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WHO Global Model Regulatory Framework for medical devices including IVDs (GMRF)

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the proposed document to a broad audience and to improve transparency of the consultation process.

The text in its present form does not necessarily represent an agreed formulation of the ECBS. Written comments proposing modifications to this text MUST be received by 3 June 2022 using the Comment Form available separately and should be addressed to: Department of Health Products Policy and Standards (HPS), World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Comments may also be submitted electronically to the Responsible Officer: Dr Agnes Kijo at kijoa@who.int.

The outcome of the deliberations of the ECBS will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the second edition of the *WHO style guide* (KMS/WHP/13.1).

Contents

Acronyms and abbreviations

AMDF	Africa Medical Devices Forum
ASEAN	Association of Southeast Asian Nations
CAB	conformity assessment body
CLSI	Clinical and Laboratory Standards Institute
GBT	Global Benchmarking Tool
GDP	Good Distribution Practice
GHTF	Global Harmonization Task Force
GHWP	Global Harmonization Working Party (formerly Asian Harmonization Working Party AHWP)
GMRF	WHO Global Model Regulatory Framework for medical devices including IVDs
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	substandard and falsified medical products
SUMD	single-use medical device
UN	United Nations
WHO	World Health Organization
WHA	World Health Assembly

1. Introduction

The regulation of medical devices including in vitro diagnostics is critical in assuring their quality and performance. In May 2014 the World Health Assembly (WHA) adopted a Resolution regarding regulatory systems for medical products (WHA 67.20). The Resolution underscored the importance effective regulatory systems as an essential component of health system strengthening and contribution to public health. WHO decided to develop guidance to support member stated that have yet to develop and implement regulatory controls relating to medical devices.

The WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices (GMRF) was published in 2017 in English and was translated into French and Russian. Since then, the GMRF served as background document in WHO workshops on medical devices and is considered a standard in the development of the Global Benchmarking Tool (GBT) when adding medical devices as a product group to GBT+.

The field of medical devices is rapidly changing. Technologies are advancing in their nature and complexity. In addition, new suppliers are entering the field, often without much relevant experience or qualifications, and often with little local regulatory oversight. Jurisdictions are adapting their laws and regulations to better and timely regulate medical devices in order to protect and promote public health. They have often also had to quickly develop greater regulatory capacity by which to implement those regulations. The COVID-pandemic clearly demonstrated the importance of ensuring equal access of safe, reliable, and appropriate quality medical devices including in vitro diagnostic medical devices (IVDs). It has also highlighted the importance of integrity in the supply chains, domestic and international, of medical devices (and related personal protective equipment). The need for reliable, appropriate, and accessible IVDs has also been demonstrated. As important as they are, vaccines are not effective if they cannot be safely delivered – typically by medical devices.

In regulating medical devices multiple stakeholders are involved. The national regulatory authority has the authority under laws adopted by legislators and policy makers to control and enforce regulatory requirements. The manufacturers, their representatives, importers, distributors and outlets are part of the supply chain in which integrity and quality of the medical devices must be secured. The users i.e. professional in the health care system, the laboratories, the patients or users, are the stakeholders that should be able to rely on the safety, quality and performance of the medical device, provided the medical device is used as intended.

The GMRF focuses on the responsibilities of the legislator and the national regulatory authority in establishing, implementing, and enforcing the legal and regulatory framework, not the industrial stakeholder. It thereby indirectly outlines the compliance obligations of industrial stakeholders. The GMRF recognizes the importance of the health care system in providing feed back on vigilance and adverse events reporting.

Many countries have neither the financial resources nor the technical expertise to transition successfully from a limited regulated market to a comprehensive medical devices law and regulatory controls in a single programme. Instead, the GMRF recommends a 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 i.e., people, funds, technology and facilities – available in any country for regulatory control of medical devices are, and probably always will be, limited. A mechanism to benefit from the regulatory work from another jurisdiction can be operationalized through reliance and recognition, a practice well-known both in countries with less developed regulatory systems in place as in mature jurisdictions.

More broadly, it should be understood that regulation of medical devices does not take place in isolation, but should be coordinated at a regional and global level.

1.1 The WHO Global Model Regulatory Framework for Medical Devices including IVDs, the revised version.

This revised Global Model Regulatory Framework for Medical Devices including IVDs 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 GMRF is written for the legislative, executive, and regulatory branches of government as they develop and establish a system of medical devices regulation. This reviewed version of the GMRF describes the role and responsibilities of a country's regulatory authority for implementing and enforcing the regulations in the field of medical devices. The

number of topics have been expanded to include Good Regulatory Practice, Good Reliance Practice, regulatory pathway for medical devices according to risk class, regulatory pathway with the mechanism of reliance, regulatory pathway for donated medical devices, regulatory pathway for emergency use, policy on medical devices testing, and local production of medical devices. It also addresses new topics such as software as a medical device, combination products, and implementation topics on stakeholder involvement, regulatory capacity building and developing a road map for regulation of medical devices.

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 regulation of 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 reliance and recognition approaches may be considered and on the importance of international convergence of regulatory practice.

Section 5 describes the regulatory pathways for several products. It provides a cleas overview of steps to be taken by the regulatory authority before a medical device will be placed on the market.

Section 6 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.

Section 7 presents some topics that are relevant for implementation of regulatory controls in an effective manner.

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

The GMRF outlines a general approach for regulation of medical devices including IVDs but cannot provide country-specific guidance on the implementation. While it does not offer

249 detailed guidance on regulatory topics it contains references to relevant documents where
250 further information may be found. It does not detail responsibilities of other stakeholders such
251 as manufacturers, distributors, procurement agencies and health-care professionals, all of whom
252 have roles in assuring the quality, safety and performance of medical devices.

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

2.1 Definition of medical device and IVD medical device[1]

The GHTF developed a definition of the terms medical device[2] and IVD. Major jurisdictions have accepted the principles of this definition. In the interest of international regulatory convergence it is recommended to promote their widespread use.

Medical device[3], 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 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 means a 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. This includes reagents, calibrators, control materials, specimen receptacles, software, and related

[1] The terms 'IVD medical device' and 'IVD' are interchangeable

[2] Medical devices' is used to indicate 'medical devices including IVDs'

[3] 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.

instruments or apparatus or other articles.[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 equipment [5] to avoid cross-infection; lead aprons to protect against radiation; some medical gases;[6] and implantable or other invasive products for a cosmetic rather than a medical purpose *(see Section 6).*

2.2 Medical devices classification and classification rules[7]

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 shall 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 use in manufacturing a medicine or biological. The risk class of an IVD is determined primarily by

[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.

[5] Whether a products is classified as personal protective equipment or not depends on the intended purpose of the product. If the device is intended exclusively for the protection of the user (the person wearing it) against one or more health and safety hazards, then the device is classified as personal protective equipment.

Whereas if a product is designed to protect patients, it is considered a medical device.

If a product can be used for both intended purposes, it is both a medical device and personal protective equipment.

https://www.johner-institute.com/articles/regulatory-affairs/and-more/marketing-personal-protective-equipment-ppe/ (accessed 14 October 2021)

[6] Gases are classified as medicinal products for administration to a patient and the associated equipment is classified as a medical device when used to administer the gas. Some gases used for medical purposes can also be classified as medical device gases where they do not have a specific therapeutic outcome for the patient. Medical gases that are considered a medical device have a mechanical or physical effect. Examples include gases for insufflation of the abdominal wall and liquid nitrogen for the removal of warts. http://www.bcga.co.uk/pages/index.cfm?page_id=29&title=medical_gases (accessed 14 October 2021)

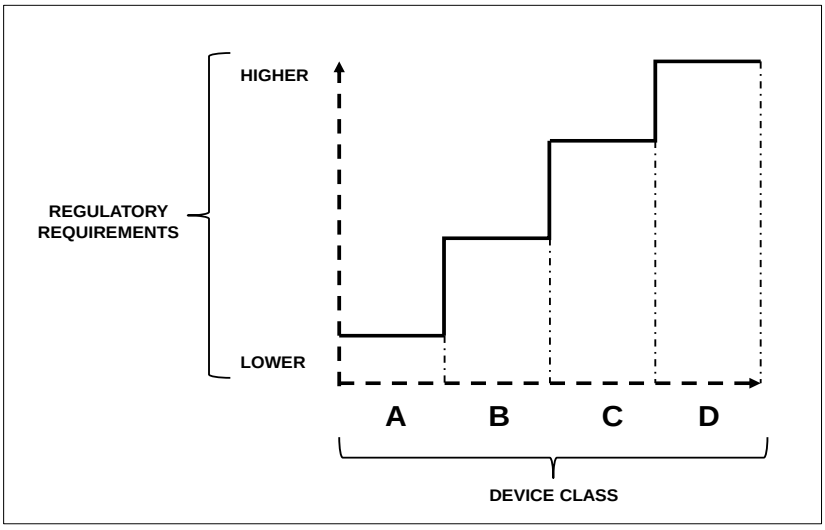
[7] Medical devices classification is similar to medical devices risk classification

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,[8] by applying a set of risk-based classification rules (2) and specifying separately the different conformity assessment procedures that should apply to each group of devices (Figure A4.1). A medical device can be classified to one risk class. If more than one risk class would apply, the highest shall be considered.

