World Health Organization

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

WHO Medical device technical series

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Contents

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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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.[1]

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.

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

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

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[1,2] 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[3] 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)*.[4] For a glossary of other relevant terms, see Appendix 1.

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).

1 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.

2 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.

3 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.

4 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.

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.

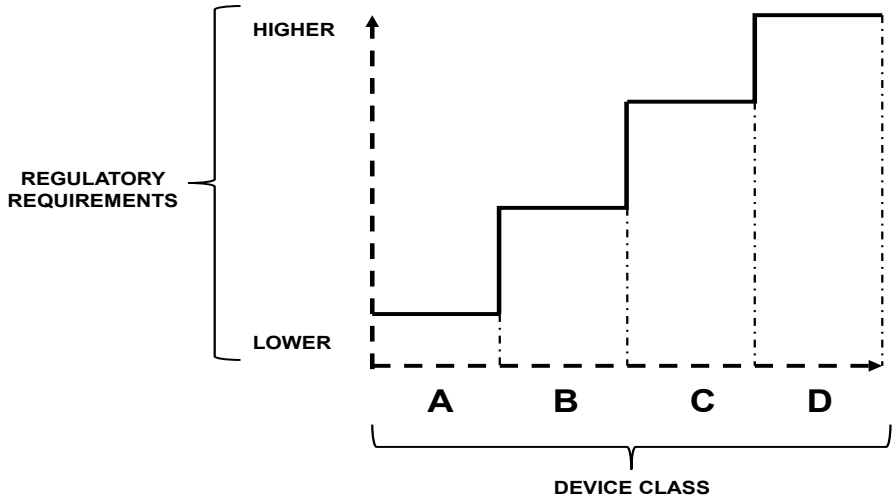
The regulation specifies the manner in which a manufacturer should demonstrate conformity with safety, performance and quality requirements. The regulatory oversight by the authority should increase in line with the potential of a medical device to cause harm to a patient or user (i.e. the hazard it 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 and the duration 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 *(2)*, 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 (2).

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.

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 *(2,3)*. Additionally, the regulatory authority may develop explanatory guidance to help a manufacturer apply the rules *(4)*. While the manufacturer has the primary obligation to classify its medical device, its decision may be challenged by the regulatory authority.

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 *(5)*. 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 *(5)* 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 *(6)*. While retaining responsibility for the decisions it makes, the regulatory authority may appoint one or more conformity assessment bodies (CABs)[5] to assist it in this task (see section 4).

5 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.

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 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 *(7)*. 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 (8)*.

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 *(6)* (see section 4) (Table A4.2).

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

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.

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 *(6).*

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 *(3)*. 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 *(5)*. 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 (8)* is therefore not suited to IVDs. A standard specific to IVDs is being developed by the ISO Technical Committee 212 *(9).*

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 (10)*. 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.

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.

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.

3.3 Implementation plan

Once national legislation on medical devices has been adopted, the appointed

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)).

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 *(11)*. 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 *(12)*.

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 *(13)*.

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 *(14)*. 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) *(15),* 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 *(16).*

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[1] 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.

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

- 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 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) *(17)*. 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.[2]

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 information *(18)*. 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

2 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.

