoring of field safety corrective actions (FSCA). Reliance and recognition are not appropriate to these activities.

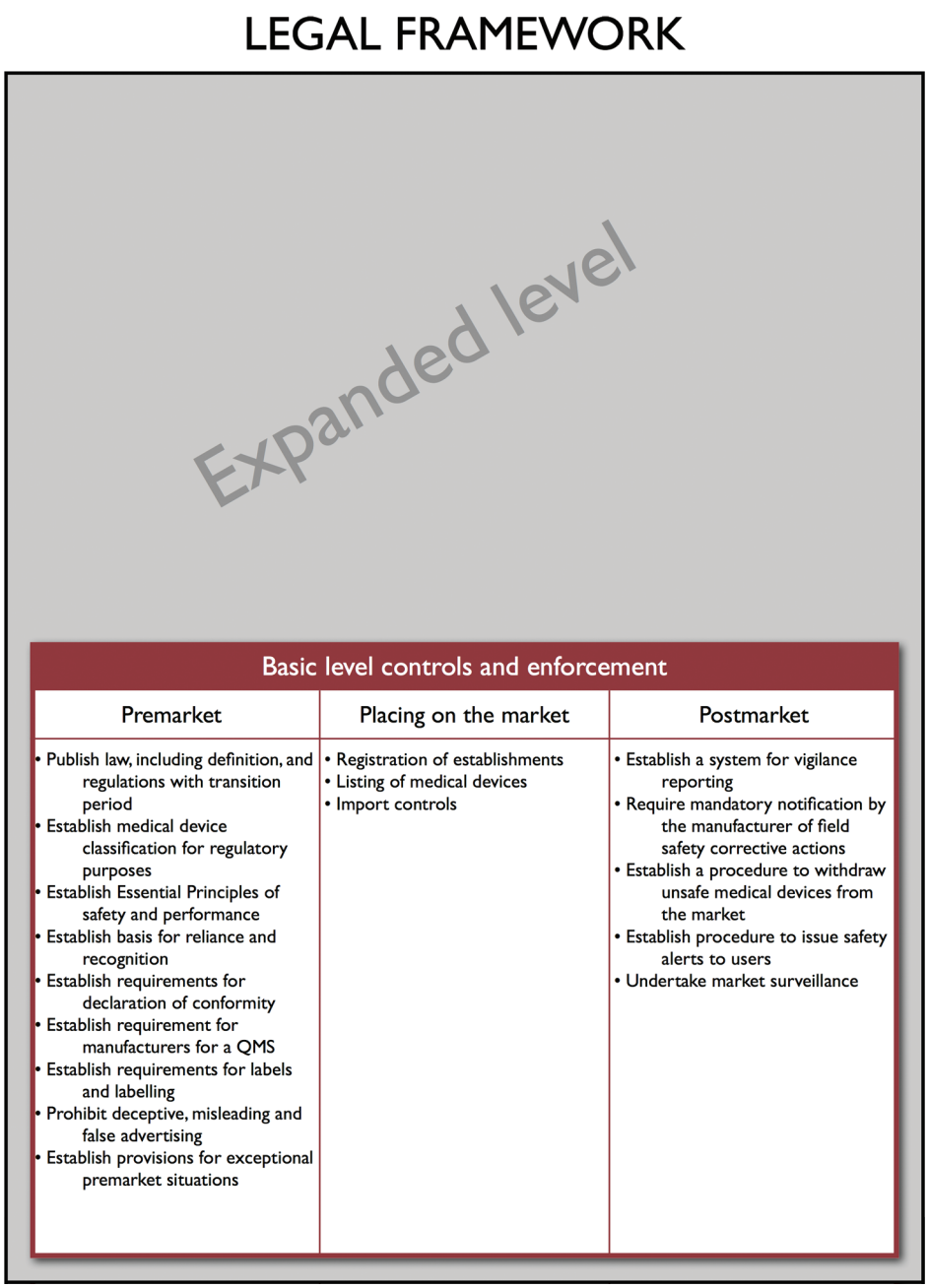
4.1.1.2 International collaboration

Where resources permit, the regulatory authority should participate in formal and informal information-sharing networks with other regulatory authorities. This will often allow earlier detection of a potential problem than would be possible within a single jurisdiction. It also facilitates reliance upon and confidence building with other regulatory authorities.

4.2 Basic-level controls and their enforcement

The Model recommends that basic-level controls are incorporated into a medical devices law that determines the scope of regulation, stipulates the responsibilities of the regulatory authority, describes conditions under which a medical device can be placed on the market, requires certain organizations to be registered, establishes import controls and requires postmarket surveillance activities. Typically the postmarket activities would include a system to act proportionately to reports of quality defects and serious adverse events associated with medical devices (Figure A4.2).

Figure A4.2
Basic-level controls and enforcement for medical devices within the legal framework



Basic level controls and enforcement		
Premarket	Placing on the market	Postmarket
• Publish law, including definition, and regulations with transition period • Establish medical device classification for regulatory purposes • Establish Essential Principles of safety and performance • Establish basis for reliance and recognition • Establish requirements for declaration of conformity • Establish requirement for manufacturers for a QMS • Establish requirements for labels and labelling • Prohibit deceptive, misleading and false advertising • Establish provisions for exceptional premarket situations	• Registration of establishments • Listing of medical devices • Import controls	• Establish a system for vigilance reporting • Require mandatory notification by the manufacturer of field safety corrective actions • Establish a procedure to withdraw unsafe medical devices from the market • Establish procedure to issue safety alerts to users • Undertake market surveillance

4.2.1 Publish law, including definition, and regulations with transition period

The national law for medical devices will set out principles and broad requirements and delegate authority to the regulatory authority (see Appendix). In particular it will:

- define the products and parties within its scope, in particular the terms medical device and IVD, using harmonized definitions (*1*);
- ensure the regulatory framework is capable of adapting to new technologies and treatment modalities;
- designate the NRA, its enforcement powers, market oversight responsibilities, powers to issue implementing regulations and to take action where the health of patients or users is compromised, and the responsibility for publishing guidance documents to aid understanding of legal requirements;
- provide the regulatory authority with administrative and enforcement discretion for reliance upon and recognition of the work or decisions of regulatory authorities in other jurisdictions (see 4.2.2.1);
- require that only safe medical devices that perform as the manufacturer describes in its labelling may be placed on the market;
- specify market entry conditions for medical devices;
- establish record keeping, registration and reporting requirements for all parties within the scope of the law, including the regulatory authority;
- specify a transition period sufficient to allow parties affected by the law to comply with its requirements and ensure minimal disruption to the continuing supply of medical devices to health facilities and other users.

To allow progressive adoption and implementation of the stepwise approach recommended in the Model, the law should foresee and include provisions covering the expanded levels of control, even though those provisions would not be likely to be implemented in the early stages.

Experience in many jurisdictions with established regulatory systems suggests that affected parties must be allowed time to adapt to the law, i.e. a transition period. Where the necessary prerequisites are in place, a reasonable transition period is three to five years. In part, the length of the period will reflect the number of potentially affected parties and the number of devices in the national market. It may be helpful to first establish new requirements on a voluntary basis, gain experience and then move to mandatory compliance.

An important role of the regulatory authority during the transition period is the development and dissemination of voluntary guidance documents to affected parties.

4.2.1.1 Establish medical device classification for regulatory purposes

The law should include a medical devices classification scheme, based on internationally harmonized practice, to provide an efficient way of regulating each medical device according to its risk class (*18*). It should include provisions for the regulatory authority to issue implementing acts and guidance on the classification of medical devices, including IVDs. The manufacturer is responsible for determining the class of its devices and its decision may be challenged by the regulatory authority (see section 2).

4.2.1.2 Establish Essential Principles of safety and performance

The law should also establish the fundamental requirement that all medical devices be shown to be safe, to perform as intended and to be of good quality for their intended purpose before they are placed on the market. It would require the manufacturer, or its authorized representative or importer, to declare and be prepared to provide timely evidence that their device is in compliance with the Essential Principles (see section 2) (*32*). Failure to make such a declaration of conformity (see 4.2.2.2) (*31*), or making a false declaration, would be grounds for enforcement action by the regulatory authority.

The preferred, but optional, way by which the manufacturer may demonstrate conformity with the Essential Principles is to apply voluntary international standards that are appropriate and relevant. The law should include provisions allowing the regulatory authority to formally recognize such standards[12] for that purpose (see section 4.3.1.3).

4.2.2 Basic-level controls and enforcement – premarket

Only medical devices that are of good quality, safe and perform as intended may be placed on the market. The safe use and performance of most medical devices requires that the manufacturer, through its labelling, provides the user with information on how to properly install, use and maintain them.

4.2.2.1 Establish a basis for reliance and recognition

The medical devices law should allow reliance and recognition techniques to be used by the regulatory authority to determine whether a medical device

[12] Standards indicated in this document are standards current at the time of publication. The reader should refer to the standards body to verify the current edition.

complies with the regulatory requirements of another jurisdiction and to use this information as the basis for allowing the medical devices to be placed on the domestic market. However, the NRA is ultimately responsible for determining whether a medical device may be supplied in its jurisdiction (see section 3.1).

4.2.2.2 Establish requirements for declaration of conformity

The medical devices law should require an organization seeking to place a medical device on the market to draw up a written declaration of conformity to attest that its device complies fully with the law and all regulatory requirements.

At a minimum, this declaration should contain the following:

- the regulation under which the declaration is made;
- the name and address of the natural or legal person with responsibility for design and/or manufacture of a medical device with the intention of making the medical device available for use under his or her name;
- description of the device and its classification according to the regulation;
- the declaration that the medical device is of good quality, is safe and will perform as intended during its lifetime when used according to the manufacturer's instructions for the manufacturer's stated intended purpose;
- information sufficient to identify the device(s) to which the declaration of conformity applies;
- the list of standards used in demonstrating compliance with Essential Principles;
- the name, position and signature of the responsible person who has completed the declaration upon the manufacturer's behalf;
- the date on which the declaration is issued.

4.2.2.3 Establish requirement for manufacturers to have a QMS

To ensure devices are designed and manufactured to meet safety and performance requirements during their lifetime, the law should require manufacturers of all classes of medical devices to establish and maintain a QMS and the associated records. The QMS should be appropriate to the specific characteristics of the manufacturer's processes and products. This Model recommends that the QMS requirements should be aligned with the specifications in ISO 13485:2016 *Medical devices Quality management systems – Requirements for regulatory purposes* (*44*) and ISO 14971:2007: *Medical devices – Application of risk management to medical devices* (*45*).

The QMS is important not only for assuring the quality, safety and performance of a device, but also for controlling the collection of technical evidence used by the manufacturer in declaring the device conforms with the Essential Principles of safety and performance.

4.2.2.4 Establish requirements for labels and labelling

The safe and effective use of most medical devices requires that the user be given information on how to use them properly and, where appropriate, how to install and maintain them. Labels, instructions for use and other labelling (e.g. displays, service manuals and information for patients) serve that purpose and help to reduce risks associated with the use of medical devices. The law should include a requirement that labels and labelling are appropriate to the intended user of a device, especially for laypersons, and set language(s) requirements.[13] To begin establishing regulatory controls, regulatory authorities must provide specific guidance on the labelling and language requirements for medical devices and fully describe any exceptions to these requirements. Regulatory authorities should ensure that labelling is in an official language or in a language acceptable for the jurisdiction. The authority should also consider whether instructions for use may be provided in addition to or instead of the printed instructions in alternative media such as via the Internet or on CD-ROMs (*17*). However, printed instructions for use shall be provided if requested by the user.

Another function of labelling is to allow the identification of medical devices, for example, by batch or lot number, or serial number. This allows traceability to facilitate field safety corrective action (FSCA) and helps in the reporting and investigation of adverse events. A recent development is the addition of an internationally harmonized unique device identifier to the label (*46*).

[13] Medical devices – Symbols to be used with medical device labels, labelling and information to be supplied – Part 1: General requirements. ISO 15223-1:2012 (http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=50335, accessed 18 November 2016).

Medical devices – Symbols to be used with medical device labels, labelling and information to be supplied – Part 2: Symbol development, selection and validation. ISO 15223-2:2010 (http://www.iso.org/iso/catalogue_detail?csnumber=42343, accessed 18 November 2016).

In vitro diagnostics – Information supplied by the manufacturer (labelling) – Part 1: Terms, definitions and general requirements. ISO 18113-1:2009 (https://www.iso.org/obp/ui/#iso:std:iso:18113:-1:ed-1:v1:en, accessed 18 November 2016).

In vitro diagnostic medical devices – Information supplied by the manufacturer (labelling) – Part 2: In vitro diagnostic reagents for professional use. ISO 18113-2:2009 (http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=40985, accessed 18 November 2016).

In vitro diagnostic medical devices – Information supplied by the manufacturer (labelling) – Part 3: In vitro diagnostic instruments for professional use. ISO 18113-3:2009 (http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=40986, accessed 18 November 2016).

4.2.2.5 Prohibit deceptive, misleading and false advertising

In addition to requirements for labelling of medical devices, consideration should be given to inclusion in the law of provisions and prohibitions with respect to advertising and promotion for medical devices, including explicit enforcement measures. The regulatory authority should issue clear guidance to make these requirements explicit.

Those basic regulatory controls should ensure that promotion, including online promotion:

- does not target inappropriate audiences;
- makes only claims that are supported by evidence;
- covers only medical devices that have been authorized for marketing;
- is consistent with indications for use and other information in the product labelling;
- does not make false or misleading claims.

As a basic-level control the regulatory authority should investigate any suspected violations that are brought to its attention. If the regulatory authority discovers that a requirement is breached, it shall take appropriate enforcement actions, which could include preventing the medical device from being placed on the market and/or recalling medical devices already placed on the market.

4.2.2.6 Establish provisions for exceptional premarket situations

In situations such as public health emergencies, exemptions from some regulatory requirements may be needed. Such exemptions should, however, be applied in such a way as to allow the regulatory authority to evaluate the risks and benefits of the specific situation and authorize the proposed deviation. Such exemptions should be clearly stipulated and explained.

The law should establish defined exemptions from, and provide enforcement discretion for, compliance with certain requirements, for example, medical devices for humanitarian use, public health emergencies, clinical investigations, exhibition use and medical devices donated to the country by charities or the manufacturer. Regulators should issue clear guidance on such exemptions (see section 5).

4.2.3 Basic-level controls and enforcement – placing on the market

Many countries depend almost entirely on imported medical devices. However, it is impractical for a medical device manufacturer to have a physical or legal presence in every country. Therefore, the law should require a manufacturer

outside the jurisdiction of the country concerned to appoint an authorized representative within the country (*6*).

4.2.3.1 Registration of establishments

A key element of basic-level controls is effective oversight of medical devices placed on the domestic market and the parties responsible for bringing medical devices to the market. The law should require local manufacturers, authorized representatives, importers and distributors (in some cases the authorized representative may also be the importer and/or distributor) who place medical devices on the market or make medical devices available for use in the jurisdiction, to register with the regulatory authority (*20*). Significant changes in a registered establishment (e.g. ownership, location, name of the responsible person or scope of activities) should be notified to the authorities to ensure that registration information is current and correct. Among other purposes, the registration process allows the regulatory authority to determine who is responsible for a product's conformity with the regulatory requirements and for taking corrective actions in the event of a problem with a device. It is also useful in facilitating regulatory actions such as compliance inspections (e.g. of warehouses or manufacturing plants), notifying and monitoring of FSCA and for law enforcement purposes. Making registration and listing information publicly accessible allows device purchasers or users of medical devices to identify products available to them and determine the identity and location of their manufacturers and/or distributors and/or importers.

4.2.3.1.1 *Authorized representatives*

The minimum requirements for registration should be that the authorized representative provides the regulatory authority with information on its place of business, the name and position of a responsible person and the manufacturer it represents (*6*). Additionally, the regulation may require the applicant's authorized representative to attest that it will act on behalf of the manufacturer in its dealings with the regulatory authority by:

- submitting a regularly updated listing of the medical devices placed on the domestic market;
- providing the regulatory authority with the information it requires when the manufacturer seeks authorization to market its devices;
- informing the manufacturer and the regulatory authority of any reportable adverse events involving death or serious injury that have occurred either within the local market (or outside it, if there are any consequences for the local market) and providing information on the corrective action the manufacturer has taken or intends to take;

- informing the regulatory authority of any FSCA to be taken within the local market;
- cooperating with the manufacturer's importers and distributors;
- ensuring training is provided to the user by the distributor, manufacturer or third party, according to the manufacturer's requirements;
- cooperating with the regulatory authority and providing it with any information it requires during market surveillance activities.

4.2.3.1.2 *Importers and distributors*

The minimum requirements for registration should be that the importer and distributor provides the regulatory authority with information on its place of business, the name and position of a responsible person and the manufacturer(s) it is acting for. Beyond this, the regulation may require the applicant importer or distributor to attest that it will, for example:

- ensure the medical devices it imports or distributes comply with the medical devices law and are accompanied by the proper documentation and labelling;
- trace medical devices through that part of the supply chain with which it is directly involved;
- comply with the manufacturer's requirements for the storage, handling, transport and, as appropriate, maintenance of medical devices.

If the device manufacturer appoints its importer or distributor to also act as its authorized representative, there should be a separate registration for each activity.

4.2.3.2 Listing of medical devices

The regulatory authority should establish a requirement and information system for authorized representatives of manufacturers outside the jurisdiction, and importers and distributors, to submit a listing of medical devices they place on the national market and to ensure information retained within the device listing system relating to those medical devices in the market is up to date (*20*). Among other elements, the listing should provide the standardized generic descriptive names of those medical devices, for example, those of the Global Medical Device Nomenclature (GMDN) (see section 4.3, Expanded-level controls). Listing of medical devices will allow the regulatory authority to determine which products are placed on the market and by whom. In the event of a suspected problem with a medical device, listing also allows the regulatory authority to contact the parties responsible for that product. The regulatory authority should have

a means by which to provide information to other parties, upon request, on medical devices legally placed on the market.

It should be understood that listing is not of itself equivalent to, or evidence of, a marketing authorization.

4.2.3.3 Import controls

Apart from the basic controls of registering establishments and listing marketed medical devices, additional import controls may be appropriate. These may include approval of importation documents *before* shipment and verification of imported products either at the port of entry or at the importer's premises. Knowing in advance what medical devices are to be imported provides an opportunity for regulators to verify whether the medical device has previously been listed and marketed in the country. It also allows a review of evidence of conformity with regulatory requirements. Collection of samples may be required for suspicious products or for routine analysis (e.g. batch testing for selected products – see section 2.4.4, Lot verification testing of IVDs). Once the processes of registration of establishments and listing of devices become mature, the imposition of these controls may be unnecessary.

There should be mechanisms for cooperation between the regulatory authority and customs service so that medical devices will not be released from the port of entry unless there is proof that the regulatory authority has authorized them to be placed on the market. It may be helpful to designate official ports of entry for medical devices so that the regulatory authority may better focus its enforcement activities.

4.2.4 Basic-level controls – postmarket

In clinical use medical devices may not always perform as expected. This may indicate potential problems in their design, manufacture, labelling, storage or distribution. It could also reflect inappropriate device selection, installation, use or maintenance.

4.2.4.1 Establish a system for vigilance reporting

At the basic level the regulatory authority should establish a system whereby users, patients and the manufacturer of medical devices, either directly or through the authorized representative, can report complaints involving medical devices, including malfunction at the device level and adverse events at the patient level, in particular those adverse events resulting in death or serious injury (*28*). For IVDs, the risk of harm is usually indirect as the device is not used on the body: for instance, for high-risk IVDs a severe adverse event may include higher-than-expected false-negative results. Reports of adverse events

received by the regulatory authority from the patient or end-user must be passed to the device manufacturer for investigation and trend analysis with possible FSCA and notification through a field safety notice. Vigilance reports may trigger investigation, trend analysis and/or possible FSCA or enforcement actions (*12*). They may also prompt the regulatory authority to exchange information with regulatory authorities in other jurisdictions on similar occurrences elsewhere (*47*).