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)

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;

[8] Some jurisdictions indicate the risk classes of medical devices differently such as class I, II, II, e.g. USFDA (https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device) or I, IIa, IIb, III e.g. European Union (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN, article 51, accessed 14 October 20210

- could modify blood or other body fluids;
- is used in combination with another medical device.

Classification of medical devices including IVDs also takes into account the technical, scientific and medical expertise of the intended user (layperson or health-care professional). The use of medical devices by lay persons puts specific requirements on the manufacturer to provide information and instruction in the labelling to ensure safe and effective use.

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

- the intended use and indications for use as specified by the manufacturer.
- the technical/scientific/medical expertise of the intended user (lay person or healthcare professional)
- the importance of the information to the diagnosis (sole determinant or one of several), taking into consideration the natural history of the disease or disorder including presenting signs and symptoms which may guide a health care professional
- the impact of the result (true or false) to the individual and/or to public health (3)

Classification may differ between jurisdictions. Rapid diagnostic tests may be classified as class A in one jurisdiction but as a class C in a country where a disease is endemic.

Reclassification of medical devices may also occur as experience and knowledge about a device increase, the original classification of a device can be changed through reclassification, whether to a higher risk class when available scientific evidence shows that existing control are not sufficient to assure the safety and effectiveness of the device. Reclassification to a lower risk class may be acceptable if the available scientific evidence shows that general controls would provide a reasonable assurance of safety and effectiveness of the device.[9]

Additionally, the regulatory authority may develop explanatory guidance to help a manufacturer apply the rules.[10] (4) (5) While the manufacturer has the primary obligation to classify its medical device, its decision may be challenged by the regulatory authority.

[9] Reference: https://www.fda.gov/about-fda/cdrh-transparency/reclassification
[10] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN, Annex VIII

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

Table A4.1

Examples of medical devices by risk class[11]

Class	Risk	Examples
A	Low	Examination gloves, patient hoists, stethoscopes, wheelchairs, surgical masks
B	Low–moderate	Surgical gloves, infusion sets.
C	Moderate–high	Condoms (unless with spermicide (class D)), infusion pumps, neonatal incubators, therapeutic and diagnostic X-ray, lung ventilators, hemodialyzers, anaesthesia equipment.
D	High	Implantable cardioverter defibrillators, pacemakers, breast implants, cardiovascular stents, spinal needle.

[11] 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.

Table A4.xx

Examples of IVD medical devices by risk class

Class	Risk	Examples
A	Low	Reagents, instruments, specimen containers intended for the collection of urine, faeces, cells or tissue specimens, instruments intended for use as an IVD such as an enzyme immunoassay analyser. Others are prepared (ready to use) microbiological culture media and single staining solutions for diagnostic use such as Gram stain.
B	Low–moderate	Pregnancy and fertility self-testing kits, Urine self-test strips to detect glucose and non-assay specific control plasmas for use in coagulation studies.
C	Moderate–high	Tests intended to detect the presence or exposure to a sexually transmitted agent, such as *N. gonorrhoeae* *C. trachomatis*, Herpes simplex virus 1 & 2 and *T. vaginalis*. Tests intended to detect (in cerebrospinal fluid or blood) the presence of an infectious agent that poses a high personal risk and has a risk of limited propagation, including tests for the C. neoformans antigens, *N. meningitidis* and *H. influenzae* type B
D	High	All tests intended to be used for blood, organ and tissue donor screening, including screening and confirmatory assays for: Human immunodeficiency virus, Hepatitis C virus, Hepatitis B virus and Syphilis. Any additional assays used to screen donors on a supplementary basis, such as those used to determine Cytomegalovirus status or to screen for Malaria. Tests intended for the diagnosis of infection with, or exposure to: Highly virulent pandemic influenza, Viral haemorrhagic fevers, such as Ebola virus or Marburg virus. IVDs intended for detecting red blood cell antigens, antibodies or genetic markers specific to the following high risk blood groups: ABO, Rhesus, Kell, Kidd and Duffy systems

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2.3 Principles of safety and performance

Regulations should specify that a medical device should be safe and perform as intended when placed on the market. IMDRF has established a list of Essential Principles of safety and performance for medical devices including IVDs[12]. (6) (7) These requirements have been widely adopted. Manufacturers shall demonstrate to the regulatory authority that their product complies with these Essential Principles and has been designed and manufactured to be safe and perform via the use of applicable standards throughout a product's life-cycle as intended when used according to the manufacturer's 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 or IVDs).

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 user's training is safe and does not compromise the clinical condition of the patient or the health of the user.
- Medical devices should perform as the manufacturer intended when used under normal_/specified conditions.
- Each medical device and IVD medical device should also be accompanied by, or direct the user to any safety and performance information relevant to the user, or any other person, as appropriate
- 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.
- The manufacturer should perform/ implement? risk control measures in eliminating or appropriately reduce risks.
- Known and foreseeable risks should be weighed against the benefits of the intended purpose.
- Performance and safety should not be affected by transport or packaging and storage, provided the instructions for packaging, transport and storage are followed.

[12] In the EU MDR the terminology has changed to 'general safety and performance requirements'. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN Annex I

Ensuring that a medical device conforms to all relevant Essential Principles (6) 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 (2) (3). While retaining responsibility for the decisions it makes, the regulatory authority may appoint one or more conformity assessment bodies (CABs)[13] to assist it in this task (*see Section 2.3*).

2.3.1 Clinical evidence for non-IVD medical devices

Clinical evidence (8) 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. 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. 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 and national standards.

Some technologies have been available for many years and their clinical safety and performance have been well characterized. Many devices, however, utilize new technologies that have 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, post market reports and adverse event data for previous versions of the device may 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

[13] 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.

changed. The manufacturer should perform a documented comprehensive clinical 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. A widely used international standard for the practice of clinical investigation is ISO 14155:2020 – *Clinical investigation of medical devices for human subjects – Good clinical practice.* (9)

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 and use over the device's life cycle. In general, the manufacturer does this through implementation of an established QMS. The degree of assessment of the QMS by the regulatory authority or CAB depends on the medical device risk class (10) (Table A4.2).

Table A4.2

Conformity assessment processes as determined by device class

Conformity assessment element	**Class A**	**Class B**	**Class C**	**Class D**
Quality management system (QMS)	Regulatory audit normally not required, except where assurance of sterility or accuracy of the measuring function is required.	The regulatory authority should have confidence that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to marketing authorization.	The regulatory authority should have confidence that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to marketing authorization.	The regulatory authority should have confidence that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to marketing authorization.

Conformity assessment element	Class A	Class B	Class C	Class D
Technical documentation[14]	Premarket submission normally not requested.	Not normally reviewed premarket. The regulatory authority may request and conduct a premarket or post marketing 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).

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

[14] There are many terms used to describe a product's technical documentation. The terms include technical file, table of contents, 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 retain 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. The authority may conduct an audit for class A if deemed necessary.

For medical devices in all classes, the regulatory authority or CAB shall 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 another nationally 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. The depth of the QMS audit is to the discretion of the national regulatory authority. 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 plan information on design and manufacturing, clinical evidence, product validation and verification, post-market surveillance plan 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. For class D a QMS audit prior to marketing authorization is usually performed. The regulatory authority could rely upon or recognize the work of another regulatory authority but the final responsibility lies with the national regulatory authority. 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 (10)

A regulatory pathway for medical devices according to risk class is described in *Section 5*.