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

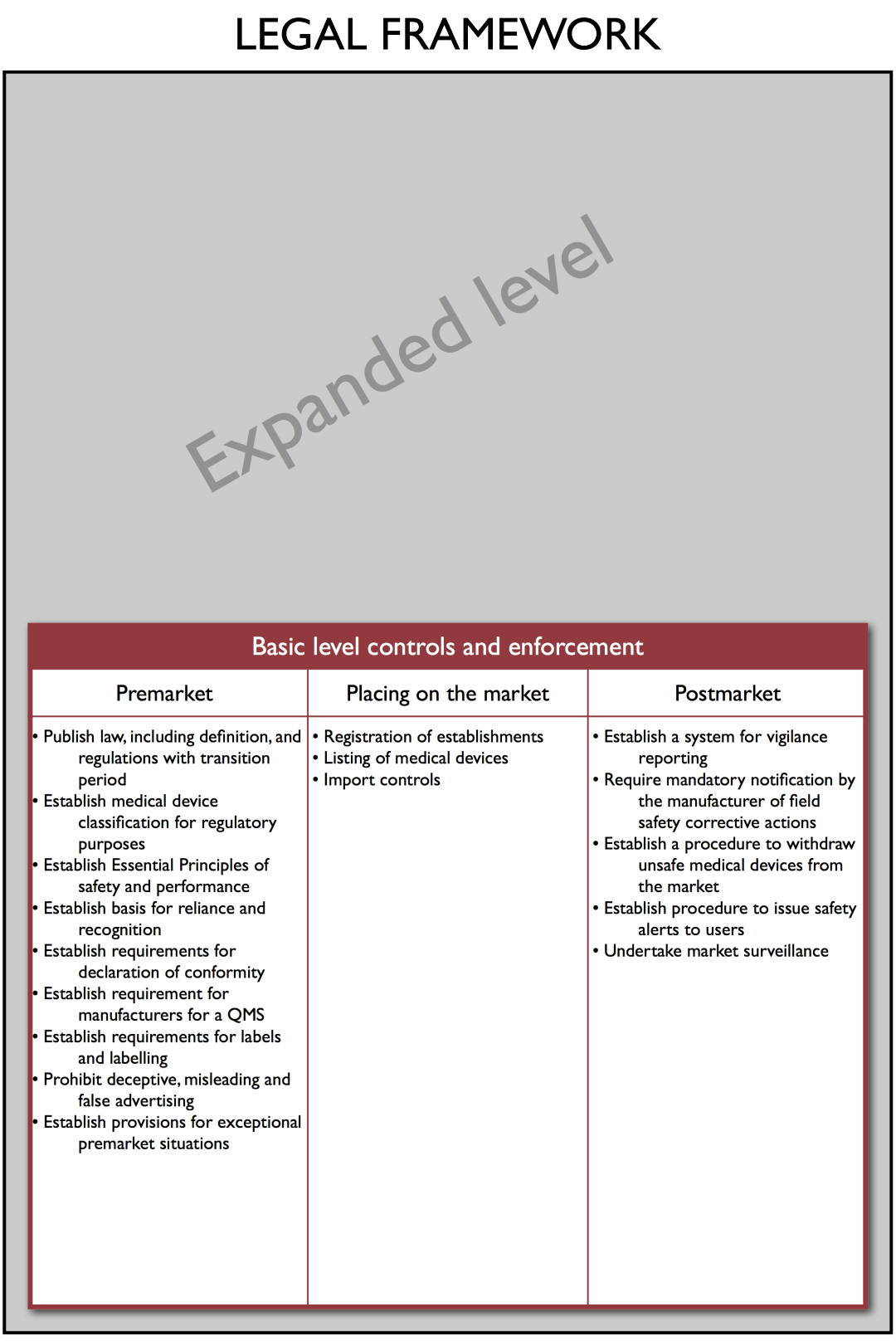
The Model recommends that basic-level controls are incorporated into a medical devices law that determines the scope of regulation, stipulates the responsibilities of the regulatory authority, describes conditions under which a medical device can be placed on the market, requires certain organizations 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).

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 2). 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

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



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 *(2)*. 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) *(5)*. Failure to make such a declaration of conformity (see 4.2.2.2) *(6)*, 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[3] 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 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 –*

3 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.

Requirements for regulatory purposes (19) and ISO 14971:2007: *Medical devices – Application of risk management to medical devices (20)*.

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.[4] 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 *(21)*. 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, lot number, or serial number. This allows traceability to facilitate 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 *(22)*.

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.

4 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 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). In vitro diagnostic medical devices – Information supplied by the manufacturer (labelling) – Part 4: In vitro diagnostic reagents for self-testing. ISO 18113-4:2009 (http://www.iso.org/iso/catalogue_detail.htm?csnumber=40987, accessed 18 November 2016).

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 *(23)*.

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 *(24)*. 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 field safety corrective action (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 *(23)*. 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 *(24)*. 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 *(25)*. 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 *(26)*. They may also prompt the regulatory authority to exchange information with regulatory authorities in other jurisdictions on similar occurrences elsewhere *(27)*.

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 *(26)*. 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 *(28)*.

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).

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 *(29)*. 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.[5] 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 (8)*.