4.2.4.2 Require mandatory notification by the manufacturer of FSCA

The law should require a manufacturer, either directly or through its authorized representative, to report to the regulatory authority in a timely manner any FSCA it is undertaking within the country. As a regulatory authority learns, either through its own work or from communications with other authorities or manufacturers, of any newly identified potential hazard associated with a device, it should have an established system for the timely issuance of alerts or advisories on FSCAs. Such a system should allow the targeting of specific parties, usually in consultation with health-care professionals, so that they may act appropriately to protect public health and to prevent unnecessary concern or confusion on the part of medical device users or patients who are not affected. It should use communications technologies appropriate and accessible to the intended recipients as well as to the urgency of the action. The regulatory authority should establish means by which the effectiveness of corrective or remedial actions may be monitored. It should prepare the regulatory authority to respond to questions from the public, clinicians, media or government and to exchange information with authorities in other jurisdictions.

4.2.4.3 Establish a procedure to withdraw unsafe medical devices from the market

Regulatory authorities have an obligation to enforce laws and regulations on medical devices to ensure that the public is protected from unsafe products. Regulators are required to monitor compliance with requirements by registered entities and to take appropriate action when the regulatory authority believes that public health has been put at risk.

Various approaches to enforcing regulations may be used, for example: suspension or withdrawal of registration of local manufacturers, authorized representatives, importers or distributors; withdrawal from the list of marketed medical devices; or recall, quarantine and disposal of medical devices. Manufacturers may be required to review and to revise labelling information (including precautions and warnings), especially for products that have been found to be associated with adverse events or those whose labelling has been shown to be inadequate. Enforcement may also include issuance of public alerts, warning letters, prosecution and financial penalties. While the regulatory

authority's primary responsibility is for the health of its own citizens, where it believes an imported medical device is unsafe or of poor quality, it should consider sharing its opinion with the regulatory authority responsible for auditing the device manufacturer's QMS, for the purpose of preventing similar devices being exported to other markets.

Regulators are also advised to collaborate and work closely with other bodies to ensure that regulations are adhered to. Such bodies include regulatory authorities from other jurisdictions, customs officials, the judiciary, manufacturers, users and patients.

4.2.4.4 Establish procedure to issue safety alerts to users

Although the manufacturer, directly or through the authorized representative, would typically have primary responsibility for notifying users of problems with a medical device, this Model recommends the regulatory authority to establish a procedure to directly notify health-care facilities that use the affected medical devices, and other users, of serious adverse incidents and FSCA by issuing safety alerts and advisories (*12*). Where possible, the text of any such alert should be discussed with the manufacturer or her or his authorized representative but the final decision lies with the regulator.

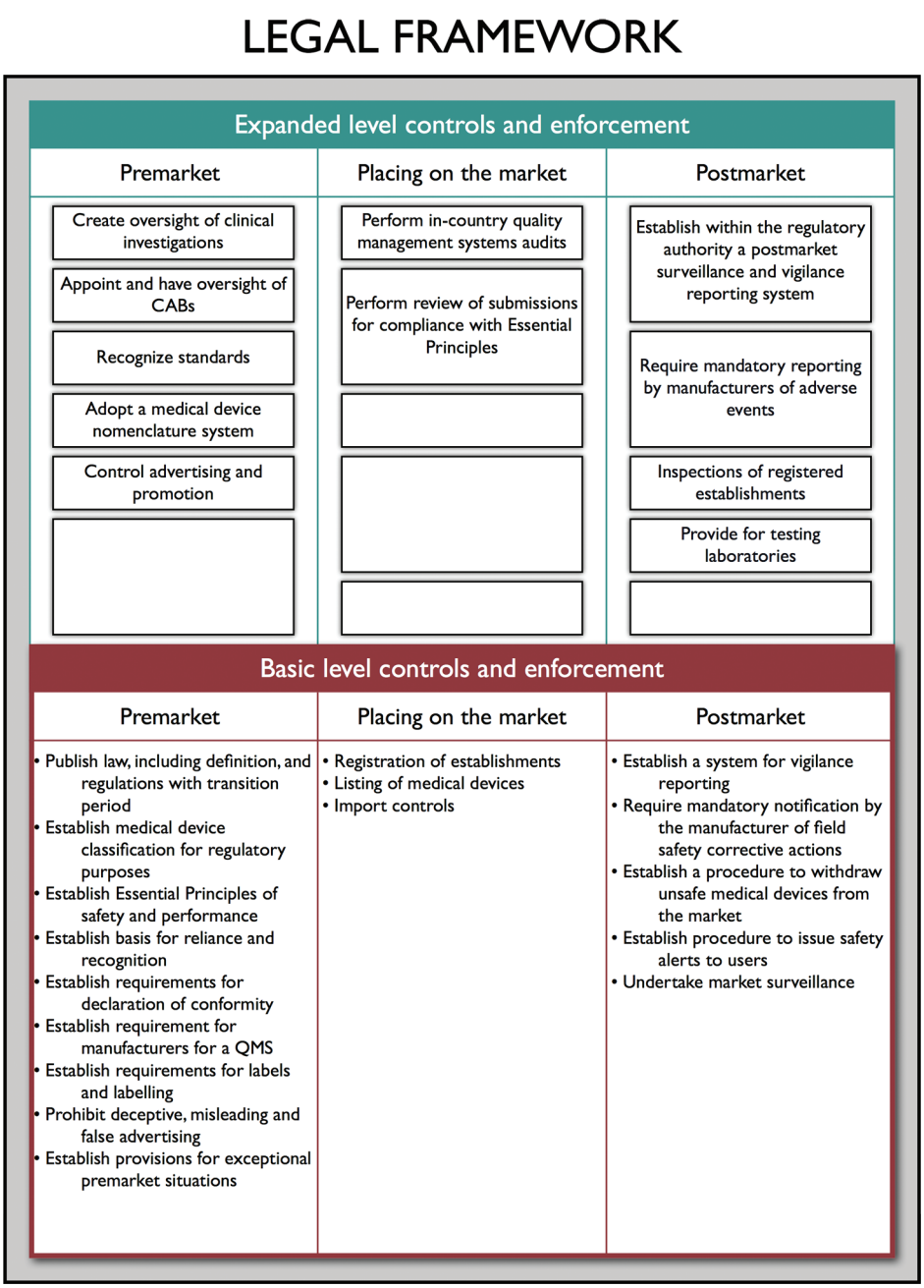
4.2.4.5 Undertake market surveillance

Market surveillance is the activity of the regulatory authority related to oversight of medical devices on the domestic market. The regulatory authority may undertake targeted activities based on a risk assessment of the distribution chain, evaluation of complaints and adverse event reporting, and information from the postmarket surveillance systems of medical device manufacturers and their authorized representatives (*48*).

4.3 Expanded-level controls

Once the basic-level controls have been implemented effectively and efficiently, the regulatory authority may consider implementing more advanced controls. To do so, the law should provide the legal basis for such expanded controls, the regulatory authority must have effectively enforced the basic controls, and additional resources (e.g. financial and technical expertise) must be available to it. Building on the basic-level controls, expanded-level controls are intended to be more comprehensive. In adopting expanded-level controls, the regulatory authority may choose to implement one or more of the controls described below according to the priorities of the country. A stepwise approach is recommended for the implementation of individual elements of expanded controls depending on the availability of technical expertise and resources (Figure A4.3).

Figure A4.3
Basic-level controls and enforcement for medical devices within the legal framework



4.3.1 Expanded-level controls – premarket

4.3.1.1 Create oversight of clinical investigations

The regulatory framework should grant to the authority the power to regulate and oversee the conduct of clinical investigations. Manufacturers have various reasons for undertaking clinical investigations in a particular country, primarily to collect and provide clinical evidence to a regulatory authority that a device for which it is seeking approval is safe and performs as intended.

The regulatory framework should clearly distinguish clinical investigations from market acceptability studies where a device is tested for factors such as ergonomics. These studies are not considered to be clinical investigations.

There should be a requirement that a sponsor (the individual or organization accepting responsibility and liability for the initiation or implementation of a clinical investigation, such as the local manufacturer, importer or local academic institution or investigator who initiates the clinical investigation) wishing to conduct a new clinical investigation, seek prior authorization from the regulatory authority (*7*). To assure adequate consideration of the design of studies and protection of the interests of participating subjects, such investigations should also be conducted under the oversight of a local ethics committee or institutional review board.[14] A widely used international standard for the practice of clinical investigation is: ISO 14155:2011 – *Clinical investigation of medical devices for human subjects – Good clinical practice* (*34*).

The NRA should also establish a mechanism for periodic progress reports and for the reporting of serious adverse events that occur during clinical investigations (*3*). In-country clinical investigations should generally not be required, unless there is a compelling and sound scientific reason.

4.3.1.2 Appoint and have oversight of CAB

Certain technical elements of the regulatory framework may be delegated to designated or recognized third-party organizations, often private, generally known as CABs (*49*, *50*). Authorities may establish criteria for designation of CABs. These bodies may perform initial certification and surveillance audits of device manufacturer QMS and/or premarketing reviews of the conformity of a device to the Essential Principles. The CAB may be designated by the regulatory authority to undertake conformity assessment of specific medical devices where it is judged to have the necessary skills (e.g. active implantable and/or IVDs and/or electromedical devices). Satisfactory compliance with

[14] The global standard for testing in humans is the Declaration of Helsinki – ethical principles for medical research involving human subjects (http://www.wma.net/en/30publications/10policies/b3/17c.pdf, accessed 7 September 2016).

requirements is typically documented with a CAB certificate (*51*). Based on the CAB evaluation, the regulatory authority makes final decisions on compliance. The CAB performs its evaluation under the oversight of the regulatory authority (*52*). The regulatory authority may consider adopting mechanisms to rely upon, or recognize, certificates issued by a CAB, even those outside its jurisdiction or direct oversight (*53*).

4.3.1.3 Recognition of standards[15]

Conformity with voluntary standards is a means by which the manufacturer may demonstrate that a medical device conforms to one or more of the Essential Principles of safety and performance, consistently throughout its life cycle (*29*).

Medical device standards can largely be grouped into three categories:

- basic standards (also known as horizontal standards), which cover fundamental concepts, principles and requirements applicable to a wide range of products and/or processes, e.g. QMS, risk management system, clinical investigation;
- group standards (also known as semi-horizontal standards), which cover aspects applicable to families of similar products or processes with reference to basic standards, e.g. sterility, electrical safety, biocompatibility;
- product standards (also known as vertical standards), which cover safety and performance aspects of specific products or processes, e.g. standards for infusion pumps, X-ray machines, blood glucose meters for self-testing and for IVDs (*54*).

At the expanded level, the regulatory authority may wish to establish a procedure to identify national versions of international standards that it accepts as providing presumption of compliance to specific Essential Principles, i.e. "recognized standards".

Preference for recognition should be given to international standards, e.g. those of the International Organization for Standardization (ISO) (*55*) and the International Electrotechnical Commission (IEC), regional standards and the national versions of international standards. It is also important that national standards correspond to the current version of international standards. As international standards are periodically revised, national standards will have to be revised accordingly and the authority should establish a transition period for manufacturers to adopt the new versions. To maintain the necessary flexibility in

[15] Standards indicated in this document are standards current at the time of publication. The reader should refer to the standards body to verify the current edition.

utilizing standards, it is better to adopt a system of recognizing standards through guidance documents or guidelines than placing the standards into legislation (*56*); they can then be updated to stay current and can be revised much faster than legislation can be updated.

4.3.1.4 Adopt a medical device nomenclature system

The regulatory authority may require the manufacturer to identify a medical device using a generic nomenclature system as a "descriptive language" for use in the listing of medical devices and other requirements such as adverse event reporting. The use of an internationally standardized nomenclature system is intended to allow for a common understanding of, and exchange of information regarding, a group of related medical devices, including IVDs. It also facilitates the exchange of information among NRAs. For these reasons the regulatory authority should adopt an international nomenclature system for medical devices.

The GMDN was endorsed by the GHTF as the global nomenclature system to be used by regulators for the classification, registration and exchange of information regarding medical devices for regulatory purposes (*57*, *58*). There are other established nomenclature systems such as the Universal Medical Device Nomenclature System (UMDNS) (*59*) and ISO 9999:2011– *Assistive products for persons with disability – Classification and terminology* (*60*).

To implement the selected nomenclature system, the regulatory authority should publish a regulation and guidance specifying that that system shall be used in any required submissions, e.g. listing, applications for marketing authorization, postmarketing surveillance and adverse event reports. The authority's administrative and information systems will have to be adapted accordingly and updated as new generic descriptive terms are adopted.

4.3.1.5 Control advertising and promotion

As part of their market development efforts, manufacturers, importers and distributors generally seek to promote medical devices to health-care professionals, users and/or patients. At a minimum, advertising and promotion should not be false, misleading or deceptive. In countries where the presence of misleading and inaccurate advertisements is a particular problem, the regulatory authority may expand controls to include review of advertising and promotional material before it is placed on the market. At this time, the regulatory authority may also contemplate a role for preclearance agencies, which act as independent entities to review advertising materials to ensure compliance with the regulatory requirements. The regulatory authority should consider whether existing rules for general advertising to consumers (e.g. under fair competition rules) are sufficient for application to medical devices, including online promotion. If not, they should consider whether specific guidance is required.

4.3.2 Expanded level controls – placing on the market

4.3.2.1 Perform in-country QMS audits

The QMS is important not only for assuring the quality, safety and performance of a device, but also as the source of much of the evidence in the technical documentation used by the manufacturer in demonstrating conformity of the device with the Essential Principles and the associated declaration of conformity. Good record keeping practices and record retention policies should be observed in the QMS.

At the basic level, the Model recommends that the law should require manufacturers of all classes of medical devices to establish and maintain a QMS. As the regulatory authority moves to enact expanded-level controls, the requirement in the law should be supplemented by an implementing act or ministerial decree that requires the regulatory authority to verify that a QMS appropriate to the medical devices under its control has been implemented.

Although manufacturers of Class A medical devices are required to implement a QMS, they are not subject to inspection by the regulatory authority prior to marketing approval nor routinely inspected by the regulatory authority after the devices have been placed on the market (see Table A4.2 for QMS requirements for medical devices in Classes B, C and D).

4.3.2.1.1 *QMS audit*

The regulatory authority should establish means to verify that the manufacturer conforms to the relevant QMS requirements. The law should include provisions for the regulatory authority to designate or recognize (*52*, *53*) CABs (see sections 2.3 and 4.3.1.2) to perform QMS audits or otherwise gather and assess evidence of the manufacturer's effective implementation of the QMS requirements (*31*).

For countries in which most medical devices are imported, the option of reliance or recognition is likely to be appropriate: it will often be sufficient for the regulatory authority to rely upon evidence, including QMS certificates, of the manufacturer's compliance with internationally-recognized QMS requirements in other jurisdictions (*53*, *61*). The receiving country thereby relies upon the information from the QMS audit or recognizes the decision of the other jurisdiction regarding the QMS audit (*62*). The regulatory authority may also review and recognize the manufacturer's own declaration of conformity and current certificates of conformity with ISO 13485:2016, issued by a recognized CAB, if any. The regulatory authority should verify that such certificates remain valid (typically for three to five years) and cover the scope of medical devices and activities appropriate for the devices being imported.

In the event of suspected noncompliance or problems with the product, the regulatory authority may perform an inspection, regardless of whether a CAB has performed a QMS audit.

4.3.2.2 Perform review of submissions for compliance with Essential Principles

The regulatory authority makes a decision on marketing authorization based on transparent criteria established in the law, regulation and guidance. The law should also prescribe the form in which approval to market is given (such as a certificate or entry in a database) and make provision for postmarket follow-up where appropriate (*31*).

At the basic level, assessing the safety and performance of medical devices depends primarily on an assessment by another regulatory authority (see section 4.1.1) supported by the manufacturer's declaration of conformity (see section 4.2.2.2). At the expanded level, the NRA may establish a requirement for the premarketing review of a manufacturer's submission. Guidance on the process for application and approval should be provided. This will usually be through completion of a prescribed form or access to the authority's Internet portal.

Internationally harmonized formats for submission of technical documentation for conformity assessment purposes have been developed by various bodies, e.g. the GHTF Summary Technical Documentation (STED (*63*, *64*)) and the Association of Southeast Asian Nations (ASEAN) Common Submission Dossier Template (CSDT) (*65*). These formats provide guidance for the presentation of evidence that a medical device conforms to the regulatory requirements for safety and performance.

The IMDRF table of content (ToC) is more recent. It describes a modular structure and format for such submissions in electronic form. Separate ToCs have been established for medical devices (*66*) and IVDs (*67*).

NRAs are encouraged to adopt such harmonized formats if they require submission of technical documentation.

Sometimes there are situations that trigger a more extensive review of the technical documentation submitted by the manufacturer. For example, when:

- the device incorporates innovative technology;
- an existing compliant device is being used for a new intended use;
- the device type is new to the manufacturer;
- the device type tends to be associated with an excessive number of adverse events, including use errors;
- the device incorporates innovative or potentially hazardous materials;
- the device type raises specific public health concerns (particularly for IVDs).

Considerations (or "triggers") for notification to the regulatory authority after initial approval could include change of specifications, change in mode of action on the human body or change in intended population for use of the device.

In premarket assessment, non-discriminatory country-specific requirements should be considered, e.g. local language labelling, electrical supply, public health policies, genetic characteristics of the population and health-care delivery conditions. The regulatory authority may also conduct a postmarket conformity assessment review in response to adverse events or uncertainty about the compliance of the manufacturer with the regulatory requirements.

The regulatory authority may be assisted in reaching its decision on premarket assessment (or any other regulatory decision) by advice from an expert medical device committee, which may include experts from outside the regulatory authority. Where advice from external experts is sought, the regulatory authority should ensure that the necessary agreements for the exchange of confidential information are in place. The final decision rests at all times with the regulatory authority.

4.3.3 Expanded-level controls – postmarket

4.3.3.1 Establish within the regulatory authority processes for postmarket surveillance and vigilance

At the basic level a system for reporting adverse events involving medical devices to the regulatory authority, in particular those resulting in death or serious injury, is established. At the expanded level, this may be extended to postmarketing surveillance and a capacity to monitor a manufacturer's investigation of adverse events. Postmarket surveillance and vigilance ensures that problems or risks associated with the use of devices, once marketed, are identified and reported to the regulatory authorities so that corrective actions may be taken to reduce the likelihood of recurrence. Properly structured postmarketing surveillance can identify serious problems in the safety, quality or performance of a medical device that may not have been foreseen or detected during product development or premarket evaluation, and provide for corrective actions. This may include exchange of alerts internationally in a standardized manner (*47*).

Regulators should establish a system for postmarket surveillance and vigilance encompassing:

- adverse event reporting and complaint handling systems with clear responsibilities for the regulator, manufacturer, authorized representative, importer and distributors;
- analysis and investigation of reported adverse events by the manufacturer and regulatory authority;
- maintenance by parties in the distribution chain (importers and distributors) of appropriate records of complaints and actions taken;
- oversight of implementation of corrective actions and preventive actions, including FSCA, when appropriate.

Where the manufacturer is located outside the jurisdiction of the regulatory authority there should be an agreement between the manufacturer and its authorized representative defining who fulfils the national regulatory requirements and maintains records of the distribution of the device. The agreement should require the authorized representative to report serious adverse events, quality problems and complaints to the manufacturer for investigation and corrective action.

4.3.3.2 Require mandatory reporting of adverse events

To the extent that investigation and information management resources allow, the regulatory authority should establish a mandatory requirement for the timely reporting, by the authorized representative or manufacturer, of adverse events associated with medical devices in the jurisdiction. It should define the threshold for reporting (i.e. what kinds of events should be reported), reporting time limits, required information and which party (or parties) shall report. In general, those criteria should be consistent with GHTF guidance on adverse event reporting (*20*).

4.3.3.3 Inspections of registered establishments

The regulatory authority may inspect periodically, scheduled or unannounced, all registered organizations to confirm they have the facilities, procedures and records in place to allow them to comply with the attestations made when they were registered. Additionally, the regulatory authority may issue licenses to the registered organization, renewable on a periodic basis. The registration – or license if such has been issued – may be withdrawn or suspended if non-conformities (*68*) are found during inspection.