2.4 Special considerations for regulation of IVDs

According to this 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 propose 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 management 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, disease staging, monitoring or surveillance, 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 IMDRF has published a document that provides a classification scheme for IVDs, including classification rules, based on risk to the individual and to public health (3) (11).[15] The classification of IVDs is determined by the intended use, the expertise of the intended user and the 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 and low public health risk
- B – moderate individual risk and/ or low public health risk
- C – high individual risk and/or; moderate public health 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. Companion diagnostics

A ‘companion diagnostic’ means an in vitro diagnostic medical device, which is essential for the safe and effective use of a corresponding medicinal product to:

[15] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02017R0746-20170505&from=EN, Annex VIII

(a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or

(b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions treatment with the corresponding medicinal product.[16] (11) Companion diagnostics are regulated as in vitro diagnostic medical devices (IVDs). These *in vitro* diagnostics, abbreviated as CDx, increase the probability of clinical success by identifying patients with the presence of predictive biomarkers and disease-specific therapeutic targets that can dramatically improve outcomes in terms of safety and/or efficacy of the treatment. This definition—combined with the introduction of a risk-based classification system for medical devices including IVDs based on the IMDRF system of device classification—has resulted in CDx being classified as high-risk class C in vitro diagnostic medical devices. (2) (3) However, countries may opt to classify CDx according to their classification rules for IVDs.

Depending on how an NRA classifies CDx, a more complex scope of regulatory controls may apply to CDx.To ensure compliance with regulatory requirements, the following scope of regulatory controls should be implemented for CDx: authorization of clinical and performance studies by the competent authority, premarket authorization or registration, audits, and market surveillance.

Some CDx are developed for use with specific medicinal products where the test may be tied specifically to certain brand(s) of medicinal products. For such tests a combined clinical study is performed together with the medicinal product.[17]

Some CDx are developed separately as stand-alone where the CDx may be used to support the use of various brands of medicinal products (with similar molecular targets). Clinical studies for such CDx are performed independently.

In such cases there is no requirement for simultaneous filing or synchronised approval for the CDx and the medicinal products. The regulatory controls (premarket authorisation and authorisation of clinical and performance studies) of the medicinal product and the device may

[16] NOTE 1: Companion diagnostics are essential for defining patients' eligibility for specific treatment with a medicinal product through the quantitative or qualitative determination of specific markers identifying subjects at a higher risk of developing an adverse reaction to the medicinal product in question or identifying patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective. Such biomarker or biomarkers can be present in healthy subjects and/or in patients.
NOTE 2: Devices that are used to monitor treatment with a medicinal product in order to ensure that the concentration of relevant substances in the human body is within the therapeutic window are not considered to be companion diagnostics.

[17] Examples of CDx combined with specific medicinal products: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

not be performed at the same time. However, the assessors for the medicinal products and for the CDx may have meetings as appropriate.

For vigilance reports, the determination of who should report and whether reporting to both medical device and medicinal product regulators are required is determined based on the cause of the reportable event and the risk assessment performed by the respective manufacturers. For instance, any reportable event arising from the failure of the CDx (e.g. inaccurate results from the test) should be reported to the medical device regulatory team. Based on the risk assessment, if this failure of the test is assessed to potentially impact the safety and/or effectiveness of corresponding medicinal product (e.g. incorrect dosage of medicinal products administered to patients), then a reporting to the medicinal product regulator by the medicinal product manufacturer will also be required.

Regulatory requirements for labelling of the CDx should specify the corresponding medicinal product with which it is intended to be used.

Since not all countries may have the capacity to perform all the regulatory controls discussed, especially in the early stages of establishing medical devices including IVDs, regulation. In this event, reliance may be used as an appropriate approach to ensure these controls are performed.

2.4.2 Essential Principles of safety and performance for IVDs

The IMDRF has developed additional Essential Principles that apply to IVDs (6). 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[18]

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 and other infections 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;

[18] ISO 17511:2020
In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples

- 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; and
- 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 IMDRF Essential Principles of Safety and Performance of Medical Devices and IVD 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 validation and verification documentation, device description, labelling, risk management plan and manufacturing information, is needed to allow a manufacturer to demonstrate conformity with the Essential Principles. (12) (13) 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 and clinical 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 14155:2020 – *Clinical investigation of medical devices for human subjects – Good clinical practice* (9) is therefore not suited to IVDs. A standard specific to IVDs has been developed by ISO*: In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice* (14).

2.4.4 Lot verification testing of IVDs

Some countries that have yet to implement effective regulation for medical devices but have a national industry or need to import high-risk (Class D) IVDs, may implement a system of lot verification of such IVDs pre-distribution to users or post distribution 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 referral[19] laboratory or other competent[20]laboratory that is assigned the overall responsibility for coordinating and conducting lot verification testing on its behalf.

[19] In the context of this publication is a referral laboratory is called a reference laboratory.
[20] Competency is the capability to apply or use a set of related knowledge, skills, and abilities required to successfully perform "critical work functions" or tasks in a defined work setting. ISO standard 15189 for medical laboratories https://www.iso.org/obp/ui/#iso:std:iso:15189:ed-3:v2:en or ISO 17025 for other testing laboratories https://www.iso.org/ISO-IEC-17025-testing-and-calibration-laboratories.html

3. Enabling conditions for effective regulation of medical devices including IVDs

Public confidence in medical devices including IVDs requires effective and efficient regulation built upon a sound legal and policy foundation, as well as good regulatory practices. (15) WHO developed Good regulatory practices in the regulation of medical products. The general principles therein should be applied when establishing a new, or revising an existing, system of regulating medical devices including IVDs. They include:

- legality;
- consistency;
- independence ;
- impartiality;
- proportionality;
- flexibility;
- clarity;
- efficiency
- transparency;

3.1 Legal requirements

Medical device regulations 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.

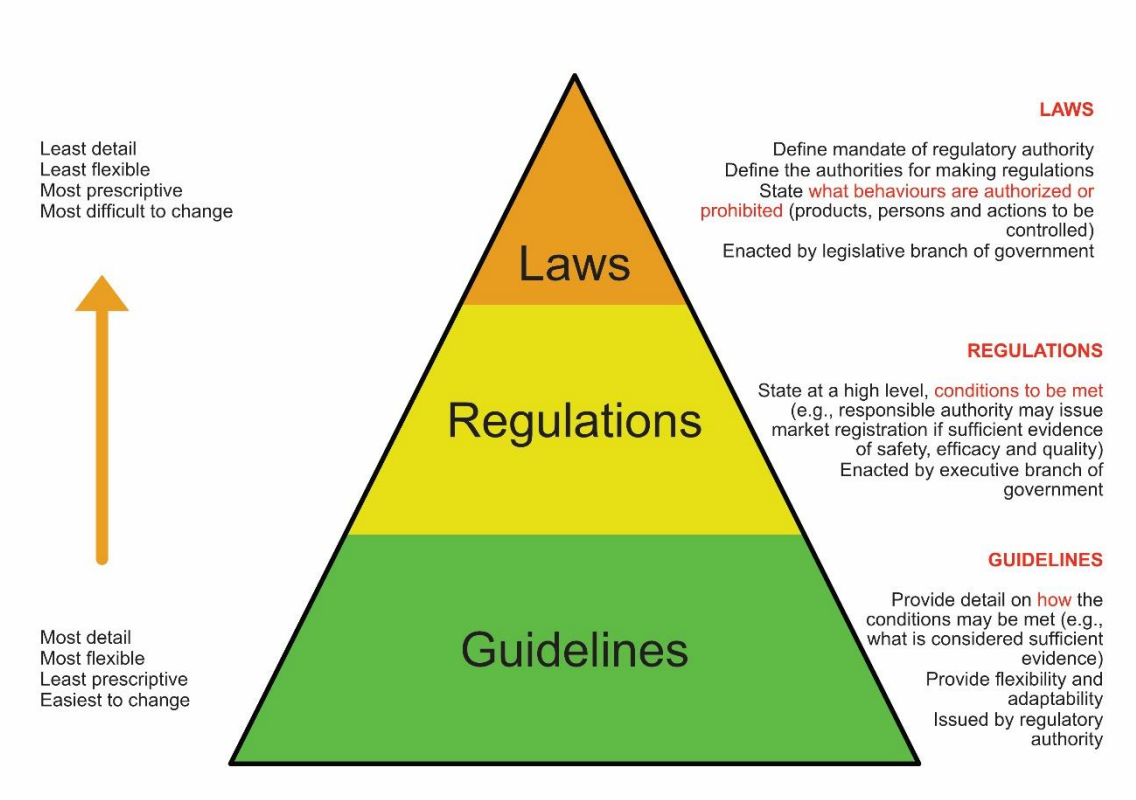


Fig X. Architecture of a regulatory framework (15)