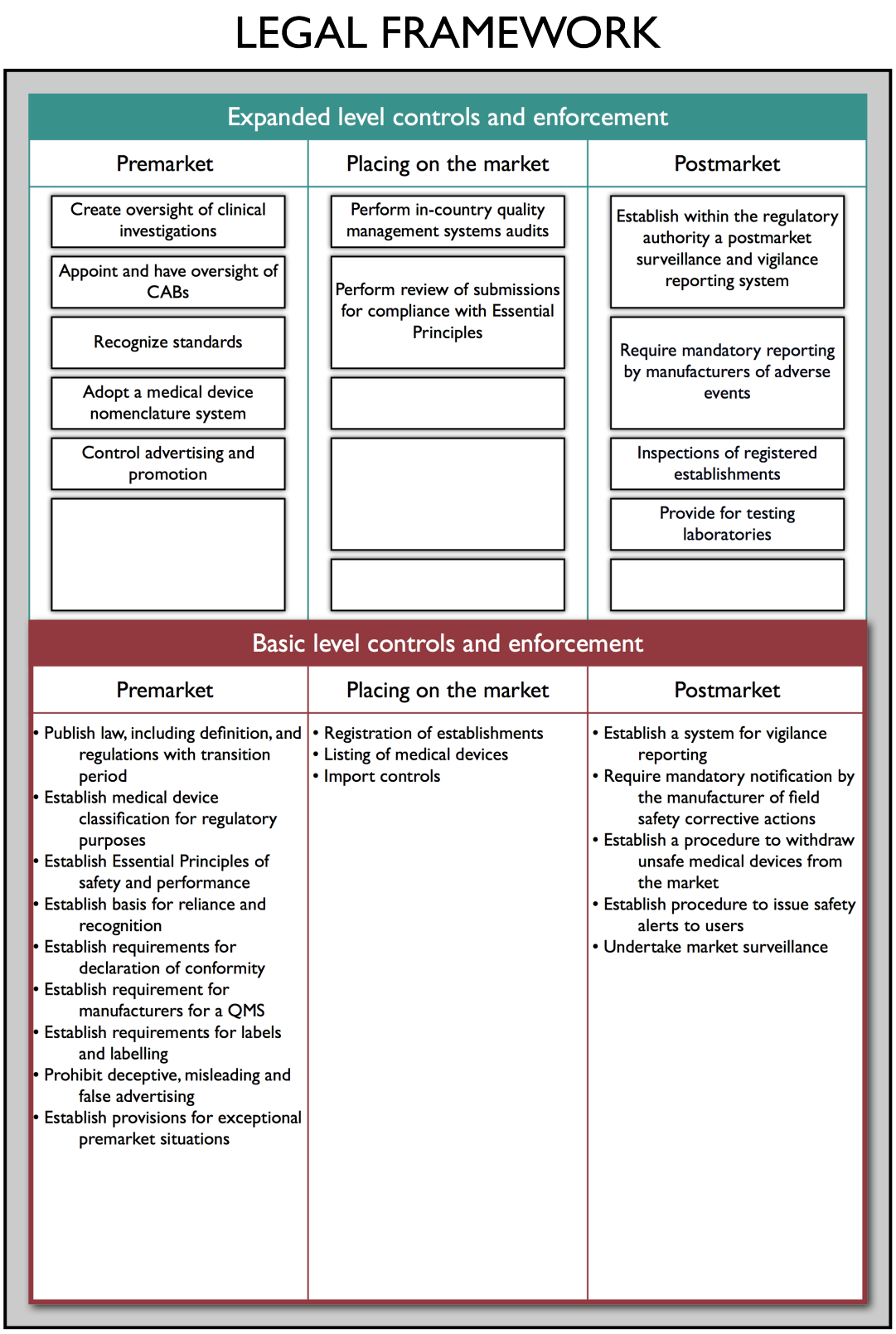
The NRA should also establish a mechanism for periodic progress reports and for the reporting of serious adverse events that occur during clinical investigations *(30)*. In-country clinical investigations should generally not be required, unless there is a compelling and sound scientific reason.

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 *(31, 32)*. Authorities may establish criteria for designation of CABs. These bodies may perform

5 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).

Figure A4.3 Expanded-level controls and enforcement for medical devices



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 requirements is typically documented with a CAB certificate *(33)*. 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 *(34)*. 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 *(35)*.

4.3.1.3 Recognition of standards[6]

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 *(36)*.

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 *(37)*.