4.3.3.3.1 *Distribution of medical devices*

The manufacturer of a medical device is required to implement a QMS covering activities of design and development, production, distribution, installation and servicing. However, quality, safety and performance of finished medical devices may be affected after release from the manufacturer by various factors such as storage conditions, warehouse environment and practices, transportation, installation, servicing, duration of storage and user training. The distributor shares responsibility for many of these activities. The manufacturer has the responsibility to:

- select appropriately qualified distributors (appropriate and adequate facilities, information systems and qualified staff);
- specify the requirements for medical device storage, handling, transport, installation, servicing and traceability of record keeping;

- periodically verify the conformity of distributors with the contract requirements.

Collection of customer feedback and implementation of correction and corrective actions, postmarket surveillance activities, and implementation of FSCA for medical devices may be conducted by the manufacturer through cooperation with its authorized representative and distributors. As with a manufacturer, a distributor would benefit from implementing a basic QMS to control its activities.

With the exponential increase in Internet connectivity, those engaged in the manufacture, distribution and supply of SF[16] medical products have gained access to a global marketplace.[17] Parties within the distribution chain will benefit from complying with good practice guidelines, such as a code of good distribution practice (GDP), as part of the global effort to combat SF medical products. Fulfilment of the requirements of GDP may be enabled by the implementation of a QMS in accordance with ISO 13485 (*44*). The Asian Harmonization Working Party (AHWP) has published guidance on the application of ISO 13485 in an organization that distributes or imports medical devices (*69*).

4.3.3.3.2 *Local production*

While many countries import most of the medical devices used in their domestic market, there are also likely to be a number of local manufacturers. In the interests of safeguarding public health, local manufacturers should be subject to the same regulatory controls as manufacturers of imported medical devices. However, because the local manufacturer is physically located in the jurisdiction of the authority, that regulatory authority would generally conduct its own QMS inspections of the manufacturer's plant(s) and warehouse(s), or designate a CAB to act on its behalf. In the case of inspections to investigate suspected noncompliance or problems with products, the regulatory authority is likely to undertake the inspection itself.

The regulatory authority should provide guidance specifically for local manufacturers.

4.3.3.4 Provide for testing laboratories

The work of the regulatory authority may benefit from having access to an independent, accredited test laboratory to supplement its own resources when

[16] The Member State mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products has recommended the World Health Assembly adopt a simplified terminology for substandard and falsified (SF) medical products (EB140/23, Annex, Appendix 3 (dated 10 January 2017)).

[17] http://www.who.int/entity/mediacentre/factsheets/fs275/en/ (accessed 5 July 2016).

testing is deemed necessary to verify the safety or performance of the device. Tasks that may be undertaken by an appropriately qualified and equipped testing laboratory include:

- examination and testing of medical devices that are suspected as SF (see section 5);
- institution of a programme of postmarket testing of specific imported devices according to specific national public health risks;
- investigation of devices allegedly involved in a serious adverse event;
- investigation of devices sent to the regulatory authority by laypersons;
- post-shipment lot verification testing of IVDs.

Given the diversity of medical devices, it is unlikely that an NRA will have all the necessary resources internally to establish and maintain its own laboratory. This Model does not recommend that a regulatory authority sets up its own testing laboratory as, if it is to be effective, it requires a significant budget and qualified staff. In many jurisdictions such organizations do not exist within the country itself, but may exist regionally.

When relying upon a testing laboratory, inside or outside the national jurisdiction, the authority should consider whether a laboratory has:

- accreditations to recognized standards (e.g. ISO 17025:2005, ISO 15189:2012);
- technical competence;
- access to external experts, as needed;
- adequate resources, such as specialized equipment;
- internal QMS and instrument calibration facilities.

4.4 Stepwise approach, harmonization, reliance, recognition

WHA Resolution 67.20 emphasizes the importance of collaboration and harmonization. It requests the Director-General "to prioritize support for establishing and strengthening regional and subregional networks of regulatory authorities, as appropriate, including strengthening areas of regulation of health products that are the least developed, such as regulation of medical devices including diagnostics" and "to promote the greater participation of Member States in existing international and regional initiatives for collaboration and cooperation in accordance with WHO principles and guidelines".

National regulation of medical devices is taking place in an increasingly globalized world, creating a need for closer alignment of regulatory requirements and practices. Accordingly, countries that align their medical device regulations

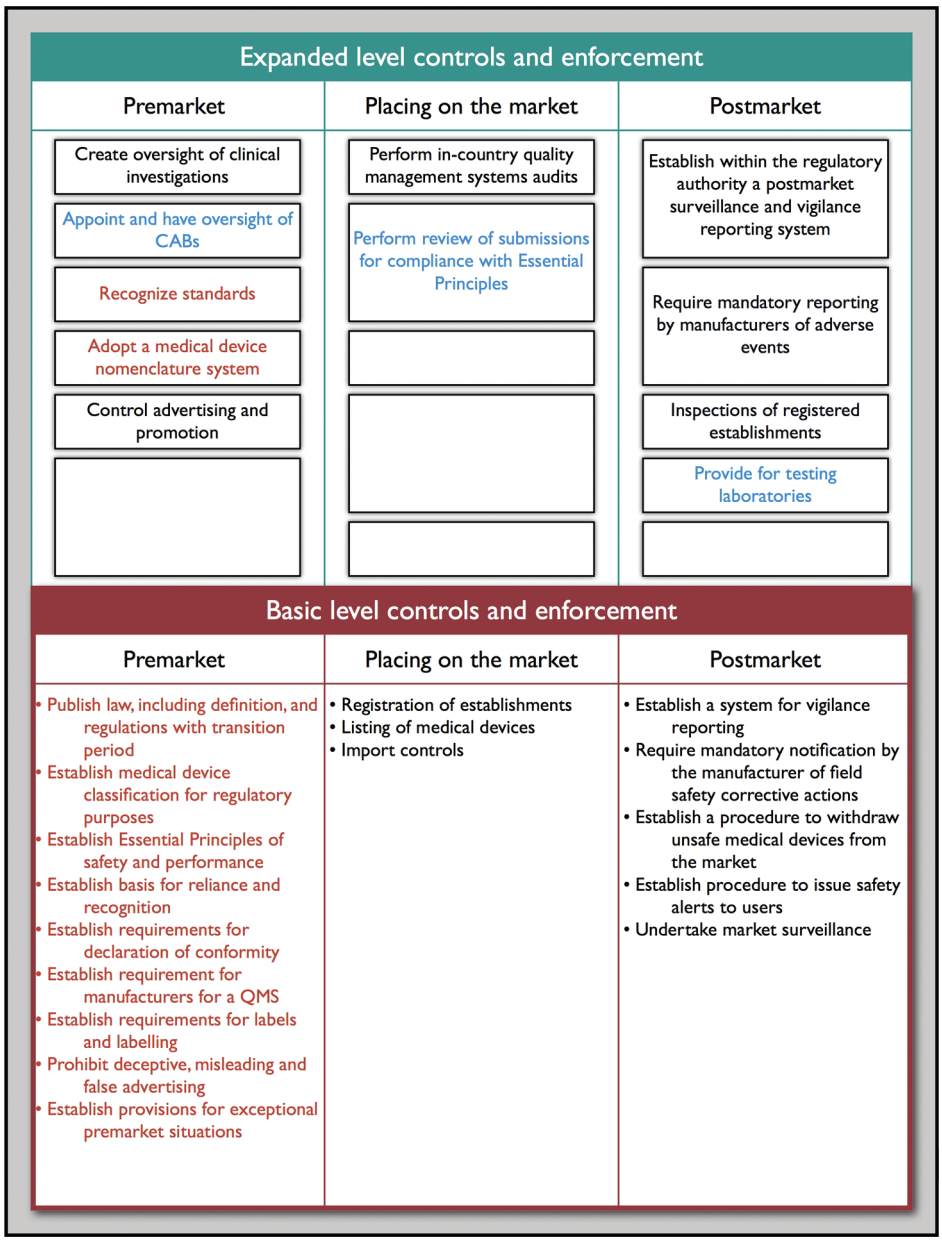
with existing harmonization guidance documents will promote this necessary regulatory convergence.

WHA Resolution 67.20 also urges Member States to "engage in global, regional and subregional networks of national regulatory authorities, as appropriate, recognizing the importance of collaboration to pool regulatory capacities to promote greater access to quality, safe, efficacious and affordable medical products" and "promote international cooperation, as appropriate, for collaboration and information sharing, including through electronic platforms".

Harmonization, recognition and reliance contribute to more effective regulatory systems. They are an essential component of health system strengthening and contribute to better public health outcomes (Figure A4.4).

Figure A4.4

Controls for medical devices showing elements for which regulatory guidance has been developed and those that may be implemented through reliance or recognition



The elements indicated in the lighter shaded area are those for which international regulatory harmonization guidance documents have been developed. Elements that may be implemented through reliance or recognition are indicated in the area with the darker shading.

5. Additional topics

Beyond the general elements described in earlier chapters, this chapter covers specific topics to be considered when developing and implementing regulations for medical devices. It explains the relevance of these topics and provides guidance for regulators to ensure they are appropriately addressed. The topics are listed in alphabetical order.

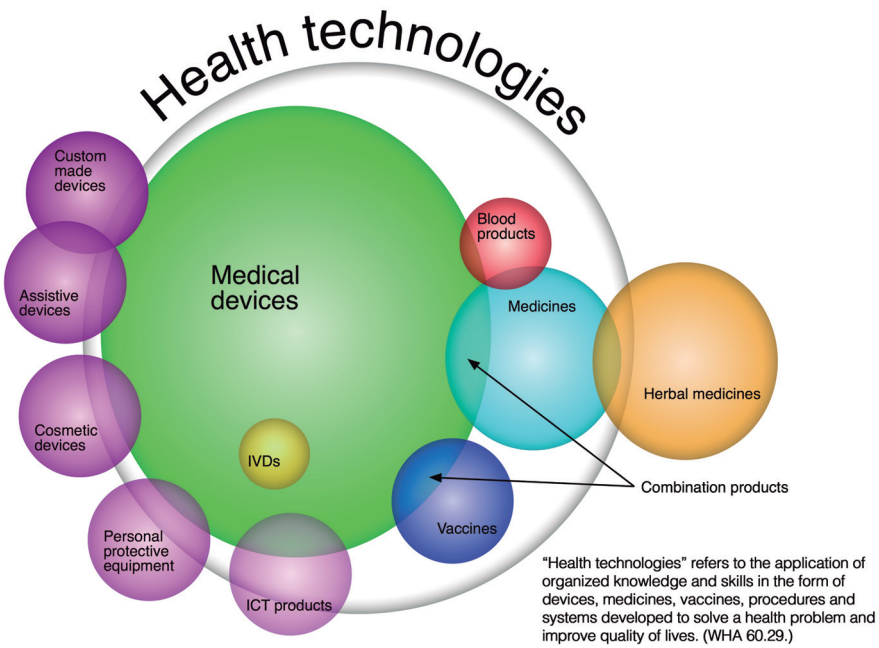
5.1 Determination to establish whether a medical product is a medical device

Many products are used in the delivery of health care, yet not all fit comfortably within an existing definition for a medical product, more specifically the term "medical device" (Figure A4.5). Examples include medical gases, some laxatives, cosmetic articles, clinical laboratory reagents and articles of protective clothing worn by medical personnel during procedures. Products that may be considered to be medical devices in some jurisdictions but not in others include disinfection substances, aids for persons with disabilities, devices incorporating animal and/or human tissues, and devices for in vitro fertilization or assisted reproduction technologies. A lack of clarity in such cases may lead to overlapping or conflicting regulatory requirements for a product, or in some jurisdictions, no separate regulation for such medical products. It is in the public interest to ensure the safety, quality and performance of all such "borderline"[18] products through appropriate regulatory controls – either those for medical devices or for other regulated product sectors (e.g. medicines including advanced therapy medicinal products, biologicals and regenerative medicine products, cosmetics, food supplements or personal protective equipment) (*70–72*).

[18] Borderline products are generally medical products for which it is unclear which legislation applies. Although they may have some of the attributes of two or more categories of regulated products, they are not combination products. A combination product is a product comprising two or more components which are regulated as medical products, i.e. medicine/medical device, or vaccine/medical device, which are physically, chemically or otherwise combined or mixed and produced as a single entity (modified from US FDA definition – http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm118332.htm). As there is no international harmonization guidance on combination products, NRAs should consider which requirements in other benchmark jurisdictions would best serve their country's needs.

Herbal medicines according to WHO include herbs, herbal materials, herbal preparations and finished herbal products, which contain as active ingredients parts of plants, or other plant materials, or combinations (http://www.who.int/medicines/areas/traditional/definitions/en/).

Figure A4.5
Interrelation of (medical) products inside and outside health care



ICT, information and communications technology; IVDs, in vitro diagnostic medical devices.

To be predictable and transparent, the regulatory authority should develop criteria and mechanisms for determining the appropriate regulatory regime for such products through guidelines. It should describe considerations and the process whereby an applicant may obtain an advisory opinion from the regulatory authority. Where necessary, that process should allow for consultation with subject matter experts as well as with regulatory authorities from other product sectors such as medicines or foods and with the manufacturers concerned. It may also take into account determinations made by regulatory authorities of other jurisdictions. A decision by the regulatory authority on the regulatory status of a product should provide the option of appeal in case the applicant does not agree with the decision.

5.2 Disposal

A medical device that reaches the end of its intended life cycle must be disposed of safely. In some cases it may be necessary to dispose of a device before the end

of its life if it is confirmed that the device can no longer perform its function properly and may cause a hazard to users or patients.

Disposal of a medical device should follow safety procedures to ensure that it does not cause harm to people or the environment. This is especially important for contaminated devices such as syringes or hypodermic needles, and devices that contain infectious, toxic or radiological materials. Medical device labelling and instructions for use should include information on proper disposal at the end of device's life, as appropriate for the type of device. Where the regulatory authority has identified SF medical products, it shall itself document a procedure for local disposal (e.g. mandatory destruction at an approved facility). This will ensure that such falsified or counterfeit products are not exported to another country where they may cause harm.

Owing to their diversity and complexity, there are many ways that medical devices may be disposed of. For durable equipment, mechanisms may include replacement and decommissioning. For disposable devices, decontamination and proper waste management practices according to the manufacturer's instructions should be required. The responsible regulatory authority, in coordination with other concerned governmental bodies, should establish criteria for replacement and decommissioning based on the manufacturer's recommendations. Consultation between the user and manufacturer is critical especially for high-technology and complicated products in order to decide the best way to dispose of them (*73–75*).

5.3 Donations

Charitable donations of medical devices and IVDs can be very helpful, may improve the efficiency of health facilities, may save costs of purchasing new equipment and may make some diagnoses or therapies accessible to patients, especially in resource-limited settings. Donations may be beneficial but they can also cause health risks if their safety and performance are not verified. Another potential issue is a lack of clear documentation or labelling on the donated medical device, its state, its origin and history and the responsibilities of donors. Quality problems associated with donated medical devices have been reported in many countries. They include short expiry dates, defective equipment and gifts of unnecessary items not requested by the recipient. These factors often result in receiving countries incurring unwanted costs for maintenance and disposal and may also create the impression that the medical devices are "substandard" and have been "dumped" on a receiving country (*76–79*). For these reasons some countries have banned donations of used equipment.

To safeguard public health, medical devices imported as donations should comply with all regulatory requirements on safety, quality and performance and should not differ from those that are imported through a regular supply chain.

Regulatory authorities should therefore establish a mechanism to verify and authorize the importation of donated medical devices. Institutions that intend to donate devices should communicate with the recipient to determine their needs before the products are shipped.[19] To avoid delay and additional expense, importation documents must be submitted to the regulatory authority of the recipient's country for approval before shipment of the consignment. Supporting documents will typically include: a list of products to be donated, manufacturer(s) of the products, expiry dates (if applicable), donation certificate[20] and a commitment letter that confirms the safety and performance of the devices to be donated. All donors are required to familiarize themselves with the donation requirements before they decide to donate medical devices. Donations that do not comply with the requirements should be rejected and sent back to the donor at the donor's expense.

5.4 Reprocessing of single-use medical devices

Single-use medical devices[21] (SUMDs) are designed and labelled for single use. They do not come with appropriate instructions for cleaning, disinfecting or sterilization procedures after use and the manufacturer has not investigated any deterioration in performance if they are subject to reprocessing. This may pose a danger to the patient when SUMDs are reprocessed and used more than once, because conformity to their original standards for safety, quality and performance cannot be assured.

The claimed advantages to health-care practices of cost–effectiveness and waste reduction must be weighed against the potential risks associated with reprocessed SUMDs. These risks include possible cross-infection as a result of the inability to assure the complete removal of viable microorganisms, inadequate cleaning, decontamination and removal of pyrogens and material alteration. Exposure to chemical cleaning agents may cause corrosion or changes in the materials of the device, and exposure to repeated sterilization processes may also change the properties or degrade the device material. The high temperature and harsh chemicals sometimes used during processing may impair the quality of reprocessed devices.

[19] Guidelines to help donors to familiarize themselves with donations requirements may be found at http://www.who.int/medical_devices/management_use/manage_donations/en/.

[20] The donation certificate confirms that the donation complies with the "Criteria for evaluating equipment donation offers" as stated in the WHO publication: *Medical device donations: considerations for solicitation and provision* (http://apps.who.int/iris/bitstream/10665/44568/1/9789241501408_eng.pdf).

[21] Single-use device: is a medical device that is intended to be used on an individual patient during a single procedure and then disposed of. It is not intended to be reprocessed and used again (http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n43-2005-labelling-medical-devices-050603.pdf).

In addition to the potential health risks associated with the use of reprocessed SUMDs, ethical considerations arise. These considerations include whether it is justifiable to treat a patient with a reprocessed SUMD that may be of lower quality, performance or cleanliness than it had when used for the first time, even with informed consent. Other considerations include liability: the entity that reprocesses a medical device becomes the new manufacturer with the associated responsibilities, and economic: to reprocess a SUMD using a validated process raises the costs; the perceived savings may therefore not be realized.

In adopting a policy on the reprocessing of SUMDs, the regulatory authority should consider the following: reprocessing of a SUMD as labelled by its manufacturer is not permitted unless the reprocessed SUMD meets the same initial standards as those of the original manufacturer. To allow their reuse, the entity that reprocesses and distributes medical devices labelled by their original manufacturer for single-use only will be subject to the same requirements of safety, quality and performance as manufacturers of new devices (*80–83*). This applies equally to a health-care facility fully reprocessing SUMDs for reuse within its own facility.

When investigating complaints and adverse events, the regulatory authority should consider the possibility that reprocessing of SUMDs may have contributed to their occurrence. The policy on the use of a reprocessed SUMD should only be enacted after appropriate risk–benefit analyses are performed on the potential risks described above.

5.5 Refurbishing electromedical devices

Some medical devices, typically durable electromedical devices, are meant to be reused many times over a long design life. In some cases, they may be subject to refurbishing by an organization or entity other than the original manufacturer to extend their service life, often for economic reasons.

Refurbishing can be described as a restoration of a device to a condition of safety and performance that is comparable to its condition when new. This includes reconditioning, repair, installation of certain software and/or hardware updates that do not change the intended use of the original device, and replacements of worn parts. Refurbished medical devices should be identified as such on the labelling.

In adopting a policy on refurbishing, the regulatory authority should clearly state that the entity responsible for refurbishing or third party must meet the same regulatory requirements as applied to the original medical device. A party that refurbishes medical devices will be subject to the same requirements of safety, quality and performance as manufacturers of new devices (*84–87*).

5.6 Substandard and falsified products

SF medical products[22] are harmful to the health of patients, damage confidence in medical products and health-care providers and increase the burden on health systems.

SF medical devices can result from genuine manufacturing errors or deliberate falsification of a product. The latter is usually a clandestine activity, is often difficult to detect and is designed to deceive a health-care provider or patient into believing that the device is the genuine article and has been carefully assessed in terms of quality, safety and effectiveness.