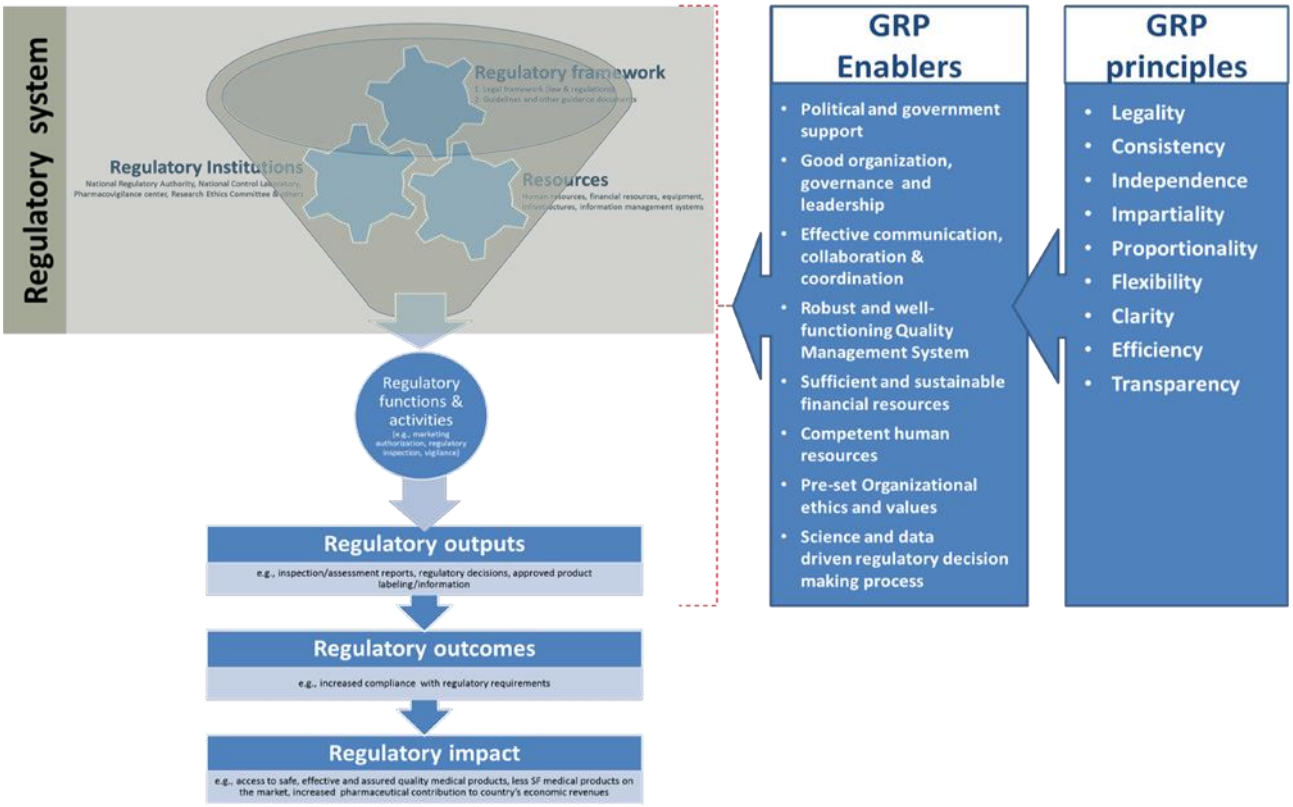
The law should define the products within its scope and identify the entities subject to regulation. It should create a general requirement that only medical devices including IVDs that are safe, perform as intended, and are of appropriate quality, may be marketed or made available for use in the jurisdiction. The law should delineate the responsibilities of the regulatory authority and establish its enforcement powers to include restricting circulation or withdrawing 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 government bodies such as the justice ministry, 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 and define the responsibilities of stakeholders in the regulatory process: manufacturers, importers, exporters, 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. It should be clear for stakeholders which authority is responsible for what. 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 3*),

taking into account assessments and regulatory decisions by authorities in other jurisdictions when taking its own regulatory actions. The law should let the regulatory authority establish approval pathways for specific circumstances and categories e.g. donated, investigational and personal use medical devices including IVDs. It should also allow the regulatory authority to respond to public health emergencies in an appropriate and timely manner. The law should accommodate a transition period from basic to expanded regulatory controls to the extent that resources allow as experience is gained.

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 for stakeholders and adopting requirements that are proportionate and offer the least burdensome ways of achieving policy goals. Regular interactions with stakeholders is key for support and commitment. Stakeholders should be consulted in the development of new laws and regulations in order to receiving feedback on proposed regulations and guidance. The provisions of laws, regulations and guidelines should be as transparent, predictable and internally consistent as possible. *(see Section 7.1)* 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 or international 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).

In the diagram below the principles, enablers of the regulatory systems are connected to the regulatory output.



Principles and enablers of good regulatory practices (GRP) and components of a regulatory system (15)

3.2 Gap analysis of existing controls

It is important at an early stage of introducing a regulatory framework, to evaluate any existing regulatory controls that apply to medical devices including IVDs. This will allow the policymaker 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 including IVDs used in the prevention, diagnosis and treatment of those diseases. Box A4.1 lists elements to be considered in a gap analysis.

Box A4.1

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

- Are medical devices including IVDs 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 including IVDs?
- What is the public health risk in the country, associated with medical devices including IVDs?
- Is there a clear definition of the term "medical device" and does it match with the definition recommended by this Model?[21]
- Is there a system of registration and marketing authorization?
- Is there a national regulatory authority with clear powers and oversight for health products ?
- Do the regulators have the proper competencies required for effective implementation and enforcement?
- Where there is a legal framework , is it enforced and does the regulatory authority have sufficient resources, expertise, and funding to perform its duties?
- What proportion of medical devices including IVDs are imported and from where?
- Are there local manufacturers of medical devices including IVDs? 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 substandard and falsified (SF) medical devices including IVDs have been placed on the market?
- Are there processes and procedures in place to prevent, detect and respond to substandard and falsified medical devices including IVDs
- Do existing laws and regulations comply with international good practices and treaty obligations?

3.3 Implementation plan

Once a national legal framework, binding legislation (15) on medical devices including IVDs has been adopted, the appointed regulatory authority should adopt and publish a plan for its implementation. The plan will be driven by public health priorities and needs and by the availability of resources, including trained competent staff to implement legislation. Risk management should be an integral part of management and decision-making and be integrated into the structure, operations, and processes of the organization. Risk management includes scope, context and criteria that are relevant for the regulatory processes.

The elements subject to risk management for medical devices including IVDs can be derived from the WHO Global Bench marking Tool Revision VI (GBT+) (16) i.e., national regulatory system, registration and marketing authorization, vigilance, market surveillance and control

[21] The definition used in this Model is from GHTF http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n071-2012-definition-of-terms-120516.pdf

(including import), licensing of establishments, regulatory inspections, laboratory testing, clinical trials oversight.

The implementation 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 including IVDs 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 guidances to ensure that medical device manufacturers, importers, distributors and purchasers are aware of their responsibilities, thereby avoiding disruption in the supply of medical devices including IVDs during the transition period.

A road map may be a useful tool of actions, timelines and deliverables to follow the implementation of the regulatory controls (17) *(see Section 7.2)*

3.4 Monitoring implementation

At the time of development of the regulatory implementation plan, goals, regulatory processes, and performance-based indicators should be established to allow progress of implementation to be assessed against a baseline that represents the most current status of medical devices including IVDs legal framework. GBT+ provides the functions and indicators which enables regulatory authorities to establish their basic level in a systematic manner and develop their institutional development plan. Progress should be reported to the legislature, parliament, and the public, bearing in mind that a strategy, a plan for implementation and enforcement should be aligned with the available resources. 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. A law with modest aims and objectives that is properly enforced is preferable to a more comprehensive one that cannot be implemented (15)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 including IVDs. 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 national regulatory authority, with the ability to exercise independent decision-making within the legal framework. That regulatory authority 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 regulations (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(conformity assessment bodies (CABs) to assist it in carrying out some of its duties. In this situation the regulations 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 well-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 including IVDS 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 including IVDs 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. A conflict of interest policy, avoiding improper bias and being transparent in their funding and decision making based on scientific criteria should be established by the regulatory authority. Leaders in the organization must set the tone by good example in their own conduct.