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) *(38)* 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 utilizing standards, it is better to adopt a system of recognizing standards through guidance documents or guidelines than placing the standards into legislation *(39);* 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

6 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.

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 *(40,41)*. There are other established nomenclature systems such as the Universal Medical Device Nomenclature System (UMDNS) *(42)* and ISO 9999:2011– *Assistive products for persons with disability – Classification and terminology (43)*.

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 *(34, 35)* 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 *(6)*.

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 *(35, 44)*. The receiving country thereby relies upon the information from the QMS audit or recognizes the decision of the other jurisdiction regarding the QMS audit *(45).* 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 *(6).*

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 *(46, 47)*) and the Association of Southeast Asian Nations (ASEAN) Common Submission Dossier Template (CSDT) *(48)*. 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 *(49)* and IVDs *(50)*.

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 *(51)*.

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 *(27)*.

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 *(51)*.

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 *(52)* 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[7] medical products have gained access to a global marketplace.[8] 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 *(19)*. The Asian Harmonization Working Party (AHWP) has published guidance on the application of ISO 13485 in an organization that distributes or imports medical devices *(53)*.

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 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;

7 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)).

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

- 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

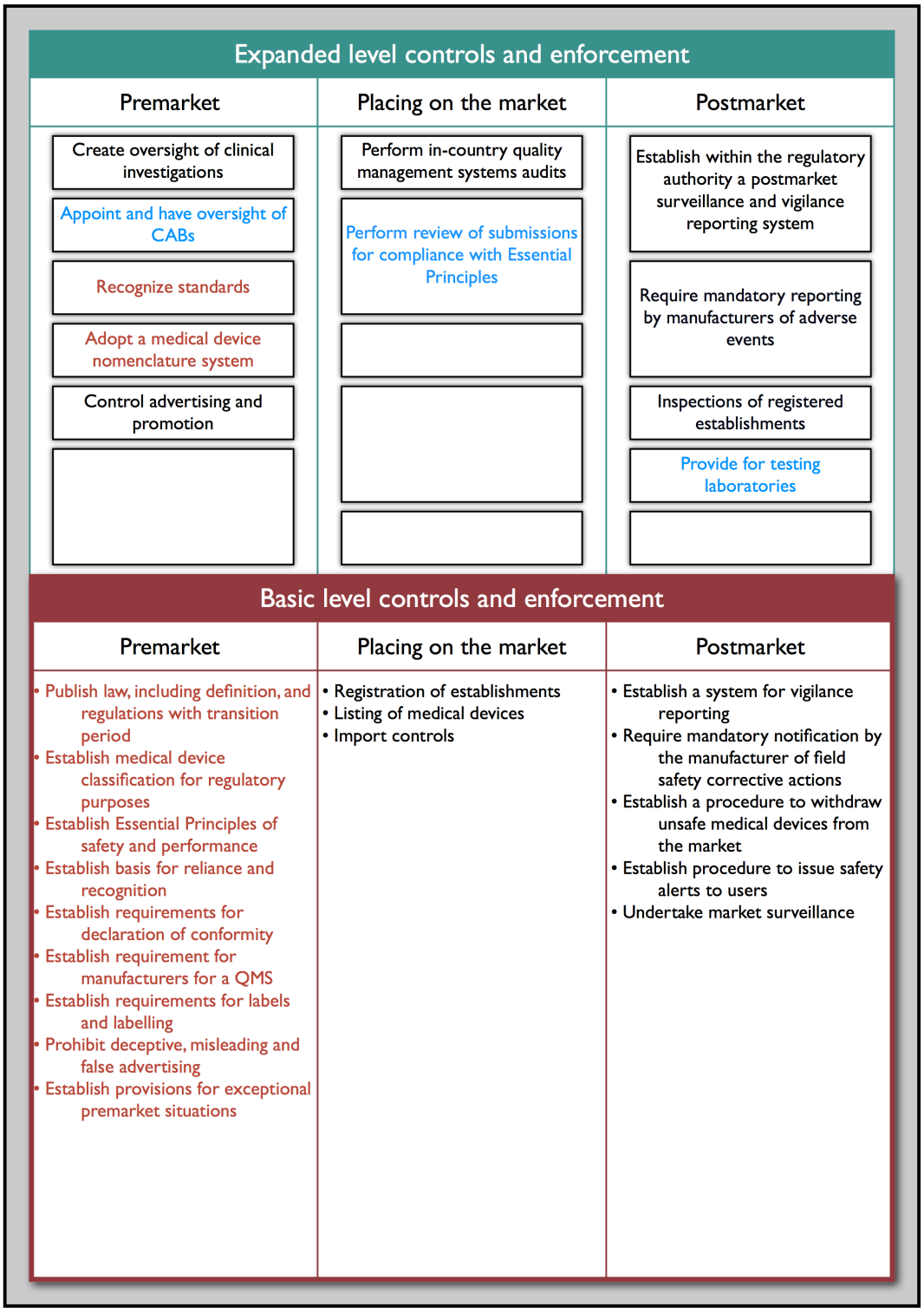
WHA Resolution 67.20 emphasizes the importance of collaboration and harmonization. It requests the Director-General "to prioritize support for establishing and strengthening regional and subregional networks of regulatory authorities, as appropriate, including strengthening areas of regulation of health 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 red are those for which international regulatory harmonization guidance documents have been developed. Elements that may be implemented through reliance or recognition are indicated in blue.