Reports of SF medical devices have emerged from all over the world. The United States Food and Drug Administration (US FDA) has issued a letter concerning contaminated surgical hernia mesh.[23] The United Kingdom's Medicines and Healthcare products Regulatory Agency raided a business following a complaint about a portable dental X-ray unit available on eBay. The unit was found to lack sufficient shielding of the X-ray tube, which means that it could emit harmful radiation levels to operator and patients.[24] Falsified condoms, contact lenses, catheters, syringes and needles have been reported from Africa, Asia and Europe (*88*). The trade in SF medical devices is driven and motivated by profit. Where a demand exists, those engaged in the manufacture and distribution of SF devices will respond. They will utilize online distribution channels as well as the regulated supply chain to market their products, often accompanied by false safety and quality certification logos. Visual identification can be extremely difficult and laboratory analysis (see section 4) may be required to distinguish the SF product from the genuine version.

The established approach is one of prevention, detection and response (*43*). The existence of a legal framework providing for proportionate regulatory requirements and powers, including dissuasive sanctions, is critical. A regulatory system, with effective oversight of importation, distribution and sale of medical devices will assist in the prevention of SF devices reaching users and patients. Balanced awareness-raising among consumers, health-care providers and distributors can help to minimize the threat posed by SF medical products while retaining confidence in health technologies. It is important to educate the general public to buy from reliable sources, particularly on the Internet.

[22] The Member State mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products has recommended the World Health Assembly adopt a simplified terminology for substandard and falsified (SF) medical products (EB140/23, Annex, Appendix 3 (dated 10 January 2017)).

[23] http://www.fda.gov/ICECI/CriminalInvestigations/ucm303541.htm (accessed 27 September 2016).

[24] https://www.gov.uk/drug-device-alerts/medical-device-alert-counterfeit-or-non-ce-marked-dental-medical-devices (accessed 27 September 2016).

Effective postmarket surveillance and vigilance systems are both methods of detecting SF medical devices early on. Regulatory authorities should establish mechanisms that enable and encourage reporting of suspicious medical devices and regulatory authorities should be responsive to those reports. Regulator engagement with relevant stakeholders, including both public and private sector organizations, law enforcement, civil society, consumer groups and patients, leads to increased reporting and earlier detection of SF products (*89–93*).

New technologies, including unique identifiers and track-and-trace technology, also provide increased assurance of the supply chain and can lead to the early detection of SF products.

Strengthening capacity among regulatory authorities to respond, transparently, consistently and proportionately, will help to maintain confidence in health systems. Working in partnership with other stakeholders, including, where necessary, law enforcement and the judiciary, will help to ensure that serious cases of falsification are dealt with in a manner commensurate with the risk to public health.

5.7 WHO Prequalification Team for IVDs

Lack of access to quality health technologies, in particular IVDs, reduces the opportunity for progress towards addressing high-burden diseases in certain countries. The WHO Prequalification Team (PQT) provides countries with the appropriate technical support, tools and guidance on the provision of IVDs and laboratory services. In addition to relying upon the work of other authorities, for some medical devices (mostly IVDs), the regulatory authority may choose to rely upon evaluations conducted by PQT for IVDs. This is a quality assurance programme that aims at promoting and facilitating access to safe, appropriate and affordable IVDs of good quality. The focus of this programme is on IVDs for priority diseases such as HIV/AIDS, malaria, hepatitis C and others, and their suitability for use in resource-limited settings (*94*).

PQT for IVDs undertakes an assessment of individual IVDs through a standardized procedure aimed at determining whether the product meets WHO prequalification requirements. The process includes three components:

- review of the technical documentation (product dossier) (*95*);
- independent performance evaluation;
- inspection of manufacturing site(s).

Prequalification requirements are based on best international practice and are designed around the Essential Principles of safety and performance. As such, prequalification requirements reflect standards, guidance and other internationally recognized documents such as those of ISO, European Norm,

Clinical & Laboratory Standards Institute (CLSI) and IMDRF/GHTF, to ensure compliance with the Essential Principles. Like other stringent regulatory reviews, prequalification assessments cover quality, safety and performance aspects.

Although prequalification requirements are aligned with the approach adopted by regulators performing stringent reviews, they have been designed in such a way as to best serve resource-limited settings. Therefore, the aspects below are reflected in prequalification assessments:

- the regulatory version marketed on the global market is assessed;
- the scrutiny level reflects individual and public health risks in resource-limited settings;
- data submitted by the manufacturer are assessed from the perspective of resource-limited settings in order to reflect the resource-limited settings' environment and users.

Countries may benefit from the programme by relying on prequalification assessment outcomes. The list of prequalified IVDs, together with the report summarizing the assessment findings, is made publicly available by WHO (*96*).

The findings of PQT for IVDs, in conjunction with other procurement criteria, are typically used by UN agencies, WHO Member States and other interested organizations to guide their procurement of IVDs.

5.8 United Nations Population Fund Prequalification Programme for intrauterine devices and condoms

A similar prequalification programme exists for the management of male latex condoms, female condoms and intrauterine devices (IUDs) (*97*). The management of this programme was delegated from WHO to the United Nations Population Fund (UNFPA) in 2005 for male condoms, and in 2006 for female condoms. WHO still maintains the normative role in setting guidelines and requirements for the prequalification programmes.

As for IVDs, the prequalification programme for male and female condoms follows a systematic process consisting of a detailed technical review of required documentation, on-site factory inspections and product testing. This process determines whether the quality of products is in accordance with international standards and WHO/UNFPA specifications and guidelines. Manufacturers of female condoms are expected to demonstrate the safety, efficacy and acceptability of new designs. UNFPA maintains a list of prequalified manufacturers and sites that have successfully completed the WHO/UNFPA prequalification process and have been approved by the WHO/Reproductive Health and Research (RHR) Technical Review Committee for male and female condoms.

The findings are used to provide independent technical information on safety, quality and performance of the products assessed to other UN agencies, WHO Member States and other interested organizations. The UNFPA/WHO prequalification status, in conjunction with other procurement criteria, is used by these entities to guide their procurement of the products covered by WHO PQTs.

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Appendix

Hierarchy of regulation

Level	Brief description	Examples	Examples of subject matter regulated in the field of medical devices
Primary legislation	Law, or executive law as used in this WHO Global Model Regulatory Framework, refers to binding and enforceable legislation, usually adopted at the level of individual countries by their respective legislatures and/or executives.	Act of parliament, bill, statutory law, EU directive, ordinance, decree, executive order.	Establishment of the regulatory authority including enforcement power; reliance and recognition; definition of a medical device; placing on the market; market withdrawal; classification of medical devices; Essential Principles of safety and performance; requirement for a quality management system; incident reporting; clinical trials; listing of medical devices; registration of establishments; process to recognize standards.
Secondary legislation	A form of law as used in this Model Regulatory Framework for Medical Devices, refers to written instruments that are binding and enforceable and are issued by the regulatory (executive) authority.	Regulations, schedule.	Requirements for reliance; conduct of quality management system (QMS) audits; vigilance reporting; criteria for recalls and field safety corrective actions (FSCAs); classification rules; responsibilities of an authorized representative.

Table *continued*

Level	Brief description	Examples	Examples of subject matter regulated in the field of medical devices
Guidelines[a]	Guidance documents that refer generally to non-binding normative documents issued by the regulatory authority, which offer guidance on recommended practices. They allow for scientifically-justified, alternative approaches and translation of a regulatory, generally acceptable approach. Guidelines set out the current thinking, practices, explanations and expectations of the regulatory authority, but compliance with such documents is not mandatory. The manufacturer (or other party) may choose not to apply or comply with such guidance, but must provide a rationale for, and justify, a deviation from that guidance.	Technical standards, recommendations.	Guidance on interpretation and application of the classification rules; interpretation of the meaning of "primary intended mode of action" (related to the definition of "medical device"); specific labelling requirements; good laboratory practices; good clinical practices.

[a] Note that the term "guideline", as used in this WHO Global Model Regulatory Framework, does not refer to guidelines within the sense of the WHO handbook for guideline development. Geneva: World Health Organization; 2014.

Annex 5

General background notes on the list of international comparator pharmaceutical products

1. List of international comparator products

The list of international comparator products provides tabulated information about pharmaceutical products on the World Health Organization (WHO) Model List of Essential Medicines (EML) (*1*), specific finished pharmaceutical products that can be selected as comparators (column headed "International comparator product") and the markets where the product's quality, safety and efficacy is considered as best documented (column headed "Market"). Comparator products recommended by the WHO Prequalification Team – Medicines (PQTm) are included in the list of international comparator products (column headed "PQ comparator product"). PQTm prequalifies pharmaceutical products included in the Expressions of Interest for priority medicines such as those used for HIV/AIDS, malaria and tuberculosis as well as for reproductive health. For more information regarding comparator products in the context of prequalification, please see the PQTm guidance documents (*2*).

1.1 Selection criteria for the international comparator product

The international comparator products that are listed in the table are selected according to the following criteria.

1. A product from a stringent regulatory authority (SRA) is listed where the same product is marketed worldwide by the same marketing authorization holder (MAH).
2. Products from the United States of America (USA) and/or the European Union (EU) are listed (if available in those markets) where the same product is not marketed worldwide by the same MAH.
3. A specific product, the MAH and the respective market is listed where the comparator product is not available in the markets of the USA or widely in the EU.
4. In order to select a specific product, preference is given to products marketed by MAHs from countries with SRAs.

5. Comparator products marketed in other countries are selected in those cases where a comparator product is not available in markets with SRAs.

The list of international comparator products is to be used in conjunction with the *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* and the *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products*. Please consult the WHO website for the most recent version of these guidance texts (*3*).

The list of international comparator products is published as a living document and will be revised and regularly adapted to the newest version of the EML on the following website: http://www.who.int/medicines/areas/quality_safety/quality_assurance/regulatory_standards/en/.

WHO relies on the support of medicines regulatory authorities and information provided by manufacturers. If an international comparator product is no longer available or is being replaced, please contact QAS@who.int.

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Annex 6

Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

Republication of *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*, WHO Technical Report Series, No. 992, Annex 7 with a new Appendix 2

Background

Following the publication of the *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* in 2015, it was noted that a text on equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients (APIs) according to the Biopharmaceutics Classification System (BCS) would be a useful addition. The method for determination of equilibrium solubility was suggested to be added as an appendix to the above-mentioned guidelines.

1. Introduction

These guidelines provide recommendations to regulatory authorities when defining requirements for approval of multisource (generic) pharmaceutical products in their respective countries. The guidance provides appropriate in vivo and in vitro requirements to assure interchangeability of the multisource product without compromising the safety, quality and efficacy of the pharmaceutical product.

National regulatory authorities (NRAs) should ensure that all pharmaceutical products subject to their control conform to acceptable standards of safety, efficacy and quality, and that all premises and practices employed in the manufacture, storage and distribution of these products comply with good manufacturing practice (GMP) standards so as to ensure the continued conformity of the products with these requirements until they are delivered to the end user.

All pharmaceutical products, including multisource products, should be used in a country only after approval by the national or regional authority.

Regulatory authorities should require the documentation of a multisource pharmaceutical product to meet the following:

- GMP;
- quality control (QC) specifications;
- pharmaceutical product interchangeability.

Multisource pharmaceutical products need to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator's (comparator) product. In addition, reasonable assurance must be provided that the multisource product is therapeutically equivalent and interchangeable with the comparator product. For some classes of products, including – most evidently – aqueous parenteral solutions, interchangeability is adequately assured by assessment of the composition, implementation of GMP and evidence of conformity with appropriate specifications including relevant pharmacopoeial specifications. For a wide range of pharmaceutical products the concepts and approaches covered by these guidelines will enable NRAs to decide whether a given multisource product can be approved. This guidance is generally applicable to orally administered multisource products as well as to non-orally administered pharmaceutical products for which systemic exposure measures are suitable for documenting bioequivalence (e.g. transdermal delivery systems and certain parenteral, rectal and nasal pharmaceutical products). Some information applicable to locally acting products is also provided in this document. For other classes of product, including many biologicals such as vaccines, animal sera, products derived from human blood and plasma and products manufactured

by biotechnology, as well as non-biological complex products, the concept of interchangeability raises issues that are beyond the scope of this document and these products are consequently excluded from consideration.

To ensure interchangeability, the multisource product must be therapeutically equivalent to the comparator product. Types of in vivo equivalence studies include comparative pharmacokinetic studies, comparative pharmacodynamic studies and comparative clinical studies.

Direct demonstration of therapeutic equivalence through a comparative clinical trial is rarely a practical choice as these trials tend to be insensitive to differences in formulation and usually require a very large number of patients. Further, such studies in humans can be financially daunting, are often unnecessary and may be unethical. For these reasons the science of bioequivalence testing has been developed over the past 50 years. According to the tenets of this science, therapeutic equivalence can be assured when the multisource product is both pharmaceutically equivalent and bioequivalent.

Assuming that, in the same subject, an essentially similar plasma concentration time course will result in essentially similar concentrations at the site(s) of action and thus in an essentially similar therapeutic outcome, pharmacokinetic data may be used instead of therapeutic results. Further, in selected cases, in vitro comparison of the dissolution profiles of the multisource product with those of the comparator product may be sufficient to provide an indication of equivalence.

It should be noted that interchangeability includes the equivalence of the dosage form as well as of the indications and instructions for use. Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. These guidelines should be interpreted and applied without prejudice to obligations incurred through the existing international Agreement on Trade-Related Aspects of Intellectual Property Rights (*1*).

2. Glossary

Some important terms used in these guidelines are defined below. They may have different meanings in other contexts.

bioavailability. The rate and extent to which the active moiety is absorbed from a pharmaceutical dosage form and becomes available at the site(s) of action. Reliable measurements of active pharmaceutical ingredient (API) concentrations at the site(s) of action are usually not possible. The substance in the systemic circulation, however, is considered to be in equilibrium with the substance at the site(s) of action. Bioavailability can therefore be defined as the rate and extent to which the API or active moiety is absorbed from a pharmaceutical dosage form and becomes available in the systemic circulation.

Based on pharmacokinetic and clinical considerations it is generally accepted that in the same subject an essentially similar plasma concentration time course will result in an essentially similar concentration time course at the site(s) of action.

bioequivalence. Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of rate (C_{max} and t_{max}) and extent of absorption (area under the curve (AUC)), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

biological pharmaceutical product. A biological pharmaceutical product is a synonym for biological product or biological (as described in the reports of the Expert Committee on Biological Standardization in the World Health Organization (WHO) Technical Report Series). The definition of a pharmaceutical substance used in treatment, prevention or diagnosis as a "biological" has been variously based on criteria related to its source, its amenability to characterization by physicochemical means alone, the requirement for biological assays or arbitrary systems of classification applied by regulatory authorities. For the purposes of WHO, including the current document, the list of substances considered to be biologicals is derived from their earlier definition as "substances which cannot be fully characterized by physicochemical means alone and which therefore require the use of some form of bioassay". However, developments in the utility and applicability of physicochemical analytical methods, improved control of biological and biotechnology based production methods and an increased applicability of chemical synthesis to larger molecules, have made it effectively impossible to base a definition of a biological on any single criterion related to methods of analysis, source or method of production. Nevertheless many biologicals are produced using in vitro culture systems.

Biopharmaceutics Classification System. The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying APIs based upon their aqueous solubility and intestinal permeability. When combined with the dissolution of the pharmaceutical product and the critical examination of the excipients of the pharmaceutical product, the BCS takes into account the major factors that govern the rate and extent of API absorption (exposure) from immediate-release oral solid dosage forms: excipient composition, dissolution, solubility and intestinal permeability.

biowaiver. The term biowaiver is applied to a regulatory pharmaceutical product approval process when the dossier (application) is approved based on evidence of equivalence other than through in vivo equivalence testing.

comparator product. The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product

for which efficacy, safety and quality have been established. If the innovator product is no longer marketed in the jurisdiction, the selection principle as described in *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (WHO Technical Report Series, No. 992, Annex 8 (2015)) should be used to identify a suitable alternative comparator product.

dosage form. The form of the completed pharmaceutical product, e.g. tablet, capsule, elixir or suppository.

equivalence requirements. In vivo and/or in vitro testing requirements for approval of a multisource pharmaceutical product for a marketing authorization.

equivalence test. A test that determines the equivalence between the multisource product and the comparator product using in vivo and/or in vitro approaches.

fixed-dose combination. A combination of two or more APIs in a fixed ratio of doses. This term is used generically to mean a particular combination of APIs irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product (FPP).

fixed-dose combination finished pharmaceutical product. An FPP that contains two or more APIs.

generic product. See multisource pharmaceutical products.

innovator pharmaceutical product. Generally the innovator pharmaceutical product is that which was first authorized for marketing, on the basis of complete documentation of quality, safety and efficacy.

interchangeable pharmaceutical product. An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice.

in vitro equivalence dissolution test. An in vitro equivalence test is a dissolution test that includes comparison of the dissolution profile between the multisource product and the comparator product, typically in at least three media: pH 1.2, pH 4.5 and pH 6.8 buffer solutions.

in vitro quality control dissolution test. A dissolution test procedure identified in the pharmacopoeia for routine QC of product batches, generally a one time-point dissolution test for immediate release products and a three or more time-points dissolution test for modified release products.

multisource pharmaceutical products. Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

non-biological. Not involving or derived from biology or living organisms.

pharmaceutical alternatives. Products are pharmaceutical alternative(s) if they contain the same active pharmaceutical moiety or moieties but differ in dosage form (e.g. tablets versus capsules), strength, and/or chemical form (e.g. different salts or different esters). Pharmaceutical alternatives deliver the same active moiety by the same route of administration but are otherwise not pharmaceutically equivalent. They may or may not be bioequivalent or therapeutically equivalent to the comparator product.

pharmaceutical equivalence. Products are pharmaceutical equivalents if they contain the same molar amount of the same APIs in the same dosage form, if they meet comparable standards and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the API solid-state properties, the excipients and/or the manufacturing process and other variables can lead to differences in product performance.

quantitatively similar amounts (concentrations) of excipients. The relative amount of excipient present in two solid oral FPPs is considered to be quantitatively similar if the differences in amount fall within the limits shown in Table A6.1.

Table A6.1
Limits on the relative difference in the amount of excipient in two solid oral finished pharmaceutical products for the products to be considered quantitatively similar in that excipient

Excipient type	Percentage difference (w/w) out of total product (core) weight
Filler	5.0
Disintegrant	
Starch	3.0
Other	1.0
Binder	0.5
Lubricant	
Calcium or magnesium stearate	0.25
Other	1.0
Glidant	
Talc	1.0
Other	0.1

If an excipient serves multiple functions (e.g. microcrystalline cellulose as a filler and as a disintegrant) then the most conservative recommended range should be applied (e.g. ± 1.0% for microcrystalline cellulose should be applied in this example). The relative concentration of an excipient present in two aqueous solution FPPs is considered to be similar if the difference is ≤ 10%.

therapeutic equivalence. Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and, after administration in the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same when administered to patients by the same route under the conditions specified in the labelling. This can be demonstrated by appropriate equivalence studies, such as pharmacokinetic, pharmacodynamic, clinical or in vitro studies.

3. Documentation of equivalence for marketing authorization

Multisource pharmaceutical products must be shown, either directly or indirectly, to be therapeutically equivalent to the comparator product if they are to be considered interchangeable. Suitable test methods to assess equivalence are:

- comparative pharmacokinetic studies in humans, in which the API and/or its metabolite(s) are measured as a function of time in an accessible biological fluid such as blood, plasma, serum or urine to obtain pharmacokinetic measures, such as AUC and C_{max} that reflect the systemic exposure;
- comparative pharmacodynamic studies in humans;
- comparative clinical trials;
- comparative in vitro tests.

The applicability of each of these four methods is discussed below. Detailed information is provided on conducting an assessment of equivalence studies using pharmacokinetic measurements and in vitro methods, which are currently the methods most often used to document equivalence for most orally administered pharmaceutical products for systemic exposure.