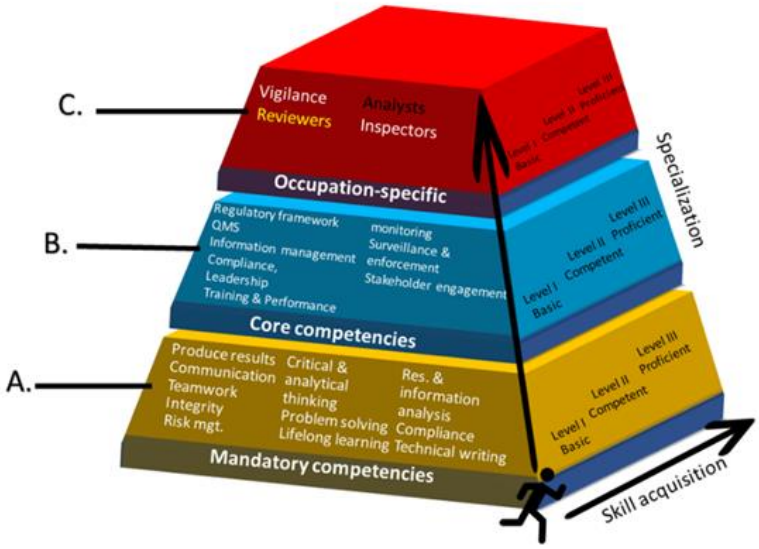
3.8 Regulatory competencies and resources

The practice of regulating medical devices including IVDs 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. 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 including IVDs, the responsibilities of the regulator, the concepts of international standards and harmonization, quality management systems, and an understanding of a range of different device technologies and their application A conflict of interest policy, avoiding improper bias and being transparent in their funding and decision making based on scientific criteria.

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 including IVDs, 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.

All regulatory staff within the regulatory authority should have mandatory and core competencies appropriate for their level. WHO Global Competence Framework models the competency framework as follows: (a) Mandatory workplace competencies, (b) Core or generic competencies, and (c) Role-specific or occupation-related competencies *(Z).*



Work functions (tasks/roles), underlying knowledge, and the skills or abilities. WHO Global Competency Framework (Z)

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 S*ection 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 including IVDs, the regulatory authority should, according to the priorities in regulating specific medical devices including IVDs, 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 including IVDs 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 (16))),), and the IMDRF *Good regulatory review practices – competence, training, and conduct requirements for regulatory reviewers*).

Based on the findings of the gap analysis, initial and continuing training of medical devices including IVDs regulators according to a training plan should be implemented. *(see Section 7.3)*

3.9 Reliance and recognition

Reliance, recognition and abridged assessment are facilitated by international regulatory convergence, a process of gradual alignment of regulatory requirements in different countries, regions or globally*).* (18)

The law should establish to what extent the relying regulatory authority may reasonably use the assessment outcomes work of a reference regulatory authority in another jurisdiction in assessing evidence that a device conforms to national requirements of the reference regulator. When regulations do not make explicit provision for the application of reliance, it may be adopted through interpretation of existing regulations, if the legal framework does not explicitly preclude application of reliance approaches by the regulatory authority. Reliance can be

implemented through policy change, as long as it is broadly consistent with national legislation. If application of reliance is prohibited, revision of the legislation should be considered within a reasonable timeframe.

Reliance may take many forms and reflect varying degrees of application in recognizing or taking account of the assessments, decisions or any other authoritative information available from other authorities and institutions. For example, a regulatory authority authorizes a medical device to be placed on its own market and the relying national regulatory authority uses this information, possibly supplemented with information from the manufacturer to reach its own decision. Recognition may be seen as a special and more complete form of reliance whereby one regulatory authority relies on the regulatory decisions of another regulatory authority, system or institution, obviating the need for additional regulatory assessment in reaching its own decision.

The usual phases of reliance and recognition evolve from confidence building in which work-sharing and joint activities are undertaken, through reliance on regulatory information from the other regulatory authority to unilateral or mutual recognition of regulatory decision by another regulatory authority.

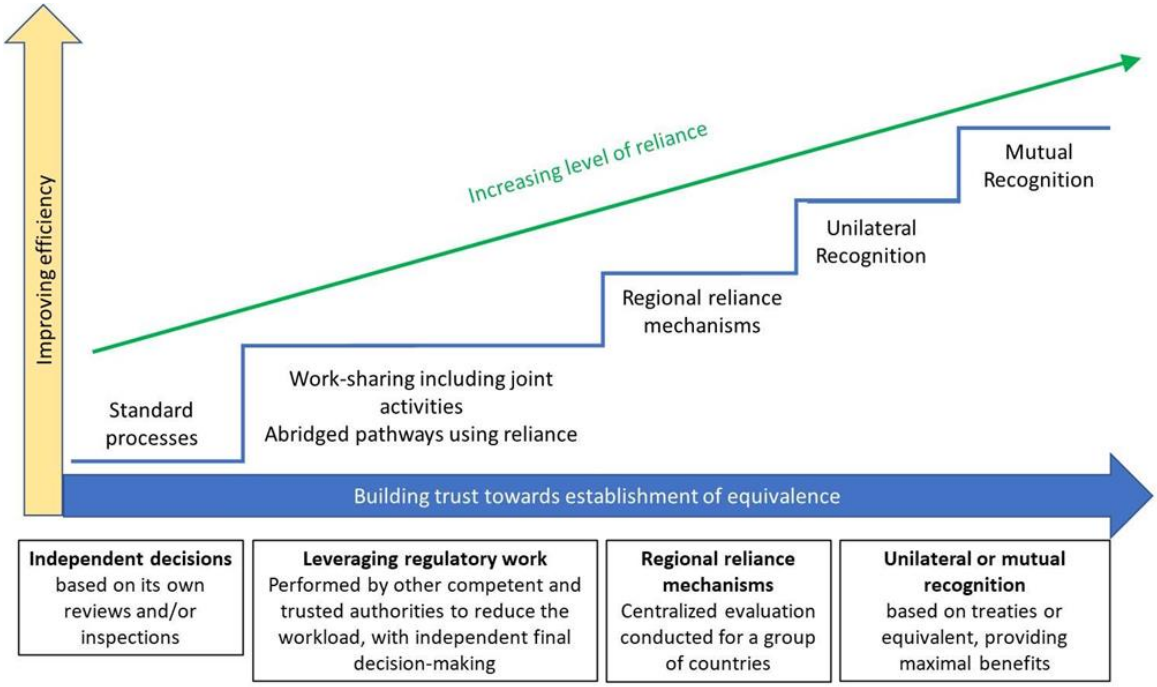


Figure 1. Key concepts of reliance
Source: WHO Good reliance practices in the regulation of medical products: high level principles and considerations. (18)

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 being implemented by the

regulatory authority who authorized the medical device to be marketed in its jurisdiction. The regulatory system upon which an authority relies or which it recognizes should be equivalent or superior to the national regulatory system, taking into consideration that reliance may refer to a specific element of the regulatory process while recognition is an overall acceptance of the regulatory decision of the reference jurisdiction. For example, medical device regulations in some jurisdictions permit a manufacturer to specify some medical devices as "export only" and only subject these medical devices to minimal controls rather than evaluating their 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, risk class, 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 the same as the product 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 variety in classification of IVDs in existing regulatory systems (which determines the level of regulatory scrutiny) and newly accepted regulations in some jurisdictions. For instance the European regulation on in vitro diagnostic medical devices (EU Regulation (EU) 2017/746) (11) replaced the in vitro diagnostic directive (EU IVD Directive 98/79/EC). The Regulation came into force in May 2017 with a transition period until 2025[22]. It implies that IVD can be on the market during that transition period and for some years after that, subject to two substantially different regulatory frameworks.

This is an example where knowledge of the regulatory system upon which reliance or recognition is based is important.[23]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. The

[22] Transition period EU IVDR https://ec.europa.eu/health/sites/default/files/md_newregulations/docs/timeline_ivdr_en.pdf

[23] 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.

same considerations apply to the outsourcing of any activities, for example to CABs and third-party parties (19)or experts (locally or internationally based).An example of a specific pathway in reliance is the CRP abridged assessment[24], whereby the relying regulatory authority may take into account the output of work performed by reference regulatory authorities, therefore performing only a limited assessment of the technical dossier such as labelling requirements, stability data or other country specific requirements. This may also extend to assessment of changes of the medical device. The rationale is that prior stringent assessment provides assurance of quality, safety and performance It relies on such an assessments of documentary evidence by a reference regulatory authority or WHO.

3.9.1 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, marketing authorization of domestically manufactured medical devices ; handling reports of incidents, including vigilance reports; market surveillance activities; communication and monitoring of field safety corrective actions (FSCA), and market withdrawal. Information sharing on incidents[25] and any FSCA as well as market surveillance is important. The regulatory activities described above should be principally performed by the responsible regulatory authority in the countries, however international collaboration and reliance approaches (for example work-sharing) can also be beneficial to facilitate these activities.

3.9.2 International collaboration

Where resources permit, the regulatory authority should participate in formal and informal information-sharing networks with other regulatory authorities. This will allow for detection of a signal that a given medical device may not be meeting quality, safety and performance requirements in another jurisdiction. It also facilitates confidence building with the possibility of work-sharing and reliance upon other regulatory authorities.