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.

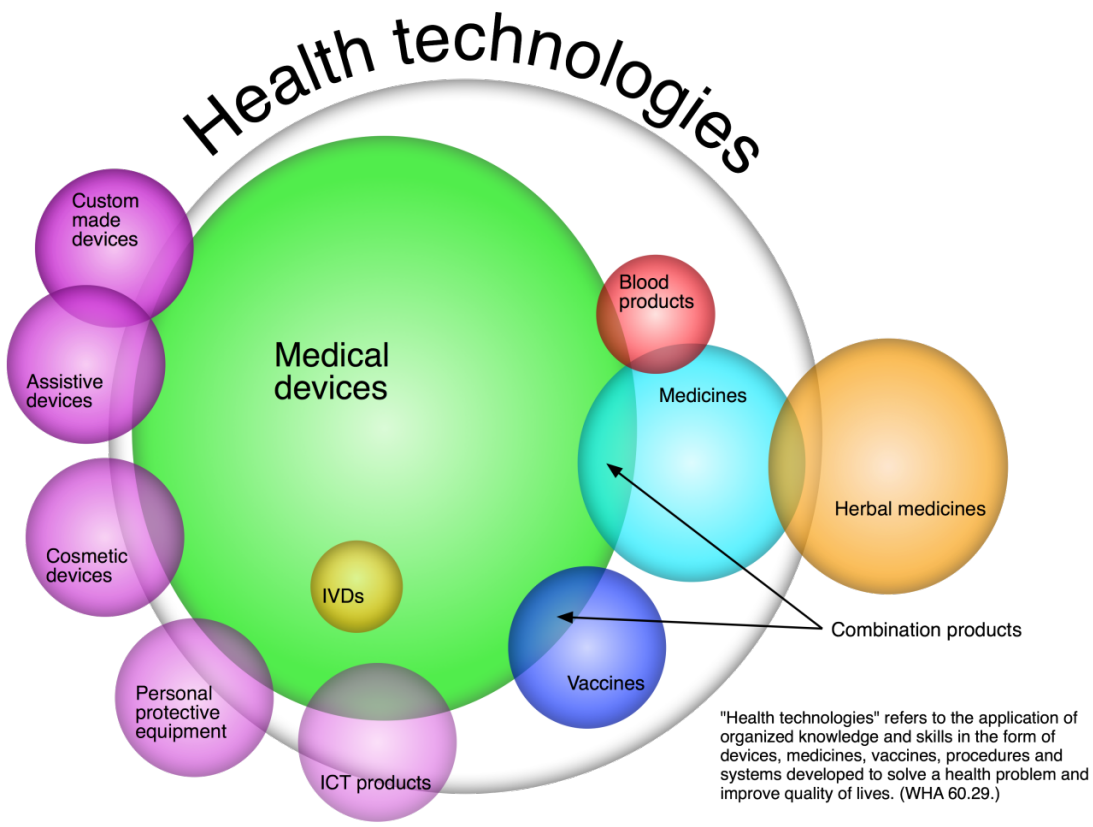
5.1 Determination to establish whether a medical product is a medical device

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" products[1] 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) *(54–56)*.