Acceptance of any test procedure in the documentation of equivalence between two pharmaceutical products by an NRA depends on many factors, including the characteristics of the API and the pharmaceutical product. Where an API produces measurable concentrations in an accessible biological fluid, such as plasma, comparative pharmacokinetic studies can be performed. This type of study is considered to be the gold standard in equivalence testing; however, where appropriate, in vitro testing, e.g. BCS based biowaivers for immediate release

pharmaceutical products, can also assure equivalence between the multisource product and the comparator product (see sections 5 and 10). Where an API does not produce measurable concentrations in an accessible biological fluid and a BCS based biowaiver is not an option, comparative pharmacodynamics studies may be an alternative method for documenting equivalence. Further, in certain cases when it is not possible to assess equivalence through other methods, comparative clinical trials may be considered appropriate.

The criteria that indicate when equivalence studies are necessary are discussed in sections 4 and 5 of these guidelines.

4. When equivalence studies are not necessary

In the following circumstances, multisource pharmaceutical products are considered to be equivalent without the need for further documentation:

(a) when the pharmaceutical product is to be administered parenterally (e.g. intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations to those in the comparator product. Certain excipients (e.g. buffer, preservative and antioxidant) may be different provided it can be shown that the change(s) in these excipients would not affect the safety and/or efficacy of the pharmaceutical product. The same principles are applicable for parenteral oily solutions but, in this case, the use of the same oily vehicle is essential. Similarly, for micellar solutions, solutions containing complexing agents or solutions containing co solvents of the same qualitative and quantitative composition of the functional excipients are necessary in order to waive equivalence studies and the change of other excipients should be critically reviewed;

(b) when pharmaceutically equivalent products are solutions for oral use (e.g. syrups, elixirs and tinctures), contain the API in the same molar concentration as the comparator product, contain the same functional excipients in similar concentrations (if the API is BCS Class I) and the same excipients in similar concentrations (for APIs from other BCS classes);

(c) when pharmaceutically equivalent products are in the form of powders for reconstitution as an aqueous solution and the resultant solution meets either criterion (a) or criterion (b) above;

(d) when pharmaceutically equivalent products are gases;

(e) when pharmaceutically equivalent products are otic or ophthalmic products prepared as aqueous solutions and contain the same

API(s) in the same molar concentration and the same excipients in similar concentrations. Certain excipients (e.g. preservative, buffer, substance to adjust tonicity or thickening agent) may be different provided their use is not expected to affect bioavailability, safety and/or efficacy of the product;

(f) when pharmaceutically equivalent products are topical products prepared as aqueous solutions and contain the same API(s) in the same molar concentration and the same excipients in similar concentrations (note that a waiver would not apply to other topical dosage forms like gels, emulsions or suspensions, but might be applicable to oily solutions if the vehicle composition is sufficiently similar);

(g) when pharmaceutically equivalent products are aqueous solutions for nebulization or nasal drops, intended to be administered with essentially the same device, contain the same API(s) in the same concentration and contain the same excipients in similar concentrations (note that this waiver does not apply to other dosage forms like suspensions for nebulization, nasal drops where the API is in suspension, nasal sprays in solution or suspension, dry powder inhalers or pressurized metered dose inhalers in solution or suspensions). The pharmaceutical product may include different excipients provided their use is not expected to affect bioavailability, safety and/or efficacy of the product.

For situations (b), (c), (e), (f) and (g) above it is incumbent upon the applicant to demonstrate that the excipients in the pharmaceutically equivalent product are the same and that they are in concentrations similar to those in the comparator product or, where applicable (i.e. (a), (e) and (g)), that their use is not expected to affect the bioavailability, safety and/or efficacy of the product. In the event that the applicant cannot provide this information and the NRA does not have access to the relevant data, it is incumbent upon the applicant to perform appropriate studies to demonstrate that differences in excipients or devices do not affect product performance.

5. When equivalence studies are necessary and types of study required

Except for the cases discussed in section 4, these guidelines recommend that documentation of equivalence with the comparator product be required by registration authorities for a multisource pharmaceutical product. Studies must be carried out using the product intended for marketing (see also section 7.3).

5.1 In vivo studies

For certain APIs and dosage forms, in vivo documentation of equivalence, through either a pharmacokinetic comparative bioavailability (bioequivalence) study, a comparative pharmacodynamic study or a comparative clinical trial, is regarded as especially important. In vivo documentation of equivalence is necessary when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence (*2*). Examples are listed below:

(a) oral, immediate-release pharmaceutical products with systemic action, except for the conditions outlined in section 10;
(b) non-oral, non-parenteral pharmaceutical products designed to act systemically (such as transdermal patches, suppositories, nicotine chewing gum, testosterone gel and skin inserted contraceptives);
(c) modified-release pharmaceutical products designed to act systemically, except for the conditions outlined in section 10;
(d) fixed-dose combination (FDC) products with systemic action, where at least one of the APIs requires an in vivo study (*3*);
(e) non-solution pharmaceutical products, which are for non-systemic use (e.g. for oral, nasal, ocular, dermal, rectal or vaginal application) and are intended to act without systemic absorption.

In the case of non-solution pharmaceutical products for non-systemic use, the equivalence is established through, e.g. comparative clinical or pharmacodynamic studies, local availability studies and/or in vitro studies. In certain cases, measurement of the concentration of the API may still be required for safety reasons, i.e. in order to assess unintended systemic absorption.

5.2 In vitro studies

For certain APIs and dosage forms, in vitro documentation of equivalence may be appropriate. In vitro approaches for systemically acting oral products are discussed in section 10.

6. In vivo equivalence studies in humans

6.1 General considerations

6.1.1 Provisions for studies in humans

Pharmacokinetic, pharmacodynamic and comparative clinical trials are clinical studies and should therefore be carried out in accordance with the provision and prerequisites for a clinical study, as outlined in the WHO *Guidelines for good clinical practice for trials on pharmaceutical products* (*4*) and with WHO good

laboratory practices (*5*). Additional guidance for organizations performing in vivo equivalence studies is available from WHO (*6*).

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki, including respect for persons, beneficence ("maximize benefits and minimize harms and wrongs") and non-maleficence ("do no harm"), as defined by the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS), or laws and regulations of the country in which the research is conducted, whichever represents the greater protection for study subjects.

6.1.2 Justification of human bioequivalence studies

Most pharmacokinetic and pharmacodynamic equivalence studies are non-therapeutic studies in which no direct clinical benefit accrues to the subject.

It is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks or benefits of the proposed human study be thoroughly considered and that the chosen design be scientifically sound and ethically justified. It is assumed that people involved in the planning of a study are familiar with the pharmacokinetic theories underlying bioavailability and bioequivalence studies. The overall design of the bioequivalence study should be based on the knowledge of the pharmacokinetics, pharmacodynamics and therapeutics of the API. Information about manufacturing procedures and data from tests performed on the product batch to be used in the study should establish that the product under investigation is of suitable quality.

6.1.3 Selection of investigators

The investigator(s) should have the appropriate expertise, qualifications and competence to undertake the proposed study. Prior to the trial, the investigator(s) and the sponsor should draw up an agreement on the protocol, monitoring, auditing, standard operating procedures (SOPs) and the allocation of trial-related responsibilities. The identity and duties of the individuals responsible for the study and safety of the subjects participating in the study must be specified. The logistics and premises of the trial site should comply with requirements for the safe and efficient conduct of the trial.

6.1.4 Study protocol

A bioequivalence study should be carried out in accordance with a protocol agreed upon and signed by the investigator and the sponsor. The protocol and its attachments and/or appendices should state the aim of the study and the procedures to be used, the reasons for proposing the study to be undertaken in humans, the nature and degree of any known risks, assessment methodology,

criteria for acceptance of bioequivalence, the groups from which it is proposed that trial subjects be selected and the means for ensuring that they are adequately informed before they give their consent. The investigator is responsible for ensuring that the protocol is strictly followed. Any change(s) required must be agreed on and signed by the investigator and sponsor and appended as amendments, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject.

The protocol, attachments and appendices should be scientifically and ethically appraised by one or, if required by local laws and regulations, more review bodies (e.g. institutional review board, peer review committee, ethics committee or NRA) constituted appropriately for these purposes and independent of the investigator(s) and sponsor.

The signed and dated study protocol should be approved by the NRA before commencing the study, if required by national and regional laws and regulations. The study report forms an integral part of the registration dossier of the multisource product in order to obtain the marketing authorization for the multisource product.

7. Pharmacokinetic comparative bioavailability (bioequivalence) studies in humans

7.1 Design of pharmacokinetic studies

Bioequivalence studies are designed to compare the in vivo performance of a multisource product with that of a comparator product. Such studies on products designed to deliver the API for systemic exposure serve two purposes:

- as a surrogate for clinical evidence of the safety and efficacy of the multisource product;
- as an in vivo measure of pharmaceutical quality.

The design of the study should maximize the sensitivity to detect any difference between products, minimize the variability that is not caused by formulation effects and eliminate bias as far as possible. Test conditions should reduce variability within and between subjects. In general, for a bioequivalence study involving a multisource product and a comparator product, a randomized, two-period, two-sequence, single-dose, cross-over study conducted with healthy volunteers is the preferred study design. In this design each subject is given the multisource product and the comparator product in randomized order. An adequate wash-out period should follow the administration of each product.

It should be noted, however, that under certain circumstances an alternative, well-established and statistically appropriate study design may be more suitable.

7.1.1 Alternative study designs for studies in patients

For APIs that are very potent or too toxic to administer in the highest strength to healthy volunteers (e.g. because of the potential for serious adverse events or because the trial necessitates a high dose), it is recommended that the study be conducted using the API at a lower strength in healthy volunteers. For APIs that show unacceptable pharmacological effects in healthy volunteers, even at lower strengths, a study conducted in patients may be required. Depending on the dosing posology this may be a multiple-dose, steady-state study. As above, such studies should employ a cross-over design if possible; however, a parallel group design study in patients may be required in some situations. The use of such an alternative study design should be fully justified by the sponsor and should include patients whose disease process is stable for the duration of the bioequivalence study if possible.

7.1.2 Considerations for active pharmaceutical ingredients with long elimination half-lives

A single-dose, cross-over bioequivalence study for an orally administered product with a long elimination half-life is preferred, provided an adequate wash-out period between administrations of the treatments is possible. The interval between study days should be long enough to permit elimination of essentially all of the previous dose from the body. Ideally the interval should not be less than five terminal elimination half-lives of the active compound or metabolite, if the latter is measured. If the cross-over study is problematic owing to a very long elimination half-life, a bioequivalence study with a parallel design may be more appropriate. A parallel design may also be necessary when comparing some depot formulations.

For both cross-over and parallel design studies of oral products, sample collection time should be adequate to ensure completion of gastrointestinal (GI) transit (approximately 2–3 days) of the pharmaceutical product and absorption of the API. Blood sampling should be conducted for up to 72 hours following administration, but sampling beyond this time is not generally necessary for immediate-release products.

The number of subjects should be derived from statistical calculations, but generally more subjects are needed for a parallel study design than for a cross-over study design.

7.1.3 Considerations for multiple-dose studies

In certain situations multiple dose studies may be considered appropriate. Multiple dose studies in patients are most useful in cases where the API being studied is considered to be too potent and/or too toxic to be administered to healthy volunteers, even in single doses (see also section 7.1.1). In this case

a multiple-dose, cross-over study in patients may be performed without interrupting therapy.

The dosage regimen used in multiple dose studies should follow the usual dosage recommendations.

Other situations in which multiple dose studies may be appropriate are as follows:

- cases where the analytical sensitivity is too low to adequately characterize the pharmacokinetic profile after a single dose;
- for extended-release dosage forms with a tendency to accumulate (in addition to single-dose studies).

In steady-state studies, the wash-out of the last dose of the previous treatment can overlap with the approach to steady state of the second treatment, provided the approach period is sufficiently long (at least five times the terminal half-life). Appropriate dosage administration and sampling should be carried out to document the attainment of a steady state.

7.1.4 Considerations for modified-release products

Modified-release products include extended-release products and delayed-release products. Extended-release products are variously known as controlled-release, prolonged-release and sustained-release products.

Owing to the more complex nature of modified-release products relative to immediate-release products, additional data are required to ensure the bioequivalence of two modified-release products. Factors such as the co-administration of food, which influences API bioavailability and also, in certain cases, bioequivalence, must be taken into consideration. The presence of food can affect product performance both by influencing the release of the API from the formulation and by causing physiological changes in the GI tract. In this regard a significant concern with regard to modified-release products is the possibility that food may trigger a sudden and abrupt release of the API leading to "dose dumping". This would most likely be manifested as a premature and abrupt rise in the plasma concentration time profile. Therefore, bioequivalence studies conducted under both fasted and fed conditions are required for orally administered, modified-release pharmaceutical products. Unless single-dose studies are not possible for reasons such as those discussed in section 7.1.1, single-dose, cross-over bioequivalence studies conducted under both fasted and fed conditions comparing the highest strength of the multisource product and the comparator product must be performed to demonstrate bioequivalence. Single-dose studies are preferred to multiple-dose studies as single-dose studies are considered to provide more sensitive measurement of the release of API from

the pharmaceutical product into the systemic circulation. In addition to single-dose studies, multiple-dose studies may be considered for extended release dosage forms with a tendency to accumulate, e.g. after a single dose of the highest strength the AUC for the dosing interval covers < 90% of AUC extrapolated to infinity. The comparator product in these studies should be a pharmaceutically equivalent, modified-release product. The bioequivalence criteria for modified-release products are essentially the same as for conventional release dosage forms except that acceptance criteria should also be applied to C_{min} (C_{tau}) in the case of multiple-dose studies. As release mechanisms of pharmaceutical products become more complex, e.g. products with an immediate-release and modified-release component, additional parameters such as partial AUC measures may be necessary to ensure the bioequivalence of two products.

The fed-state bioequivalence study should be conducted after the administration of an appropriate standardized meal at a specified time (usually not more than 30 minutes) before taking the pharmaceutical product. A meal that will promote the greatest change in GI tract conditions relative to the fasted state should be given. See section 7.4.3 for more recommendations for the content of the meal. The composition of the meal should take local diet and customs into consideration. The composition and caloric breakdown of the test meal should be provided in the study protocol and report.

7.2 Subjects

7.2.1 Number of subjects

The number of subjects required for a bioequivalence study is determined by:

- the error variance (coefficient of variation) associated with the primary parameters to be studied, as estimated from a pilot experiment, from previous studies or from published data;
- the significance level desired (5%);
- the statistical power desired;
- the mean deviation from the comparator product compatible with bioequivalence and with safety and efficacy;
- the need for the 90% confidence interval around the geometric mean ratio to be within bioequivalence limits, normally 80–125%, for log-transformed data.

The number of subjects to be recruited for the study should be estimated by considering the standards that must be met using an appropriate method (see, for example, Julious 2004 (*7*)). In addition, a number of extra subjects should be recruited, dosed appropriately, and their samples analysed based on

the expected rate of drop-outs and/or withdrawals, which depends on the safety and tolerability profile of the API. The number of subjects recruited should always be justified by the sample size calculation provided in the study protocol. A minimum of 12 subjects is required.

In some situations, reliable information concerning the expected variability in the parameters to be estimated may not be available. In such situations a two-stage sequential study design can be employed as an alternative to conducting a pilot study (see section 7.6.1 for more information).

7.2.2 Drop-outs and withdrawals

Sponsors should select a sufficient number of study subjects to allow for possible drop-outs or withdrawals. Because replacement of subjects during the study could complicate the statistical model and analysis, drop-outs generally should not be replaced. Reasons for withdrawal (e.g. adverse reaction or personal reasons) must be reported. If a subject is withdrawn due to an adverse event after receiving at least one dose of the study medication the subject's plasma/serum concentration data should be provided.

The concentration–time profiles of subjects who exhibit pre-dose concentrations higher than 5% of the corresponding C_{max} should be excluded from the statistical analysis. The concentration–time profiles of subjects who exhibit pre-dose concentrations equal to or less than 5% of the corresponding C_{max} should be included in the statistical analysis without correction.

7.2.3 Exclusion of subject data

Extreme values can have a significant impact on bioequivalence study data because of the relatively small number of subjects typically involved; however, it is rarely acceptable to exclude data. Potential reasons for excluding subject data and the procedure to be followed should be included in the study protocol. Exclusion of data for statistical or pharmacokinetic reasons alone is not acceptable. Retesting of subjects is not recommended.

7.2.4 Selection of subjects

Bioequivalence studies should generally be performed with healthy volunteers. Clear criteria for inclusion and exclusion should be stated in the study protocol. If the pharmaceutical product is intended for use in both sexes, the sponsor should include both males and females in the study. The potential risk to women will need to be considered on an individual basis and, if necessary, they should be warned of any possible dangers to the fetus if they should become pregnant. The investigators should ensure that female volunteers are not pregnant or likely to become pregnant during the study. Confirmation should be obtained

by urine tests just before administration of the first and last doses of the product under study.

Generally subjects should be between the ages of 18 and 55 years and their weight should be within the normal range with a body mass index between 18 and 30 kg/m². The subjects should have no history of alcohol or drug abuse problems and should preferably be non-smokers.

The volunteers should be screened for their suitability using standard laboratory tests, a medical history and a physical examination. If necessary, special medical investigations may be carried out before and during studies, depending on the pharmacology of the individual API being investigated, e.g. an electrocardiogram if the API has a cardiac effect. The ability of the volunteers to understand and comply with the study protocol has to be assessed. Subjects who are being or have previously been treated for any GI problems or convulsive, depressive or hepatic disorders, and in whom there is a risk of a recurrence during the study period, should be excluded.

If a parallel design study is planned, standardization of the two groups of subjects is important in order to minimize variation not attributable to the investigational products (see section 7.2.6).

If the aim of the bioequivalence study is to address specific questions (e.g. bioequivalence in a special population) the selection criteria should be adjusted accordingly.

7.2.5 Monitoring the health of subjects during the study

In keeping with GCP (*4*) the health of volunteers should be monitored during the study so that the onset of side-effects, toxicity or any intercurrent disease may be recorded and appropriate measures taken. The incidence, severity, seriousness and duration of any adverse event observed during the study must be reported. The probability that an adverse event is due to the FPP should be judged by the investigator. Health monitoring before, during and after the study must be carried out under the supervision of a qualified medical practitioner licensed in the jurisdiction in which the study is conducted.

7.2.6 Considerations for genetic phenotyping

Phenotyping for metabolizing activity can be important for studies with high-clearance APIs that are metabolized by enzymes that are subject to genetic polymorphism, e.g. propranolol. In such cases slow metabolizers will have a higher bioavailability of the API while the bioavailability of possible active metabolites will be lower. Phenotyping of subjects can be considered for studies of APIs that show phenotype-linked metabolism and for which a parallel group design is to be used, because it allows fast and slow metabolizers to be evenly distributed between the two groups of subjects. Phenotyping could also be

important for safety reasons, determination of sampling times and wash-out periods in cross-over design studies.

7.3 Investigational product

7.3.1 Multisource pharmaceutical product

The multisource pharmaceutical product used in the bioequivalence studies for registration purposes should be identical to the planned commercial pharmaceutical product. Therefore, not only the composition and quality characteristics (including stability), but also the manufacturing methods (including equipment and procedures) should be the same as those to be used in the future routine production runs. Test products must be manufactured under GMP regulations. Batch control results, lot number, manufacturing date and, if possible, expiry date for the multisource product should be stated. Samples should ideally be taken from batches of industrial scale. When this is not feasible, pilot or small-scale production batches may be used, provided that they are not smaller than 10% of expected full production batches, or 100 000 units, whichever is larger, and are produced with the same formulation and similar equipment and process to that planned for commercial production batches. A biobatch of less than 100 000 units may be accepted provided that this is the proposed production batch size, with the understanding that future scale-up for production batches will not be accepted unless supported by in vitro and/or in vivo data as applicable.

7.3.2 Choice of comparator product

The innovator pharmaceutical product is usually the most logical comparator product for a multisource pharmaceutical product because its quality, safety and efficacy should have been well assessed and documented in premarketing studies and postmarketing monitoring schemes. Preferably this will mean employing the innovator product available on the market when studying multisource products for national and regional approval. There will be situations, however, where this is not feasible. Detailed guidance for the selection of comparator products for use in national and regional applications is provided in the comparator guidance (*8*).