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[24] Abridged regulatory pathways a regulatory procedures facilitated by reliance, whereby a regulatory decision is solely or partially based on application of reliance.
The CRP provides unredacted reports on the assessment, inspection and performance evaluation (in the case of in-vitro diagnostics) upon request (and with the consent of the manufacturer) to participating regulatory authorities.
https://apps.who.int/iris/bitstream/handle/10665/340323/9789240020900-eng.pdf

[25] Incident: Malfunction or deterioration in the safety, quality or performance of a device made available on the market, any inadequacy in the information supplied by the manufacturer and undesirable side-effects. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN Note: Depending on jurisdictions, the term adverse event (in its post-market meaning) and incident can typically be used interchangeably

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 stepwise approach – from basic to expanded level regulatory controls. Building a risk-based regulatory system requires a solid legal foundation that provides a consistent description of the risk management process. (*See 3.1*) The regulatory framework must be sustainable, expandable and accommodate advances in clinical practices, public health needs and evolving technologies. The basic level regulatory controls will form the foundation for the expanded level regulatory 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 (20)

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 which lays down the regulatory foundation, the elements of expanded controls will be of limited value and difficult to manage effectively.

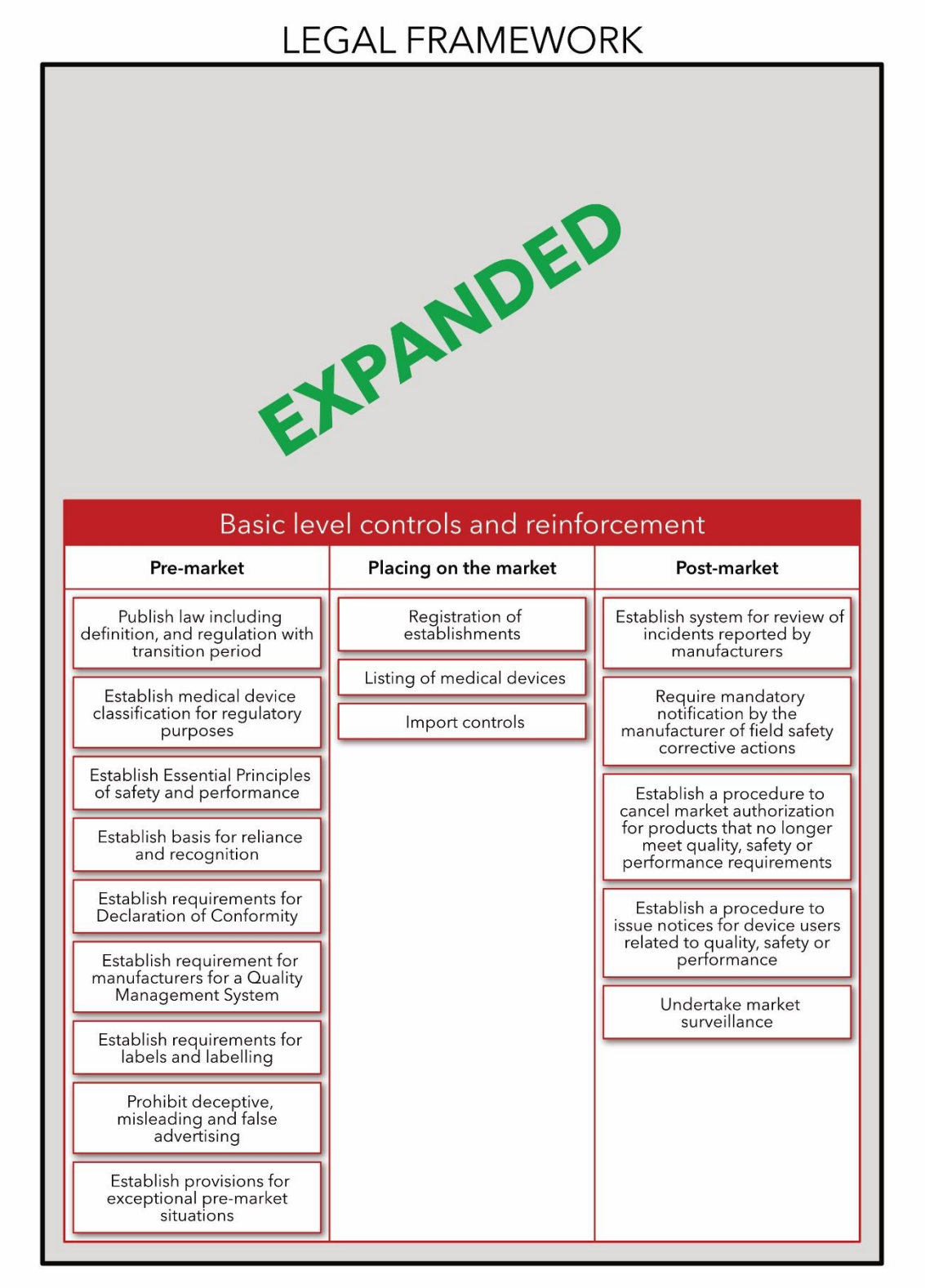
The regulatory authority may reduce the demands on its own staff by either relying upon or recognizing the work or decisions made by other regulatory authorities or trusted institutions such as WHO. Initially, resources may then be targeted to post-market controls, which are the responsibility of the national regulatory authority. 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.

4.2 Basic-level regulatory controls and their enforcement

The Model recommends that basic-level regulatory 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 that place medical devices on the market to be registered, establishes import controls and requires post-market surveillance activities. Typically, the post-market activities of the regulatory authority would include a system to ensure that manufacturers act proportionately to reports of quality, safety or performance problems associated with use of a medical device. (*Figure A4.2*).

Figure A4.2

Basic-level controls and enforcement for medical devices within the legal framework



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 3.1*). In particular it includes:

- 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 regulatory authority, its enforcement powers, market oversight responsibilities, powers to issue implementing regulations and to take action where the health of patients or users is compromised, and the responsibility for publishing guidance documents to aid understanding of legal requirements;
- provide the regulatory authority with administrative and enforcement discretion for reliance upon and recognition of the work or decisions of regulatory authorities in other jurisdictions (*see Section 3.9*);
- require that only safe medical devices that perform as the manufacturer intends may be placed on the market;
- specify market entry requirements for medical devices;
- establish record keeping, registration and reporting requirements for all parties within the scope of the law, including the regulatory authority;
- create the option of appeal to a regulatory decision;
- 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;
- specify that after the transition period manufacturers shall comply with the regulatory requirement
- specify regulatory approaches during special situations such as public health emergencies.

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 stakeholders must be allowed time to adapt to the law, i.e. a transition period. In some situations, an extension of the transition period is required. In this case, the changes should be announced in advance and explanations should be published regarding the new transitional period and the regulations for medical devices. 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 potential stakeholders and the number of devices on 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 stakeholders.

4.2.1.1 Establish medical device classification for regulatory purposes

The law should include a medical devices classification scheme, based on internationally harmonized guidance , to provide an efficient way of regulating each medical device according to its risk class (2) (3). It should include provisions for the regulatory authority to issue implementing acts and guidance on the classification of medical devices, including IVD medical devices. 'The manufacturer determines the risk class of a medical device based on the classification rules established by the regulatory authority. Its decision may be disputed by the regulatory authority during the review and evaluation of the application for market approval (*see Section 2.2 and 2.4*).

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 2.3 and 2.4*) (6). Failure to make such a declaration of conformity (see below) *(*(10)or making a false declaration, would be grounds for enforcement action by the regulatory authority.

The preferred, 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[26] 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 require that the manufacturer, through its labelling, provides the user with information on how to properly install, use, maintain and dispose them. Information on contradictions, precautions and anticipated incidents should be place.

4.2.2.1 Establish a basis for reliance and recognition

The medical devices law should allow reliance and recognition approaches to be used by the regulatory authority to determine whether a medical device complies with the regulatory requirements for allowing the medical devices to be placed on the domestic market. However, the regulatory authority is ultimately responsible for determining whether a medical device may be supplied in its jurisdiction (18)

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 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;
- the regulation under which the declaration is made;
- 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 in the intended purpose statement;

[26] 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.

- 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 and
- the date on which the declaration is issued.

The regulatory authority performs a risk-based verification of the relevant documents submitted by the importer or the authorized representative.

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[27] *Medical devices Quality management systems – Requirements for regulatory purposes* and ISO 14971:2019: *Medical devices – Application of risk management to medical devices* (21)

The QMS is important not only for assuring the quality, safety and performance of a device during its life cycle, 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, maintain and dispose them. Labels, instructions for use and other labelling (e.g. displays, service manuals and information for patients through web appliances) 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.[28] To begin establishing regulatory controls, regulatory authorities must provide

[27] The latest version of the ISO Standards apply.
[28] Medical devices – Symbols to be used with medical device labels, labelling and information to be supplied – Part 1: General requirements. ISO 15223-1:2021 (https://www.iso.org/standard/77326.html, , accessed 30 August 2021)

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 through web appliances However, printed instructions for use shall be provided if requested by the user.