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.

1 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.

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 *(57–59)*.

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 *(60–63)*. 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.[2] 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[3] 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[4] (SUMDs) are designed and labelled for single use. They do not come with appropriate instructions for cleaning, disinfecting or

2 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/.

3 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).

4 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).

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.

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 *(64–67)*. 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 *(68–71)*.

5.6 Substandard and falsified products

SF medical products[5] 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.[6] The United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) 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.[7] Falsified condoms, contact lenses, catheters, syringes and needles have been reported from Africa, Asia and Europe *(72)*. 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 *(18)*. 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.

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

5 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)).

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

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

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 *(73– 77)*.

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 the 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 *(78)*.

The 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) *(79)*;
- 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 *(80)*.

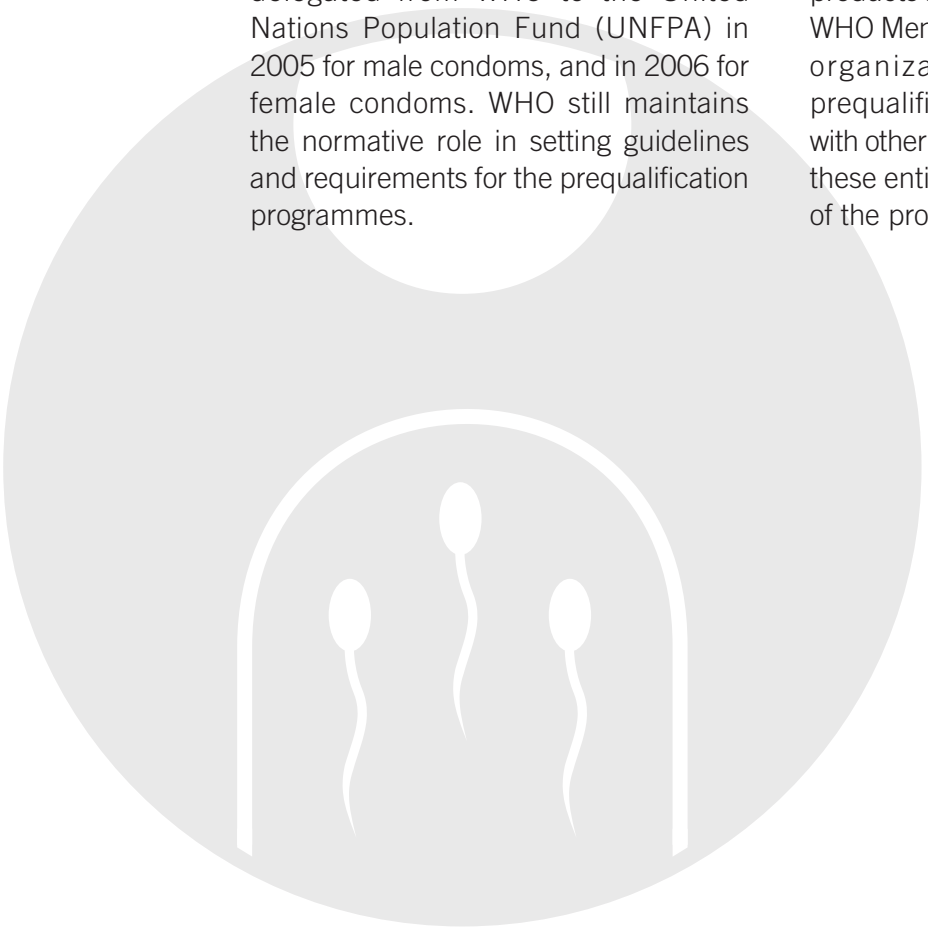
The findings of the PQT for IVDs, in conjunction with other procurement criteria, are typically used by UN agencies, WHO Member States and other interested organizations to guide their procurement of IVDs.

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) *(81)*. 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 the PQTs.



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Appendix 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 *(8).*

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 *(8).*

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 *(8).*

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 765/2008 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 7656/2008 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, or
    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 *(8).*

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.

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Appendix 2

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.
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.

Notes

Notes

Department of Essential Medicines and Health Products
World Health Organization
20 Avenue Appia
CH-1211 Geneva 27
Switzerland
E-mail: medicaldevices@who.int
http://www.who.int/medical_devices/en/

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