It is recommended that potency and in vitro dissolution characteristics of the multisource and the comparator pharmaceutical products be ascertained prior to the performance of an equivalence study. Content of the API(s) of the comparator product should be close to the label claim and the difference between two products being compared should not be more than ± 5%. If, because of the lack of availability of different batches of the comparator product, it is not possible to study batches with potencies within ± 5%, potency correction may be required on the statistical results from the bioequivalence study.

7.4 Study conduct

7.4.1 Selection of strength

In bioequivalence studies the molar equivalent dose of multisource and comparator product must be used. For a series of strengths that can be considered proportionally formulated (see section 10.3) the strength with the greatest sensitivity for bioequivalence assessment should be administered as a single unit. This will usually be the highest marketed strength. A higher dose, i.e. more than one dosage unit, may be employed when analytical difficulties exist. In this case, the total single dose should not exceed the maximal daily dose of the dosage regimen. In certain cases a study performed with a lower strength can be considered acceptable if this lower strength is chosen for reasons of safety or if the API is highly soluble and its pharmacokinetics are linear over the therapeutic range.

7.4.1.1 Non-linear pharmacokinetics

When the API in a series of strengths, which are considered proportionally formulated, exhibits non-linear pharmacokinetics over the range of strengths, special consideration is necessary when selecting the strength for study.

For APIs exhibiting non-linear pharmacokinetics within the range of strengths resulting in greater than proportional increases in AUC with increasing dose, the comparative bioavailability study should be conducted on at least the highest marketed strength.

For APIs with non-linear pharmacokinetics within the range of strengths due to saturable absorption and resulting in less than proportional increases in AUC with increasing dose, the bioequivalence study should be conducted on at least the lowest strength (or a strength in the linear range).

For APIs with non-linear pharmacokinetics within the range of strengths due to limited solubility of the API and resulting in less than proportional increases in AUC with increasing dose, bioequivalence studies should be conducted on at least the lowest strength (or a strength in the linear range) and the highest strength.

7.4.2 Study standardization

Standardization of study conditions is important to minimize variability other than in the pharmaceutical products. Standardization between study periods is critical to a successful study. Standardization should cover exercise, diet, fluid intake and posture, as well as the restriction of the intake of alcohol, caffeine, certain fruit juices and concomitant medicines for a specified period before and during the study.

Volunteers should not take any other medicine, alcoholic beverages or over-the-counter medicines and supplements for an appropriate interval before,

or during, the study. In the event of emergency the use of any non-study medicine must be reported (dose and time of administration).

Physical activity and posture should be standardized as far as possible to limit their effects on GI blood flow and motility. The same pattern of posture and activity should be maintained for each day of the study. The time of day at which the study product is to be administered should be specified.

7.4.3 Co-administration of food and fluid with the dose

FPPs are usually given after an overnight fast of at least 10 hours and participants are allowed free access to water. On the morning of the study no water is allowed during the hour prior to FPP administration. The dose should be taken with a standard volume of water (usually 150–250 mL). Two hours after FPP administration, water is again permitted as often as desired. A standard meal is usually provided four hours after FPP administration. All meals should be standardized and the composition stated in the study protocol and report.

There are situations when the investigational products should be administered following consumption of a meal (under fed conditions). These situations are described below.

7.4.3.1 Immediate-release formulations

Fasted state studies are generally preferred. However, when the product is known to cause GI disturbances if given to subjects in the fasted state, or if the labelling of the comparator product restricts administration to subjects in the fed state, then a fed-state study becomes the preferred approach.

For products with specific formulation characteristics (e.g. microemulsions, solid dispersions), bioequivalence studies performed under both fasted and fed conditions are required, unless the product is only taken in a fasted or fed state.

Typically a meal meeting the composition recommendations identified in section 7.4.3.2 should be employed in fed state studies. The exact composition of the meal may depend on local diet and customs as determined by the NRA. For studies conducted with immediate-release products there may be situations where it is appropriate to employ a pre-dose meal with a different caloric/fat content from a meal meeting the composition recommendations identified in section 7.4.3.2.

The test meal should be consumed beginning 30 minutes prior to administration of the FPP.

7.4.3.2 Modified-release formulations

In addition to a study conducted under fasted conditions, food effect studies are necessary for all multisource, modified-release formulations to ensure that the interaction between the varying conditions in the GI tract and the product

formulations does not differentially impact the performance of the multisource and comparator products. The presence of food can affect product performance both by influencing the release of the API from the formulation and by causing physiological changes in the GI tract. A significant concern with regard to modified-release products is the possibility that food may trigger a sudden and abrupt release of the API leading to "dose dumping". In these cases the objective is to select a meal that will challenge the robustness of the new multisource formulation to prandial effects on bioavailability. To achieve this, a meal that will provide a maximal perturbation to the GI tract relative to the fasted state should be employed, e.g. a high-fat (approximately 50% of the total caloric content of the meal), high-calorie (approximately 800 to 1000 kilocalories) test meal has been recommended (*2*). The meal selected should take into account local customs and diet. The caloric breakdown of the test meal should be provided in the study report.

The subject should start eating the meal 30 minutes before the FPP is administered and complete eating the meal prior to FPP administration.

7.4.4 Wash-out interval

The interval (wash-out period) between doses of each formulation should be long enough to permit the elimination of essentially all of the previous dose from the body. The wash-out period should be the same for all subjects and should normally be more than five times the median terminal half-life of the API. Consideration should be given to extending this period in some situations, e.g. if active metabolites with longer half-lives are produced or if the elimination rate of the API has high variability between subjects. In this second case a longer wash-out period should be considered to allow for the slower elimination in subjects with lower elimination rates. Just prior to administration of the treatment during the second study period, blood samples should be collected and assayed to determine the concentration of the API or metabolites. The minimum wash-out period should be at least seven days unless a shorter period is justified by a short half-life. The adequacy of the wash-out period can be estimated from the pre-dose concentrations of the API in the second study period and should be less than 5% of the observed C_{max}.

7.4.5 Sampling times

Blood samples should be taken at a frequency sufficient for assessing C_{max}, AUC and other parameters. Sampling points should include a pre-dose sample, at least 1–2 points before C_{max}, 2 points around C_{max} and 3–4 points during the elimination phase. Consequently at least seven sampling points will be necessary for estimation of the required pharmacokinetic parameters. For most APIs the number of samples necessary will be higher to compensate for between-

subject differences in absorption and elimination rate and thus enable accurate determination of the maximum concentration of the API in the blood (C_{max}) and terminal elimination rate constant in all subjects. Generally, sampling should continue for long enough to ensure that 80% of the $AUC_{0-\infty}$ can be accrued but it is not necessary to sample for more than 72 hours. The exact duration of sample collection depends on the nature of the API and the input function from the administered dosage form.

7.4.6 Sample fluids and their collection

Under normal circumstances blood should be the biological fluid sampled to measure the concentrations of the API. In most cases the API or its metabolites are measured in serum or plasma. If it is not possible to measure the API in blood, plasma or serum, the API is excreted unchanged in the urine and there is a proportional relationship between plasma and urine concentrations; urine can be sampled for the purpose of estimating exposure. The volume of each urine sample must be measured at the study centre, where possible immediately after collection, and the measurements included in the report. The number of samples should be sufficient to allow the estimation of pharmacokinetic parameters. However, in most cases the exclusive use of urine excretion data should be avoided as this does not allow estimation of the tmax and the maximum concentration. Blood, plasma, serum and urine samples should be processed and stored under conditions that have been shown not to cause degradation of the analytes. Details of these conditions should be included in the analytical validation report (see section 7.5).

The sample collection methodology must be specified in the study protocol.

7.4.7 Parameters to be assessed

In bioavailability studies, the shape and area under the plasma concentration versus time curves are mostly used to assess rate (C_{max}, t_{max}) and extent (AUC) of exposure. Sampling points or periods should be chosen such that the concentration versus time profile is sufficiently defined to allow calculation of relevant parameters. For single-dose studies, the following parameters should be measured or calculated:

- area under the plasma, serum or blood concentration–time curve from time zero to time *t* (AUC_{0-t}), where t is the last sampling time-point with a measurable concentration of the API in the individual formulation tested. The method of calculating AUC values should be specified. Non-compartmental methods should be used for pharmacokinetic calculations in bioequivalence studies;

– C_{max} is the maximum or peak concentration observed representing peak exposure of API (or metabolite) in plasma, serum or whole blood.

Usually AUC_{0-t} and C_{max} are considered to be the most relevant parameters for assessment of bioequivalence. In addition it is recommended that the following parameters be estimated:

- area under the plasma, serum or blood concentration–time curve from time zero to time infinity ($AUC_{0-\infty}$) representing total exposure, where $AUC_{0-\infty} = AUC_{0-t} + C_{last}/K_e$; C_{last} is the last measurable analyte concentration and Ke is the terminal or elimination rate constant calculated according to an appropriate method;
- t_{max} is the time after administration of the FPP at which C_{max} is observed.

For additional information the elimination parameters can be calculated:

- $t_{1/2}$ is the plasma (serum, whole blood) half-life.

For multiple-dose studies conducted with modified-release products, the following parameters should be calculated:

- AUC_{τ} is AUC over one dosing interval (τ) at steady state;
- C_{max};
- C_{min} (C_{tau}) is concentration at the end of a dosing interval;
- peak trough fluctuation is percentage difference between C_{max} and C_{min}.

As release mechanisms of pharmaceutical products become more complex, e.g. products with an immediate-release and a modified-release component, additional parameters such as partial AUC measures may be necessary to ensure the bioequivalence of two products.

When urine samples are used, cumulative urinary recovery (A_e) and maximum urinary excretion rate are employed instead of AUC and C_{max}.

7.4.8 Studies of metabolites

Generally evaluation of bioequivalence will be based on the measured concentrations of the API released from the dosage form rather than the metabolite. The concentration–time profile of the API is more sensitive to changes in formulation performance than a metabolite which is more reflective of metabolite formation, distribution and elimination.

In rare cases it may be necessary to measure concentrations of a primary active metabolite rather than those of the API if concentrations of the API are too low to allow reliable analytical measurement in blood, plasma or serum for an adequate length of time, or when the parent compound is unstable in the biological matrix.

It is important to decide beforehand and state in the study protocol, which chemical entities (API or metabolite) will be analysed in the samples and to identify the analyte whose data will be used to assess bioequivalence.

It is also important to note that measurement of one analyte, API or metabolite carries the risk of making a type 1 error (the consumer's risk) to remain at the 5% level. However, if more than one of several analytes is selected retrospectively as the bioequivalence determinant, then both the consumer and producer risks change (*9*). The analyte whose data will be used to assess bioequivalence cannot be changed retrospectively.

When measuring active metabolites, wash-out period and sampling times may need to be adjusted to enable adequate characterization of the pharmacokinetic profile of the metabolite.

7.4.9 Measurement of individual enantiomers

A non-stereoselective assay is acceptable for most bioequivalence studies. A stereospecific assay measuring the individual enantiomers should be employed when the enantiomers exhibit different pharmacokinetic properties, different pharmacodynamic properties and the exposure of the enantiomers, as estimated by their AUC ratio or C_{max} ratio, changes when there is a change in the rate of absorption.

7.5 Quantification of active pharmaceutical ingredient

For the measurement of concentrations of the active compound and/or metabolites in biological matrices, such as serum, plasma, blood and urine, the applied bioanalytical method should be well characterized, fully validated and documented to a satisfactory standard in order to yield reliable results.

The validation of bioanalytical methods and the analysis of subject samples for clinical trials in humans should be performed following the principles of good clinical practice (GCP), good laboratory practice (GLP) and the most up-to-date guidelines from stringent regulatory authorities (SRAs) on the topic of bioanalytical method validation.

State-of-the-art principles and procedures for bioanalytical method validation and analysis of study samples should be employed. The main characteristics of a bioanalytical method that are essential to ensure the acceptability of the performance and the reliability of analytical results are:

– selectivity;

- lower limit of quantification;
- the response function and calibration range (calibration curve performance);
- accuracy;
- precision;
- matrix effects;
- stability of the analyte(s) in the biological matrix;
- stability of the analyte(s) and of the internal standard in the stock and working solutions, and in extracts throughout the entire period of storage and processing conditions.

In general:

- the analytical method should be able to differentiate the analyte(s) of interest and, if employed, the internal standard from endogenous components in the matrix or other components in the sample;
- the lower limit of quantification (LLOQ), being the lowest concentration of analyte in a sample, should be estimated to prove that the analyte at this concentration can be quantified reliably, with an acceptable accuracy and precision;
- the response of the instrument with regard to the concentration of analyte should be known and should be evaluated over a specified concentration range. The calibration curve should be prepared in the same matrix as the matrix of the intended subject samples by spiking the blank matrix with known concentrations of the analyte. A calibration curve should consist of a blank sample, a zero sample and 6–8 non-zero samples covering the expected range;
- within-run and between-run accuracy and precision should be assessed on samples spiked with known amounts of the analyte, the QC samples, at a minimum of three different concentrations;
- matrix effects should be investigated when using mass spectrometric methods;
- stability of the analyte in the stock solution and in the matrix should be proven covering every step taken during sample preparation and sample analysis, as well as the storage conditions used;
- when more than one analyte is present in subject samples, it is recommended to demonstrate the stability of the analytes in the matrix in the presence of the other analytes under standard conditions such as freeze–thaw testing, short-term room temperature storage and long-term freezer storage;

- where changes are made to an analytical method that has already been validated, a full validation may not be necessary depending on the nature of the changes implemented. A partial validation may be acceptable;
- a cross-validation is needed in cases where data are obtained from different methods within and across studies or when data are obtained within a study from different laboratories applying the same method;
- analysis of subject samples should be carried out after validation of the analytical method. Before the start of the analysis of the subject samples, the performance of the bioanalytical method should have been verified;
- calibration and QC standards should be processed in an identical manner and at the same time as the subjects' samples from the same run;
- reasons for reanalysis, reinjection and reintegration of subject samples should be predefined in the protocol, study plan or SOP. Reinjection of a full analytical run or of individual calibration standard samples or QC samples, simply because the calibration or QCs failed, without any identified analytical cause, is considered unacceptable. For bioequivalence studies, reanalysis, reinjection or reintegration of subject samples for reasons related to pharmacokinetic fit is normally not acceptable as this may affect and bias the outcome of such a study;
- when analysing subject samples, the precision and accuracy of the method should be confirmed by reanalysing subject samples in a separate analytical run on a different day (incurred samples reanalysis (ISR)). ISR should be performed for each bioequivalence trial. The extent of testing done should be based on an in-depth understanding of the analytical method and analyte used;
- the samples from one subject (all periods) should be analysed in the same analytical run if possible.

Validation procedures, methodology and acceptance criteria should be specified in the analytical protocol and/or the SOP. All experiments used to support claims or draw conclusions about the validity of the method should be described in a report (method validation report).

The results of subject sample determination should be given in the analytical report together with calibration and QC sample results, repeat analyses, reinjections and reintegrations (if any) and a representative number of sample chromatograms.

7.6 Statistical analysis

The primary concern in bioequivalence assessment is to limit the risk of a false declaration of equivalence. Statistical analysis of the bioequivalence trial should demonstrate that a clinically significant difference in bioavailability between the multisource product and the comparator product is unlikely. The statistical procedures should be specified in the protocol before the data collection starts.

The statistical method for testing bioequivalence is based on the determination of the 90% confidence interval around the ratio of the log-transformed population means (multisource/comparator) for the pharmacokinetic parameters under consideration and by carrying out two one-sided tests at the 5% level of significance (*10*). To establish bioequivalence, the calculated confidence interval should fall within a preset bioequivalence limit. The procedures should lead to a decision scheme which is symmetrical with respect to the formulations being compared (i.e. leading to the same decision whether the multisource formulation is compared to the comparator product or the comparator product to the multisource formulation).

All concentration-dependent pharmacokinetic parameters (e.g. AUC and C_{max}) should be log-transformed using either common logarithms to the base 10 or natural logarithms. The choice of either common or natural logs should be consistent and should be stated in the study report.

Logarithmically transformed, concentration-dependent pharmacokinetic parameters should be analysed using analysis of variance (ANOVA). Normally the ANOVA model should include formulation, period, sequence and subject factors. Parametric methods, i.e. those based on normal distribution theory, are recommended for the analysis of log-transformed bioequivalence measures.

The general approach is to construct a 90% confidence interval for the quantity $\mu T - \mu R$ and to reach a conclusion of pharmacokinetic equivalence if this confidence interval is within the stated limits. The nature of parametric confidence intervals means that this is equivalent to carrying out two one-sided tests of the hypothesis at the 5% level of significance (*10*, *11*). The antilogs of the confidence limits obtained constitute the 90% confidence interval for the ratio of the geometric means between the multisource and comparator products. The same procedure should be used for analysing parameters from steady-state trials or cumulative urinary recovery if required.

For t_{max} descriptive statistics should be given. Where t_{max} is considered clinically relevant, median and range of tmax should be compared between test and comparator to exclude numerical differences with clinical importance. A formal statistical comparison is rarely necessary. Generally the sample size is not calculated to have enough statistical power for t_{max}. However, if t_{max} is to be subjected to a statistical analysis, this should be based on non-parametric methods and should be applied to untransformed data. A sufficient number

of samples around predicted maximal concentrations should have been taken to improve the accuracy of the t_{max} estimate. For parameters describing the elimination phase ($t_{1/2}$) only descriptive statistics should be given. See section 7.2.3 for information on the handling of extreme data.

Exclusion of data for statistical or pharmacokinetic reasons alone is not acceptable.

7.6.1 Two-stage sequential design

In some situations reliable information concerning the expected variability in the parameters to be estimated may not be available. In such situations a two-stage sequential study design can be employed such that an accurate estimate of the variability can be determined in the first stage of the study. The number of subjects employed in the first stage is generally based on the most likely intra- subject variance estimate with some added subjects to compensate for drop-outs. The analysis undertaken at the end of the first stage is treated as an interim analysis. If bioequivalence is proven at this point the study can be terminated. If bioequivalence is not proven at the end of the first stage, the second stage is conducted employing an appropriate number of additional subjects as determined based on the variance estimates and point estimate calculated from the stage 1 data. At the end of the second stage, the results from both groups combined are used in the final analysis. In order to use a two-stage design, adjustments must be made to protect the overall Type 1 error rate and maintain it at 5%. To do this, both the interim and final analyses must be conducted at adjusted levels of significance with the confidence intervals calculated using the adjusted values.

It is recommended that the same alpha for both stages be employed. This gives an alpha of 0.0294 for this case (*12*), however, the amount of alpha to be spent at the time of the interim analysis can be set at the study designer's discretion. For example, the first stage may be planned as an analysis where no alpha is spent in the interim analysis since the objective of the interim analysis is to obtain information on the point estimate difference and variability and where all the alpha is spent in the final analysis with the conventional 90% confidence interval. In this case no test against the acceptance criteria is made during the interim analysis and bioequivalence cannot be proven at that point. The proposed statistical plan must be clearly defined in the study protocol, including the adjusted significance level that is to be employed during each analysis.

A factor for stage should be included in the ANOVA model for the final analysis of the combined data from the two stages.

This approach can be employed in both cross-over and parallel study designs.

7.7 Acceptance ranges

AUC_{0-t} - ratio

The 90% confidence interval for this measure of relative bioavailability should lie within a bioequivalence range of 80.00–125.00%. If the API is determined to possess a narrow therapeutic index (NTI) the bioequivalence acceptance range should be restricted 90.00–111.11%.

The same criterion applies to the parameter AUCτ in multiple-dose studies and for partial AUCs if they are necessary for comparative testing of a modified-release product.

C_{max} - ratio

For maximal concentration data, the acceptance limit of 80.00–125.00% should be applied to the 90% confidence interval for the mean C_{max} ratio. However, this measure of relative bioavailability is inherently more variable than, for example, the AUC ratio, and in certain cases this variability can make proving bioequivalence challenging. See section 7.9.3 for information on an approach for proving bioequivalence when the intra-subject variability for the C_{max} parameter is high. If the API is determined to possess a narrow therapeutic index, the bioequivalence acceptance range may need to be restricted to 90.00–111.11%, if appropriate. The same criterion applies to the parameters C_{max} and C_{tau} in multiple-dose studies.

t_{max} - difference

Statistical evaluation of tmax makes sense only if there is a clinically relevant claim for rapid onset of action or concerns about adverse effects. In such a case, comparison of the median and range data for each product should be undertaken. For other pharmacokinetic parameters the same considerations as outlined above apply.