Another function of the label is to allow the identification of medical devices for example by batch or lot number, or serial number. This allows traceability by users to facilitate FSCA and helps when reporting incidents. A recent development is the addition of an internationally harmonized unique device identifier (UDI) to the label to identify the medical device both in human- and machine readable form*).*

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 and

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Medical devices – Symbols to be used with medical device labels, labelling, and information to be supplied – Part 2: Symbol development, selection and validation. ISO 15223-2:2010 (http://www.iso.org/iso/catalogue_detail?csnumber=42343, 30 August 2021).
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 30 August 2021).
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 30 August 2021).
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 30 August 2021)
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 30 August 2021).
In vitro diagnostic medical devices – Information supplied by the manufacturer (labelling) – Part 5: In vitro diagnostic instruments for self-testing. ISO 18113-5:2009 (http://www.iso.org/iso/catalogue_detail.htm?csnumber=40988, accessed 30 August 2021).
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- does not make false or misleading claims.

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

4.2.2.6 Establish provisions for exceptional premarket situations

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

The law should establish defined exemptions from, and provide enforcement discretion for, compliance with certain requirements, for example, medical devices for humanitarian use, public health emergencies, clinical investigations, exhibition use and medical devices donated to the country by charities or the manufacturer. Regulators should issue clear guidance on such exemptions (*See 3.1*).

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 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 up to date and correct. Identity and location of the manufacturer and/or distributor, or importer should be

provided on the medical devices or on the outer packing of medical devices. It is also useful in facilitating regulatory actions such as compliance inspections (e.g. of warehouses or manufacturing plants), notifying and monitoring of FSCA and for law enforcement purposes. Making registration and listing information publicly accessible allows device purchasers or users of medical devices to identify products available to them and determine the identity and location of their manufacturers and/or distributors, exporters and/or importers. It is the responsibility of the regulatory authority to periodically check the validity of the registered establishments and determine the interval for these checks.

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, contact information and the manufacturer it represents 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 listing of medical devices placed on the domestic market and keep the list updated by notifying renewals or withdrawals to the regulatory authority;
- providing the regulatory authority with the information it requires when the manufacturer seeks authorization to market its devices;
- informing the manufacturer of all user feedback. In certain jurisdictions the authorized representative may also be responsible for reporting incidents to the regulatory authority within the local market and ensuring users act on any field safety corrective actions initiated by the manufacturer;
- in certain jurisdictions the authorized representative will report FSCA to the regulator on behalf of the manufacturer
- 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 and
- 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 any person/entity to engage in importation or distribution of medical devices should be that they are registered by the NRA. Beyond this, the regulation may require the importer or distributor to attest that it will at minimum:

- ensure the medical devices it imports or distributes comply with safety and performance requirements and are accompanied by the proper documentation including labelling information, IFU and label;
- trace medical devices through that part of the supply chain with which it is directly involved and
- 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 for authorized representatives of manufacturers outside the jurisdiction, and importers and distributors, to submit and maintain 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 Among other elements, the listing should provide the standardized generic descriptive names of those medical devices, where possible using globally harmonized nomenclature (*See section 4.3.1.4, Expanded-level controls*). Listing of medical devices will allow the regulatory authority to determine which products are placed on the market and by whom. The manufacturer should provide information about the medical devices intended to be listed. The regulatory authority should develop a set of information to be submitted for listing purposes. 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 e.g., a portal consisting of a medical devices function, 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. The information shall be in compliance with the technical documentation of the medical device.

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 such as quality management system certificates, proof of marketing authorization in the exporting country, declaration of conformity and test reports. These may include approval of importation documents by the regulatory authority 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 compliance conformity with regulatory requirements. For the purpose of listing the regulatory authority determines which categories of medical devices or risk class of medical devices would require additional import controls. Collection of samples may be required for suspected substandard or falsified medical devices including IVDs (inspection and/or panel testing) based on product risk (e.g., lot testing for IVDs – *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, customs service and other relevant government officials 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. The regulatory authority shall be equipped with enforcement power to halt medical devices that do not comply with regulatory requirements entering the country. 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 – post-market

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

4.2.4.1 Establish a system for incident reporting[29]

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 incidents at the patient level, in particular those incidents events resulting in death or serious injury*)*.Manufacturers should be obliged to report to the regulator if any of the following circumstances occur within their jurisdiction:

- Discovery of a serious public health threat
- When use of a medical device led to:
  – death of a user, patient/client or other person;
  – serious deterioration in health of a user, patient/client or other person.
- No death or serious deterioration in health of a user, patient/client or other person occurred but might have

For IVDs, the risk of harm is usually indirect as the device is not used on the body: for instance, for high-risk IVDs any false negative result is reportable Reports of incidents received by the regulatory authority from the health care professional, the patient or end-user or obtained during regulatory controls, must be passed to the device manufacturer or the authorized representative for investigation and trend analysis. The manufacturer or its authorized representative should inform the regulatory authority of the outcome of the investigation and if necessary take steps or an FSCA and notification by means of issuing a field safety notice. The regulator may also conduct a risk assessment, to ensure public safety is immediately protected. Incident of a more serious nature or serious public health threats may trigger investigation by the manufacturer and/or possible FSCA or enforcement actions by the regulator NRAs may consider to exchange information, if they possess any information that indicates the consequences of using a medical device:

- have led or are highly likely to lead to serious public health threat;
- may affect other jurisdictions.

This process can be used to exchange early information on significant concerns or potential trends that individual regulatory authorities have observed, but that have not yet resulted in FSCA .

[29] Note: Depending on jurisdictions, the term adverse event (in its post-market meaning) and incident can typically be used interchangeably

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 market surveillance or through information exchange with other regulators or manufacturers, of any newly identified potential hazard associated with a device, it should have an established procedure to issue information notices to users and have a publicly accessible repository such as a website for these records. Such a system should also, in addition to the Field Safety Notice (FSN) sent by the manufacturer, 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 appropriate to the intended recipients as well as to the urgency of the action. The regulatory authority should have in place means by which the effectiveness of corrective or remedial actions by the manufacturer or its authorized representative shall 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, substandard and falsified 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 and inform the public of this action through appropriate means.

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; quarantine and disposal of medical devices. Manufacturers may be required to review the technical documentation 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. Enforcement measures shall have a basis in law. 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 or CAB 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 incidents and serious public health threats by issuing safety alerts and advisories 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. Market surveillance activities should be prioritized using a risk-based approach. The regulatory authority may undertake targeted activities based on a risk assessment of the distribution chain, evaluation of complaints and incidents reporting, and information from the post-market surveillance systems of medical device manufacturers and their authorized representatives .