7.8 Reporting of results

The report of a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation in compliance with GCP and GLP rules. The relevant International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline (*13*) can be used in the preparation of the study report. The responsible investigator(s) should sign the respective sections of the report. Names and affiliations of the responsible investigator(s), site of the study and period of its execution should be stated.

The names and batch numbers of the pharmaceutical products used in the study as well as the composition(s) of the tests product(s) should be given. Results of in vitro dissolution tests conducted in media with pHs of 1.2, 4.5

and 6.8 and the QC media, if different, should be provided. In addition, the applicant should submit a signed statement confirming that the test product is identical to the pharmaceutical product that is submitted for registration.

The bioanalytical validation report should be attached. This report should include the information recommended in the SRA guidance chosen as a guide for the bioanalytical portion of a study (see section 7.5).

All results should be presented clearly. All concentrations measured in each subject and the sampling time should be tabulated for each formulation. Tabulated results showing API concentration analyses according to analytical run (including runs excluded from further calculations, together with all calibration standards and QC samples from the respective run) should also be presented. The tabulated results should present the date of run, subject, study period, product administered (multisource or comparator) and time elapsed between FPP administration and blood sampling, in a clear format. The procedure for calculating the parameters used (e.g. AUC) from the raw data should be stated. Any deletion of data should be documented and justified.

Individual blood concentration/time curves should be plotted on a linear/linear and log/linear scale. All individual data and results should be given, including information on subjects who dropped out. The drop-outs and/or withdrawn subjects should be reported and accounted for. All adverse events that occurred during the study should be reported together with the study physician's classification of the events. Further, any treatments given to address adverse events should be reported.

Results of all measured and calculated pharmacokinetic parameters should be tabulated for each subject–formulation combination together with descriptive statistics. The statistical report should be sufficiently detailed to enable the statistical analyses to be repeated if necessary. If the statistical methods applied deviate from those specified in the study protocol the reasons for the deviations should be stated.

7.9 Special considerations

7.9.1 Fixed-dose combination products

If the bioequivalence of FDC products is assessed by in vivo studies, the study design should follow the same general principles as described in previous sections. The multisource FDC product should be compared with the pharmaceutically equivalent comparator FDC product. In certain cases (e.g. when no comparator FDC product is available on the market) separate products administered in free combination can be used as a comparator (*3*). Sampling times should be chosen to enable the pharmacokinetic parameters of all APIs to be adequately assessed. The bioanalytical method should be validated with respect to all analytes measured in the presence of the other analytes. Statistical analyses should be

performed with pharmacokinetic data collected on all active ingredients; the 90% confidence intervals of test/comparator ratio of all active ingredients should be within acceptance limits.

7.9.2 Clinically important variations in bioavailability

Innovators should make every effort to provide formulations with good bioavailability characteristics. If a better formulation is later developed by the innovator, this should then serve as the comparator product. A new formulation with a bioavailability outside the acceptance range for an existing pharmaceutical product is not interchangeable by definition.

7.9.3 "Highly variable active pharmaceutical ingredients"

A "highly variable API" has been defined as an API with an intrasubject variability of > 30% in terms of the ANOVA CV (*14*). Proving the bioequivalence of FPPs containing highly variable APIs can be problematic because the higher the ANOVA CV, the wider the 90% confidence interval. Thus large numbers of subjects must be enrolled in studies involving highly variable APIs to achieve adequate statistical power.

Although there is variability in how regulatory authorities deal with the issue of highly variable APIs, the most rigorous of the current approaches involve the scaling of bioequivalence acceptance criteria based on the intrasubject standard deviation observed in the relevant parameters for the comparator product (*15–17*). Of the two most common assessment parameters C_{max} is subject to the highest variability and hence is the parameter for which a modified approach is most needed.

For highly variable FPPs it is recommended that a three-way partial replicate (where the comparator product is administered twice) or a four-way fully replicated cross-over bioequivalence study be conducted and reference-scaled average bioequivalence be employed to widen the acceptance interval for the Cmax parameter, if the intrasubject variability for C_{max} following replicate administrations of the comparator product is > 30%. If this is the case the acceptance criteria for C_{max} can be widened to a maximum of 69.84–143.19%. The applicant should justify that the calculated intrasubject variability is a reliable estimate and that it is not the result of outliers.

The extent of the widening of the acceptance interval for C_{max} is defined based upon the intrasubject variability seen in the bioequivalence study using scaled average bioequivalence according to $[U, L] = \exp [\pm k \cdot sWR]$, where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and sWR is the intrasubject standard deviation of the log-transformed values of C_{max} of the reference product. Table A6.2 gives examples of how different levels of variability lead to different acceptance limits using this methodology.

Table A6.2
Acceptance limits for different levels of variability

Intrasubject CV (%)	Lower limit	Upper limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥ 50	69.84	143.19

$$CV(\%) = \sqrt{(e\text{^}(\ [\![S\_WR]\!]\ \text{^}2\ ) - 1)}$$

The geometric mean ratio (GMR) for C_{max} should lie within the conventional acceptance range of 80.00–125.00%.

The standard bioequivalence acceptance criterion for AUC should be maintained without scaling. If the intrasubject variability for C_{max}, following replicate administration of the comparator, is found to be < 30%, standard bioequivalence acceptance criteria should be applied to both AUC and C_{max} without scaling.

For multiple-dose studies, a similar approach can be applied to the following parameters if the intrasubject variability for the parameter is found to be > 30%: C_{max}, C_{tau} and partial AUCs if required. The standard bioequivalence acceptance criterion will apply to AUCτ without scaling.

The approach to be employed should be clearly defined prospectively in the study protocol. The regulatory authority of the country to which the study data will be submitted should be consulted before commencing the study to confirm that the proposed approach is acceptable for that jurisdiction.

8. Pharmacodynamic equivalence studies

Studies in healthy volunteers or patients using pharmacodynamic measurements may be used for establishing equivalence between two pharmaceutical products when the pharmacokinetic approach is not feasible. Pharmacodynamic equivalence studies may become necessary if quantitative analysis of the API and/or metabolite(s) in blood, serum, plasma or urine cannot be made with sufficient accuracy and sensitivity; however, this is extremely unlikely given current technology. Furthermore, pharmacodynamic equivalence studies in humans are required if measurements of API concentrations cannot be used as

surrogate end-points for the demonstration of efficacy and safety of the particular pharmaceutical product as is the case with pharmaceutical products designed to act locally. However, local availability studies based on pharmacokinetic studies alone or in combination with in vitro dissolution studies are being considered as surrogate end-points for the demonstration of equivalent biopharmaceutical quality and release at the site of action for some products acting locally. In addition, bioequivalence studies are also required in order to demonstrate equivalent systemic exposure for systemic safety purposes.

Pharmacodynamic studies are not recommended for orally administered pharmaceutical products for systemic action when the API is absorbed into the systemic circulation and a pharmacokinetic approach can be used to assess systemic exposure and establish bioequivalence. This is because the sensitivity to detect differences between products in their biopharmaceutical quality, release and absorption is lower with pharmacodynamic or clinical end-points. As the dose–response curve for pharmacodynamics or clinical end-points is usually flatter than the relationship between dose and pharmacokinetic parameters, it is essential to ensure the internal validity of the study by showing assay sensitivity, i.e. the ability to distinguish the response obtained by adjacent doses (twofold or even fourfold difference in dose). It is essential to perform the comparison at the dose level at which the dose-response is steepest, which may require firstly doing a pilot study for its identification. Furthermore, variability in pharmacodynamic measures is usually greater than that in pharmacokinetic measures. In addition, pharmacodynamic measures are often subject to significant placebo effects, which add to the variability and complicate experimental design. The result is often that huge numbers of patients would have to be enrolled in pharmacodynamic studies to achieve adequate statistical power.

If pharmacodynamic studies are to be used they must be performed as rigorously as bioequivalence studies and the principles of GCP must be followed (*4*).

The following requirements must be recognized when planning, conducting and assessing the results of a study intended to demonstrate equivalence by measuring pharmacodynamic responses.

- The response measured should be a pharmacological or therapeutic effect which is relevant to the claims of efficacy and/or safety.
- The methodology must be validated for precision, accuracy, reproducibility and specificity.
- Neither the multisource product nor the comparator product should produce a maximal response during the course of the study since it may be impossible to detect differences between formulations given in doses which give maximum or near maximum effects.Investigation of dose–response relationships may be a necessary part of the design.

- The response should be measured quantitatively, preferably under double blind conditions, and be recordable by an instrument that produces and records the results of repeated measurements to provide a record of the pharmacodynamic events, which are substitutes for measurements of plasma concentrations. Where such measurements are not possible, recordings on visual analogue scales may be used. Where the data are limited to qualitative (categorized) measurements, appropriate special statistical analysis will be required.
- Participants should be screened prior to the study to exclude non-responders. The criteria by which responders are distinguished from non-responders must be stated in the protocol.
- In situations where an important placebo effect can occur, comparison between pharmaceutical products can only be made by *a priori* consideration of the potential placebo effect in the study design. This may be achieved by adding a third phase with placebo treatment during the design of the study.
- The underlying pathology and natural history of the condition must be considered in the study design. There should be confirmation that the baseline conditions are reproducible.
- A cross-over design can be used. Where this is not appropriate, a parallel-group study design should be chosen.

The basis for the selection of the multisource and comparator products should be the same as described in section 7.3.

In studies in which continuous variables can be recorded, the time course of the intensity of the action can be described in the same way as in a study in which plasma concentrations are measured and parameters can be derived that describe the area under the effect–time curve, the maximum response and the time at which the maximum response occurred.

The comparison between the multisource and the comparator product can be performed in two different ways:

(a) *dose-scale analysis or relative potency*: this is defined as the ratio of the potency of the multisource product to that of the comparator product. It is a way of summarizing the relationship between the dose–response curves of the multisource and comparator product;

(b) *response-scale analysis*: this consists of demonstration of equivalence (for at least two dose levels) at the pharmacodynamic end-point.

For either approach to be acceptable a minimum requirement is that the study has assay sensitivity. To meet this requirement, at least two non-zero levels need to be studied and one dose level needs to be shown to be superior to the other.

Therefore, it is recommended that unless otherwise justified more than one dose of both the multisource and comparator products are studied. However, it is essential that doses on the steep part of the dose–response curve are studied. If the chosen dose is too low on the dose–response curve, then demonstrating equivalence between two products is not convincing, as this dose could be subtherapeutic. Equally if a dose at the top of the dose–response curve is included, similar effects will be seen for doses much higher than that studied and hence demonstrating equivalence at this dose level would also not be convincing.

The results using both approaches should be provided. In both cases the observed confidence intervals comparing multisource and comparator products should lie within the chosen equivalence margins to provide convincing evidence of equivalence. As for bioequivalence studies, 90% confidence intervals should be calculated for relative potency whereas 95% confidence intervals should be calculated for the response-scale analysis. It should be noted that the acceptance range as applied for bioequivalence assessment may not be appropriate. For both approaches the chosen equivalence ranges should be prespecified and appropriately justified in the protocol.

9. Clinical equivalence studies

In some instances (see example (e) in section 5.1, In vivo studies) plasma concentration time–profile data may not be suitable for assessing equivalence between two formulations. Although in some cases pharmacodynamic equivalence studies can be an appropriate tool for establishing equivalence, in others this type of study cannot be performed because of a lack of meaningful pharmacodynamic parameters that can be measured; a comparative clinical trial then has to be performed to demonstrate equivalence between two formulations. However, it is preferable to assess equivalence by performing a pharmacokinetic equivalence study rather than a clinical trial that is less sensitive and would require a huge number of subjects to achieve adequate statistical power. For example, it has been calculated that 8600 patients would be required to give adequate statistical power to detect a 20% improvement in response to the study API compared with placebo (*18*, *19*). Similarly it was calculated that 2600 myocardial infarct patients would be required to show a 16% reduction in risk. A comparison of two formulations of the same API based on such end-points would require even greater numbers of subjects (*19*).

If a clinical equivalence study is considered as being undertaken to prove equivalence, the same statistical principles apply as for the bioequivalence studies, although a 95% confidence interval might be necessary for pharmacodynamic and clinical end-points in contrast to the 90% confidence level employed conventionally for pharmacokinetic studies. The number of patients to be included in the study will depend on the variability of the target parameters and

the acceptance range and is usually much higher than the number of subjects needed in bioequivalence studies.

The methodology for establishing equivalence between pharmaceutical products by means of a clinical trial with a therapeutic end-point conducted in patients is not yet as far advanced as that for bioequivalence studies. However, some important items that need to be defined in the protocol can be identified as follows:

- the target parameters that usually represent relevant clinical end-points from which the onset, if applicable and relevant, and intensity of the response are to be derived;
- the size of the acceptance range has to be defined case by case, taking into consideration the specific clinical conditions. These include, among others, the natural course of the disease, the efficacy of available treatments and the chosen target parameter. In contrast to bioequivalence studies (where a conventional acceptance range is applied) the size of the acceptance range in clinical trials should be set individually according to the therapeutic class and indication(s);
- the currently used statistical method is the confidence interval approach;
- the confidence intervals can be derived from either parametric or non-parametric methods;
- where appropriate a placebo arm should be included in the design;
- in some cases it is relevant to include safety end-points in the final comparative assessments.

The selection basis for the multisource and comparator products should be the same as described in section 7.3.

10. In vitro equivalence testing

Over the past three decades dissolution testing has evolved into a powerful tool for characterizing the quality of oral pharmaceutical products. The dissolution test, at first exclusively a QC test, is now emerging as a surrogate equivalence test for certain categories of orally administered, pharmaceutical products. For these products (typically solid oral dosage forms containing APIs with suitable properties) similarity in in vitro dissolution profiles, in addition to excipient comparisons and a risk–benefit analysis, can be used to document equivalence of a multisource product with a comparator product.

It should be noted that although the dissolution tests recommended in *The International Pharmacopoeia* (Ph.Int.) (*20*) for QC have been designed to be compatible with the biowaiver dissolution tests, they do not fulfil all the

requirements for evaluating equivalence of multisource products with comparator products. Dissolution tests for QC purposes, including those described in other pharmacopoeias, do not address all test conditions required for evaluating equivalence of multisource products and should not be applied for this purpose.

10.1 In vitro equivalence testing in the context of the Biopharmaceutics Classification System

10.1.1 Biopharmaceutics Classification System

The BCS is based on aqueous solubility and intestinal permeability of the API. It classifies the API into one of four classes:

- Class 1: high solubility, high permeability;
- Class 2: low solubility, high permeability;
- Class 3: high solubility, low permeability;
- Class 4: low solubility, low permeability.

Combining the dissolution results and a critical examination of the excipients of the pharmaceutical product with these two properties of the API takes the four major factors that govern the rate and extent of API absorption from immediate release, solid dosage forms into account (*21*). On the basis of their dissolution properties, immediate-release dosage forms can be categorized as having "very rapid", "rapid", or "not rapid" dissolution characteristics.

On the basis of solubility and permeability of the API, excipient nature, excipient content and dissolution characteristics of the dosage form, the BCS approach provides an opportunity to waive in vivo bioequivalence testing for certain categories of immediate release FPPs. Oral FPPs containing an API possessing a narrow therapeutic index are not eligible for a so-called biowaiver based on the BCS approach.

10.1.1.1 High solubility

An API is considered highly soluble when the highest single therapeutic dose as determined by the relevant regulatory authority, typically defined by the labelling for the innovator product, is soluble in 250 mL or less of aqueous media over the pH range of 1.2–6.8. The pH solubility profile of the API should be determined at 37 ± 1 °C in aqueous media. A minimum of three replicate determinations of solubility at each pH condition is recommended.

10.1.1.2 High permeability

An API is considered highly permeable when the extent of absorption in humans is 85% or more based on a mass balance determination or in comparison with an intravenous comparator dose. Ideally the mass balance study or comparison

with an intravenous comparator dose would be conducted at the same dose as that used for the solubility classification. If this is not possible, dose linearity of pharmacokinetics should be used to justify the use of other doses.

Absolute bioavailability or mass balance study data obtained from published literature may be accepted as evidence if it can be clearly established that the data were derived from appropriately designed studies.

In vivo intestinal perfusion in humans is an acceptable alternative test method.

When this method is used for permeation studies, suitability of the methodology should be demonstrated, including determination of permeability relative to that of a reference compound whose fraction of dose absorbed has been documented to be at least 85%, as well as use of a negative control.

Supportive data can be provided by the following additional test methods:

(i) in vivo or in situ intestinal perfusion using animal models;

(ii) in vitro permeation across a monolayer of cultured epithelial cells (e.g. Caco 2) using a method validated using APIs with known permeabilities, although data from neither method (i) nor (ii) would be considered acceptable on a stand-alone basis.

In these experiments, high permeability is assessed with respect to the high permeability of a series of reference compounds with documented permeabilities and values of the absorbed fraction, including some for which fraction of dose absorbed is at least 85% (*22*).

10.1.2 Determination of dissolution characteristics of multisource products in consideration of a biowaiver based on the Biopharmaceutics Classification System

For exemption from an in vivo bioequivalence study, an immediate release, multisource product should exhibit very rapid or rapid in vitro dissolution characteristics (see sections 10.1.2.1 and 10.1.2.2), depending on the BCS properties of the API. In vitro data should also demonstrate the similarity of dissolution profiles between the multisource and comparator products.

10.1.2.1 Very rapidly dissolving

A multisource product is considered to be very rapidly dissolving when no less than 85% of the labelled amount of the API dissolves in 15 minutes at 37 ± 1 °C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

– pH 1.2 HCl solution or buffer;

– a pH 4.5 acetate buffer;
– a pH 6.8 phosphate buffer.

Pharmacopoeial buffers (e.g. Ph.Int.) are recommended for use at these three pH values. Surfactants should not be used in the dissolution media. Enzymes (pepsin at pH 1.2 and pancreatin at pH 6.8) may be used if the pharmaceutical product contains gelatin (e.g. capsules or caplets) due to the possibility of cross-linking.

(See also section 10.2, Dissolution profile comparison.)

10.1.2.2 Rapidly dissolving

A multisource product is considered to be rapidly dissolving when no less than 85% of the labelled amount of the API dissolves in 30 minutes at 37 ± 1 °C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

– pH 1.2 HCl solution or buffer;
– pH 4.5 acetate buffer;
– pH 6.8 phosphate buffer.

Surfactants should not be used in the dissolution media. Enzymes (pepsin at pH 1.2 and pancreatin at pH 6.8) may be used if the pharmaceutical product contains gelatin (e.g. capsules or caplets) due to the possibility of cross-linking.

10.2 Qualification for a biowaiver based on the Biopharmaceutics Classification System

A biowaiver based on the BCS considers:

(a) the solubility and intestinal permeability of the API (see section 10.1);
(b) the similarity of the dissolution profiles of the multisource and comparator products in pH 1.2, 4.5 and 6.8 media (see below);
(c) the excipients used in the formulation (see below);
(d) the risks of an incorrect biowaiver decision in terms of the therapeutic index of and clinical indications for the API (see section 5.1 for cases where an in vivo study would be required to demonstrate bioequivalence).

Only when there is an acceptable risk–benefit balance in terms of public health and risk to the individual patient should bioequivalence testing be waived and the in vitro methods described in this section applied as a test of product equivalence.

Risk reduction and assessment of excipients

The risk of reaching an incorrect decision that the multisource product is equivalent to the comparator product can be reduced by correct classification of the API and by following the recommendations for dissolution testing and comparison of the dissolution profiles. In all cases it should be further demonstrated that the excipients included in the formulation of the multisource product are well established for use in products containing that API and that the excipients used will not lead to differences between the comparator and multisource product with respect to processes affecting absorption (e.g. by effects on GI motility or interactions with transport processes) or which might lead to interactions that alter the pharmacokinetics of the API.

In all cases, well established excipients in usual amounts should be used in multisource products. Excipients that might affect the bioavailability of the API, e.g. mannitol, sorbitol or surfactants, should be identified and an assessment of their impact provided. These critical excipients should not differ qualitatively and must be quantitatively similar between the test product and comparator product.

For biowaivers for products containing Class 1 APIs there is some flexibility in the excipients employed, with the exception of critical excipients as discussed above. It is recommended that the excipients employed be present in the comparator product or be present in other products which contain the same API as the multisource product and which have marketing authorizations in ICH associated countries.

For biowaivers for products containing Class 3 APIs all excipients in the proposed product formulation should be qualitatively the same and quantitatively similar to that of the comparator product, as defined by the WHO quality limits on allowable quantitative changes in excipients for a variation (*23*).

As a general rule, the closer the composition of the multisource product to that of the comparator product with regard to excipients, the lower the risk of an inappropriate decision on equivalence using a biowaiver based on the BCS.

Sub- and supra-bioavailable products

A further consideration is the potential risk to public health and to the individual patient, should an inappropriate decision with respect to bioequivalence be reached. Essentially there are two possible negative outcomes.

The first arises when the multisource product is sub bioavailable. In this case substitution of the comparator with the multisource product could lead to reduced therapeutic efficacy. APIs which must reach a certain concentration to be effective (e.g. antibiotics) are most susceptible to problems of sub bioavailability.

The second negative outcome arises when the multisource product is supra bioavailable. In this case substitution of the comparator with the

multisource product could lead to toxicity. APIs which exhibit toxic effects at concentrations close to the therapeutic range are most susceptible to problems of supra bioavailability. For these reasons therapeutic index is an important consideration in determining whether the biowaiver based on BCS can be applied or not.

Dissolution profile comparison

Approval of multisource formulations using comparative in vitro dissolution studies should be based on the generation of comparative dissolution profiles rather than a single point dissolution test. For details refer to Appendix 1.

10.2.1 Dissolution criteria for biowaivers based on the Biopharmaceutics Classification System according to the properties of active pharmaceutical ingredients

The major application of BCS is to provide criteria for biowaiver of multisource products. It is recommended that products containing the following BCS classes of APIs be eligible for a biowaiver:

- BCS Class 1 APIs, if the multisource and comparator product are *very rapidly dissolving or similarly rapidly dissolving*;
- BCS Class 3 APIs, if the multisource and comparator product are *very rapidly dissolving*.

In summary, biowaivers for solid oral dosage forms based on BCS can be considered under the following conditions.

1. Dosage forms of APIs that are highly soluble, highly permeable (BCS Class 1) with acceptable excipient content and favourable risk–benefit analysis and which are rapidly dissolving, are eligible for a biowaiver based on the BCS provided:

   (i) the dosage form is rapidly dissolving (as defined in section 10.1.2.2) and the dissolution profile of the multisource product is similar to that of the comparator product in aqueous buffers at pH 1.2, pH 4.5 and pH 6.8 using the paddle method at 75 rpm or the basket method at 100 rpm and meets the criteria of dissolution profile similarity, $f_2 \geq 50$ (or equivalent statistical criterion);

   (ii) if both the comparator and the multisource dosage forms are very rapidly dissolving (as defined in section 10.1.2.1) the two products are deemed equivalent and a profile comparison is not necessary.

2. Dosage forms of APIs that are highly soluble and have low permeability (BCS Class 3) are eligible for biowaivers provided all the criteria (a–d) listed

in section 10.2 are met and the risk–benefit is additionally addressed in terms of extent, site and mechanism of absorption.

In general, the risks of reaching an inappropriate biowaiver decision need to be more critically evaluated when the extent of absorption is lower (especially if absolute bioavailability < 50%); therefore it is essential that the excipients in the proposed product formulation be scrutinized carefully. In order to minimize the risk of an inappropriate decision, excipients in the proposed product formulation should be qualitatively the same and quantitatively similar to that of the comparator.

If it is deemed that the risk of reaching an inappropriate biowaiver decision and its associated risks to public health and for individual patients is acceptable, the multisource product is eligible for a biowaiver based on BCS when both the comparator and the multisource dosage forms are very rapidly dissolving (85% dissolution in 15 minutes as described in section 10.1.2.1).

10.3 In vitro equivalence testing based on dose-proportionality of formulations

Under certain conditions, approval of different strengths of a multisource product can be considered on the basis of dissolution profiles if the formulations have proportionally similar compositions.

10.3.1 Proportional formulations

For the purpose of this guidance proportional formulations can be defined in two ways, based on the strength of dosage forms.

(i) All active and inactive ingredients are exactly in the same proportions in the different strengths (e.g. a tablet of 50 mg strength has exactly half of all the active and inactive ingredients contained in a tablet of 100 mg strength and twice what would be contained in a tablet of 25 mg strength). For immediate release products, coating components, capsule shell, colour agents and flavours are not generally required to meet this requirement.

(ii) For an FPP, where the amount of the API in the dosage form is relatively low (up to 10 mg per dosage unit or not more than 5% of the weight of the dosage form), the total weight of the dosage form remains similar for all strengths.

For (ii) a waiver is considered:

- if the amounts of the different excipients or capsule contents are the same for the strengths concerned and only the amount of the API has changed;

- if the amount of filler is changed to account for the change in amount of API: the amounts of other core excipients or capsule content should be the same for the strengths concerned.

10.3.2 Qualification for biowaivers based on dose-proportionality of formulations

10.3.2.1 Immediate-release tablets

A biowaiver based on dose proportionality of formulations for a series of strengths of a multisource product, when the pharmaceutical products are manufactured with the same manufacturing process, may be granted when:

(i) an in vivo equivalence study has been performed on at least one of the strengths of the formulation. As described in section 7.4.1, the strength studied will usually be the highest strength, unless a lower strength is chosen for reasons of safety or the API is highly soluble and displays linear pharmacokinetics);

(ii) all strengths are proportionally similar in formulation to that of the strength studied;

(iii) the dissolution profiles for the different strengths are similar at pH 1.2, 4.5, 6.8 and for the QC media, unless justified by the absence of sink conditions. If the different strengths of the test product do not show similar dissolution profiles owing to the absence of sink conditions in any of the above media, this should be substantiated by showing similar dissolution profiles when testing the same dose per vessel (e.g. two tablets of 5 mg versus one tablet of 10 mg) or by showing the same behaviour in the comparator product.

As for the BCS based biowaiver, if both strengths release 85% or more of the label amount of the API in 15 minutes, using all three dissolution media as recommended in section 10.2, the profile comparison with an f_2 test is unnecessary.

In the case where an immediate release dosage form with several strengths deviates from proportionality a bracketing approach is possible, so that only two strengths representing the extremes need to be studied in vivo.

If approval of one strength of a product is based on a BCS based biowaiver instead of an in vivo equivalence study, other strengths in the series of strengths should also be assessed based on BCS based biowaivers as opposed to a biowaiver based on dose-proportionality.

10.3.2.2 Delayed-release tablets and capsules

For delayed release tablets, for a series of strengths of a multisource product where the strengths are proportionally similar in formulation to that of the

strength studied in an in vivo equivalence study, a lower strength can be granted a biowaiver if it exhibits similar dissolution profiles, $f_2 \geq 50$, in the recommended test condition for delayed release product, e.g. dissolution test in acid medium (pH 1.2) for 2 hours followed by dissolution in pH 6.8. When evaluating proportionality in composition, it is recommended to consider the proportionality of gastro resistant coating with respect to the surface area (not to core weight) to have the same gastro resistance (mg/cm2).

For delayed release capsules where different strengths have been achieved solely by means of adjusting the number of beads containing the API, similarity in the dissolution profile of the new (lower) strength to that of the approved strength ($f_2 > 50$) under the test conditions recommended for delayed release products (see above) is sufficient for a biowaiver.

10.3.2.3 Extended-release tablets and capsules

(a) For extended-release tablets, when there is a series of strengths of a multisource product that are proportionally similar in their active and inactive ingredients and have the same API release mechanism, in vivo bioequivalence studies should be conducted with the highest proposed strength. Subsequently, lower strengths in the series can be granted a biowaiver if they exhibit similar dissolution profiles to the highest strength, $f_2 \geq 50$, in three different pH buffers (between pH 1.2 and 7.5) and the QC media by the recommended test method.

(b) For extended-release tablets with an osmotic pump release mechanism, the dissolution profile comparison ($f_2 \geq 50$) under one recommended test condition is sufficient for a biowaiver based on dose proportionality of formulation.

(c) For extended-release, beaded capsules where different strengths have been achieved solely by means of adjusting the number of beads containing the API, a dissolution profile comparison ($f_2 \geq 50$) under one recommended test condition is sufficient for a biowaiver based on dose proportionality of formulation.

10.3.3 Dissolution profile comparison for biowaivers based on dose-proportionality of formulations

As for biowaivers based on the BCS, a model-independent mathematical approach (e.g. f_2 test) can be used for comparing the dissolution profiles of two products.The dissolution profile of the two products (reference strength and additional strength) should be measured under the same test conditions. The dissolution sampling times for both reference strength and additional strength profiles should be the same. For example:

– for immediate release products 5, 10, 15, 20, 30, 45 and 60 minutes;
– for 12-hour extended-release products 1, 2, 4, 6, 8 and 12 hours;
– for 24-hour extended-release products 1, 2, 4, 6, 8, 16 and 24 hours.

For the application of the f_2 value see Appendix 1.

10.4 In vitro equivalence testing for non-oral dosage forms

In the case of intravenous micellar solutions with the same qualitative and quantitative composition of the surfactant, but significant changes to other excipients, an in vitro comparison might avoid the need for in vivo studies if a similar micellar system and API release from the micelle after dilution of the FPP or API administration into the blood system is ensured (*24*).

Locally applied, locally acting products in the form of aqueous suspensions containing the same API(s) in the same molar concentration and essentially the same excipients in comparable concentrations might be waived from the demonstration of equivalence by means of local availability, pharmacodynamic or clinical studies if in vitro characterization is able to ensure a similar crystallographic structure and particle size distribution as well as any other in vitro test specific for each dosage form, e.g. dissolution. The methodological details for the techniques mentioned below are not covered in these guidelines. Additional information regarding these techniques should be sought from guidelines produced by SRAs or from state-of-the-art literature.

(a) Suspensions for nebulization with the same qualitative and quantitative composition as the comparator product might be waived from in vivo studies if the particles in the suspensions are shown to have the same crystallographic structure and particle size distribution as those from the comparator product, as well as comparability in any other appropriate in vitro test, e.g. dissolution. In addition, the nebulized droplets should exhibit a similar aerodynamic particle size distribution to that of the comparator product.

(b) Suspensions for nebulization with different qualitative and quantitative composition might be granted a waiver if, in addition to the requirements defined above under (a), the difference in excipient composition does not alter the nebulizer efficiency (e.g. by the presence or absence of a different surfactant or preservative) and the aerodynamic particle size distribution (e.g. altering product hygroscopicity by the presence of a different amount of salt as isotonic agent). To this end the appropriate state-of-the-art in vitro test should be conducted to ensure product equivalence.

Any difference in excipients should be critically reviewed because certain excipients that are considered irrelevant in other dosage forms (e.g. preservative, substance to adjust tonicity or thickening agent) may affect safety and/or efficacy of the product.

(c) Nasal drops where the API is in suspension with the same qualitative and quantitative composition as the comparator product might be waived from in vivo studies if the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution to that of the comparator product, as well as comparability in any other appropriate in vitro test, e.g. dissolution.

(d) Nasal drops where the API is in suspension, with qualitative or quantitative differences in excipient composition with respect to the comparator product, might be waived from in vivo studies if, in addition to the requirements defined above under (c), the difference in excipient composition does not affect efficacy and safety (e.g. a different preservative may affect the safety profile due to greater irritation of the nasal passages and a different viscosity or thixotropy may affect the residence time in the site of action). Therefore any difference in excipients should be critically reviewed.

(e) Nasal sprays in solution with the same qualitative and quantitative composition in excipients can be granted waivers based on a battery of in vitro tests as defined by SRAs (*18*, *25*).

(f) Nasal sprays in solution with qualitative and quantitative differences in the excipient composition might be waived if, in addition to showing similarity in the battery of in vitro tests referenced under (e), differences in excipients are critically reviewed as described above under (d).

(g) Nasal sprays in suspension with the same qualitative and quantitative composition in excipients might be waived if, in addition to the battery of in vitro tests referenced above under (e), the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution, as well as comparability in any other appropriate in vitro test, e.g. dissolution.

(h) Nasal sprays in suspension with qualitative and quantitative differences in excipient composition might be waived if, in addition to the battery of in vitro tests referenced above under (e) and (g), differences in excipients are critically reviewed as described above under (d).

(i) In the case of pressurized metered dose inhalers in solution or suspension, in vivo studies might be waived if similarity is shown in a battery of in vitro tests as described in specific guidelines produced by SRAs (*26*). A waiver of in vivo studies for a dry powder inhaler (DPI) is not considered feasible unless the device for the DPI is identical to the comparator.

(j) For pharmaceutically equivalent topical gel products, equivalence can be demonstrated by means of in vitro membrane diffusion studies when the products contain essentially the same excipients in comparable concentrations and the API(s) in the product are in solution (*27*).

(k) Otic and ophthalmic suspensions with the same qualitative and quantitative composition in excipients might be granted a waiver if the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution, as well as comparability in any other appropriate in vitro test, e.g. dissolution.

(l) Products acting locally in the GI tract containing highly soluble APIs (as defined by the BCS) in immediate release dosage forms might be waived from in vivo equivalence studies based on the same dissolution requirements as are applied for the BCS-based biowaiver.

10.5 In vitro equivalence testing for scale-up and post-approval changes

Although these guidelines refer primarily to registration requirements for multisource pharmaceutical products, it should be noted that under certain conditions, following permissible changes to formulation or manufacturing after FPP approval, in vitro dissolution testing may also be suitable to confirm similarity of product quality and performance characteristics. More information on when dissolution testing may be used to support product variations is provided in WHO guidance on variations in pharmaceutical products.

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Further reading

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Appendix 1

Recommendations for conducting and assessing comparative dissolution profiles

The dissolution measurements of the two finished pharmaceutical product (FPPs) (e.g. test and comparator or two different strengths) should be made under the same test conditions. A minimum of three time points (zero excluded) should be included, the time points for both reference (comparator) and test product being the same. The sampling intervals should be short for a scientifically sound comparison of the profiles (e.g. 5, 10, 15, 20, 30, 45 and 60 minutes for an immediate-release dosage form). The 15-minute time-point is critical to determine whether a product is very rapidly dissolving and to determine whether f_2 must be calculated. For extended-release FPPs the time-points should be set to cover the entire duration of expected release, e.g. in addition to earlier time-points: samples at 1, 2, 3, 5 and 8 hours should be collected for a 12-hour release and additional test intervals would be necessary for longer duration of release.

Studies should be performed in at least three media covering the physiological range, including pH 1.2 hydrochloric acid, pH 4.5 buffer and pH 6.8 buffer. Ph. Int. buffers are recommended; other pharmacopoeial buffers with the same pH and buffer capacity are also acceptable. Water may be considered as an additional medium, especially when the API is unstable in the buffered media to the extent that the data are unusable.

If both the test and reference (comparator) products show more than 85% dissolution in 15 minutes the profiles are considered similar (no calculations required). Otherwise:

- similarity of the resulting comparative dissolution profiles should be calculated using the following equation that defines a similarity factor (f_2)

  $f_2 = 50 \text{ LOG } \{[1+1/n \sum nt=1 (Rt- Tt)2] -0.5 \times 100\}$

  where Rt and Tt are the mean per cent API dissolved in reference (comparator) and test product, respectively, at each time-point.

  An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar;
- a maximum of one time point should be considered after 85% dissolution of the reference (comparator) product has been reached;

- in the case where 85% dissolution cannot be reached owing to poor solubility of the API or the release mechanism of the dosage form, the dissolution should be conducted until an asymptote (plateau) has been reached;
- at least 12 units should be used for determination of each profile. Mean dissolution values can be used to estimate the similarity factor, f_2. To use mean data the percentage coefficient of variation at time-points up to 10 minutes should be not more than 20% and at other time-points should be not more than 10%;
- when delayed-release products (e.g. enteric coated) are being compared, the recommended conditions are acid medium (pH 1.2) for 2 hours and buffer pH 6.8 medium;
- when comparing extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, one condition (normally the release condition) will suffice;
- surfactants should be avoided in comparative dissolution testing.

A statement that the API is not soluble in any of the media is not sufficient, and profiles in the absence of surfactant should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

Appendix 2

Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the Biopharmaceutics Classification System

Introduction

The BCS was proposed in 1995 by Amidon et al. (*1*). It is a scientific framework that divides active pharmaceutical ingredients (APIs) into four groups according to their solubility and permeability. The recommended method for determination of the solubility is described below. Please refer to the *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* for further explanation of BCS classification and qualification of multisource products for a biowaiver based on the BCS (*2*).

This text was drafted based on the *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms* (*3*), the *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*2*) and the *Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system* (*4*).

Recommendations for conducting experiments for assessing solubility of APIs

Prior to the experiment, a solubility study protocol should be prepared describing the equipment and procedures in detail. The protocol should include, for example, methods of sample preparation, experimental conditions such as temperature, method and rate of agitation, method of solid/solution separation of the API, and method of sample analysis. The source and purity of the API to be used in the study should also be recorded in the protocol, as well as the methods that will be used to characterize the material.

Characterization of the solid API should be completed prior to the investigation. The depth of the characterization will depend on the existing knowledge of the solid-state properties of the API in question. For example, if it has been established that the API exists as a single polymorphic form, then less solid-state characterization is needed. In some cases, it may be necessary to characterize the solid starting material as well as the solid residue remaining after equilibrium has been reached and sampling has been completed. For a

discussion of the factors that should be considered when planning the solid-state characterization studies, see Avdeef et al. (*5*).

Solubility experiments should preferably be carried out with the shake-flask method, which is used to determine equilibrium solubility, although other methods are possible if justified. A discussion of the factors that should be considered when designing the study can be found in Avdeef et al. (*5*). The conditions employed should be fully described in the study protocol.

The pH-solubility profile of the API should be determined over the pH range of 1.2–6.8 at 37 ± 1 °C. Measurements should be made in triplicate under at least three pH conditions, pH 1.2, 4.5 and 6.8, as well as at the pH of any known solubility minima in aqueous media within that pH range. Pharmacopoeial buffer solutions are recommended for use in solubility experiments (see, e.g. chapter 5.5 Dissolution test for solid oral dosage forms in *The International Pharmacopoeia* (*6*)). Factors such as common ion effects and ionic strength should be considered when selecting buffers for the study. The pH should be verified after addition of the API and at the end of the experiment with a calibrated pH meter. Samples should be taken at several time-points to ensure that the equilibrium solubility has been reached. Strong agitation followed by a period of sedimentation is suggested, to achieve solubility equilibrium.

A description of the method(s) of solid/solution separation employed, including details such as filter type and pore size or centrifugation speed, should be provided in the study protocol. Sedimentation, centrifugation and filtration are the standard methods of separation. The factors described by Avdeef et al. (*5*) should be considered when selecting the most appropriate approach for the API under study.

A validated, stability-indicating analytical method should be employed for determination of the solubility of APIs, e.g. high-performance liquid chromatographic analysis (see chapter 1.14.4 High-performance liquid chromatography in *The International Pharmacopoeia* (*6*)) or an alternative, validated stability-indicating assay.

A study report should be created after the experiment detailing the actual experimental conditions, results (raw data plus mean values with standard deviations), and any observations, for example, the degradation of an API as a result of pH or buffer composition. The section describing the experimental conditions should include initial and equilibrium pH of solutions and de facto buffer concentrations. If applicable, filter adsorption studies should be documented. Any deviations from the protocol should be noted and justified.

The dose/solubility ratio is calculated as follows: highest single therapeutic dose (mg) divided by solubility (mg/mL). An API is considered highly soluble when the highest single therapeutic dose is soluble in 250 mL or less of aqueous media over the pH range of 1.2–6.8, i.e. the dose/solubility ratio is ≤ 250 (*2*).

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