4.3 Expanded-level regulatory controls

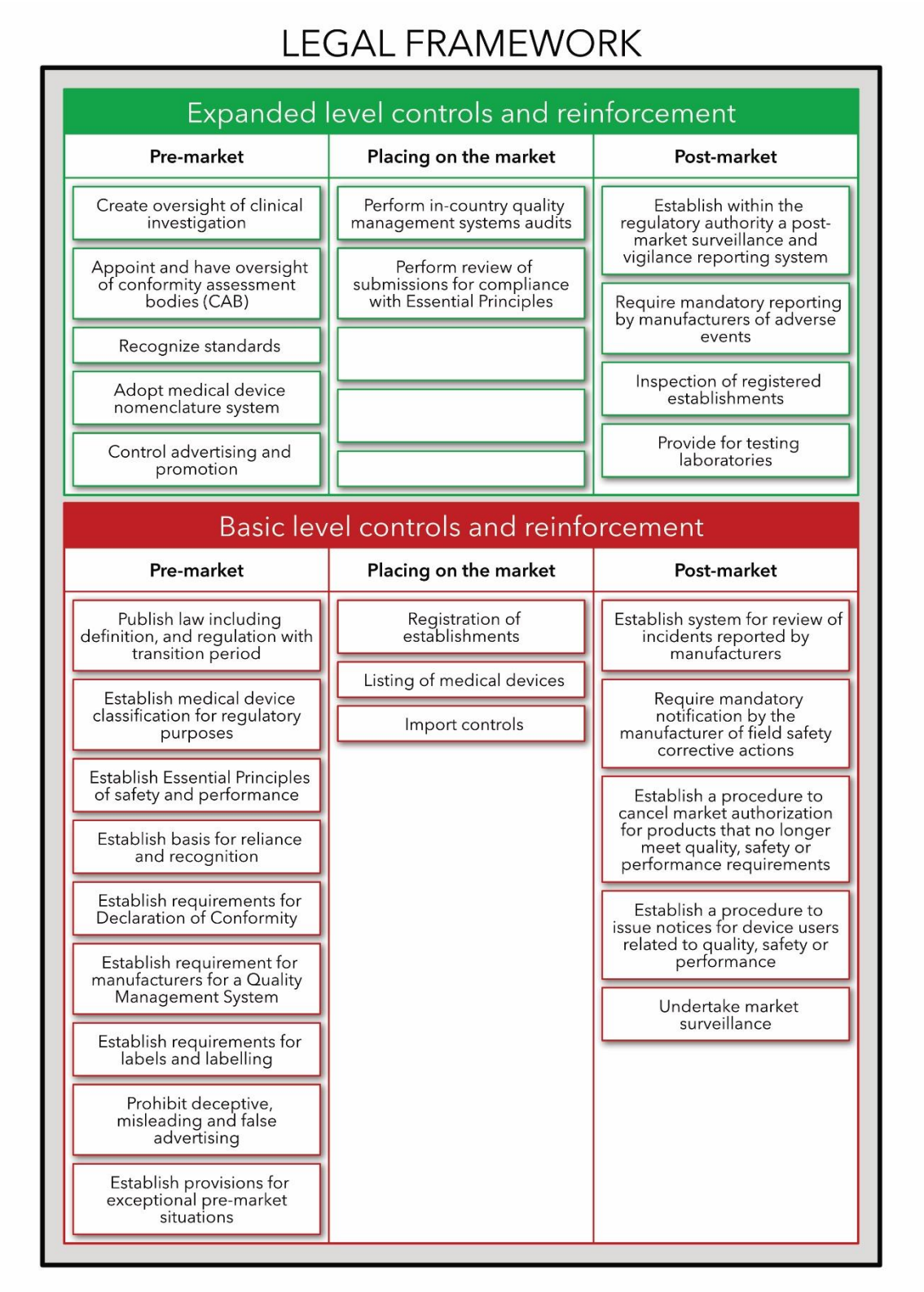
Once the basic-level controls have been implemented effectively and efficiently, the regulatory authority may consider implementing more advanced controls. To do so, the law should provide the legal basis for such expanded controls, the regulatory authority must have effectively enforced the basic controls, 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). Implementation should always be consistent with available resources: enforcing a limited set of requirements and publishing them is preferable to covering

a large area of regulatory controls without properly enforcing them. This requires a flexible response system to serious incidents and violations of legal requirements (*See 3.4*).

Figure A4.3

Expanded-level regulatory controls and enforcement for medical devices

Note: For the expanded level controls the diagram shows empty boxes indicating the option for a regulatory authority to set its activities based on the national priorities.



4.3.1 Expanded-level controls – premarket

4.3.1.1 Create oversight of clinical investigations

The national 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. Different factors should be taken into account when establishing mandatory clinical investigation for medical device such as risk class, technologies used, level of invasiveness.

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. To assure adequate consideration of the design of studies and protection of the interests of participating subjects -including informed consent- , such investigations should also be conducted under the oversight of a local ethics committee or institutional review board.[30] A widely used international standard for the practice of clinical investigation is: ISO 14155:2020 – *Clinical investigation of medical devices for human subjects – Good clinical practice* (9)

The regulatory authority should also establish a mechanism for periodic progress reports and for the reporting of serious incidents that occur during clinical investigations *(30)*. The regulatory authority should also have provisions in place to suspend or terminate clinical investigation in case of identified harm to patients and/or public health. In-country clinical investigations i.e. a requirement to systematically conduct the investigation in the country of registration, should generally not be required, unless there is a compelling and sound scientific reason.

[30] The global standard for testing in humans is the Declaration of Helsinki – ethical principles for medical research involving human subjects (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

4.3.1.2 Appoint and have oversight of CAB

Certain technical elements of the regulatory framework may be delegated to designated or recognized competent third-party organizations, often private, generally known as CABs Authorities may establish criteria for designation of CABs. These bodies may perform initial certification and surveillance audits of device manufacturer QMS and/or premarketing reviews of the conformity of a device to the Essential Principles. The CAB may be designated by the regulatory authority to undertake conformity assessment of specific medical devices where it is judged to have the necessary skills (e.g., active implantable and/or IVDs and/or electromedical devices). Satisfactory compliance with requirements is typically documented with a CAB certificate (19). 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 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

4.3.1.3 Recognition of standards[31]

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

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; and
- 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.

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”.

[31] 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.

Preference for recognition should be given to international standards, e.g., those of the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC), regional standards and the national 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 they can then be updated to stay current and can be revised much faster than legislation can be updated.

4.3.1.4 Select and implement a medical device nomenclature system

Medical devices include a wide range of health technologies, from simple products such as single use devices, to more complex medical equipment such as hemodialysis machines. This variability presents challenges in the recording and reporting of medical devices across the whole life cycle of a medical device.

A globally harmonized medical device nomenclature system(22)includes a framework for standardizing the use of global nomenclatures and supporting collaboration between current systems among key stakeholders to ensure convergence toward use of an international coding and classification of medical devices[32].

A nomenclature system provides for consistent and accurate identification of medical devices with similar characteristics by a variety of stakeholders including policy makers (national lists), regulators, manufacturers, trade and customs, insurance payers, device managers (health care settings) users (e.g., healthcare professionals and patients).

A nomenclature system improves product distribution and use and
supports timely and accurate post market vigilance activities and medical record keeping.

For example, identification of a potential medical device safety issue depends on:

- correct and timely medical record keeping by the healthcare provider;

[32] A nomenclature system specifically for assistive devices is ISO 9999:2016– *Assistive products for persons with disability – Classification and terminology* https://www.iso.org/obp/ui/#iso:std:iso:9999:ed-6:v1:en, accessed July 2021, accessed 13 April 2022

- exchange of adverse event information between the healthcare provider and the manufacturer and/or regulator;
- comprehensive data analyses of all adverse events of a particular device type by the manufacturer and/or regulator;
- dialogue between the manufacturer and regulator regarding any performance concerns and appropriate next steps; and
- communication to the healthcare provider about precautions to take with a particular device type.

There exist several different nomenclature systems used to identify medical devices developed to support regulatory decision making, procurement and supply, customs, as well as inventory and maintenance management. The benefits of a nomenclature system are only realized when the same nomenclature system is used consistently and accurately by all relevant stakeholders and that nomenclature is globally harmonized. To this end, selection of globally harmonized nomenclature system should consider the needs of each stakeholder individually (e.g., ministry of health, regulator, manufacturer, healthcare industry, health care providers trade and customs, patients) and as a system.

Use of a globally harmonized nomenclature supports information being aggregated and analyzed not only within a given jurisdiction but also internationally. (23) A globally harmonized nomenclature system is particularly relevant for low- and middle-income countries who are recipients to medical devices from developed economies. (24) (25)If economies have their own nomenclature systems that are jurisdiction specific, accessibility of a tracking system of those devices in a health system is significantly hindered. The decision trees provide a suggested processes for selecting and implementing a globally harmonized nomenclature. The processes include use of a national selection committee with representation from relevant stakeholders. The selection committee would perform a landscape analysis of national nomenclature activities and, select and implement a globally harmonized nomenclature system that is best suited to national requirements.

Considerations in selecting a nomenclature system include:

- *Harmonization*

Selection of a nomenclature system should consider whether the system is harmonized between various countries, regionally or globally to allow for pooling of data and experience worldwide.

Currently, hundreds, perhaps thousands of nomenclature systems are available for selection. Selection should first be limited to those nomenclature systems that are globally harmonized, meaning that the nomenclature agency is actively contributing their terms and codes toward ongoing harmonization efforts (e.g. mapping of codes and terms with other nomenclature systems).

- *Accessibility and Ease of Use*

Selection of a nomenclature system should balance the needs of all stakeholders in the healthcare landscape to support consistent implementation. Access to the nomenclature should have no restrictions on use including but not limited to making the codes and terms freely available and downloadable.

- *Governance*

Selection of a nomenclature system should consider whether the system is managed in a transparent manner with a transparent process for obtaining feedback from all stakeholders and a quality system for managing changes to terminology.

Processes for the classification should have a transparent methodology of coding, and establishment of nomenclature terms.

- *Timely Updates*

Selection of a nomenclature system should consider the mechanism and periodicity of updates to medical device terms. The frequency of updates should balance rapid innovation of new types of medical devices with the need for clear, consistent implementation across all stakeholders.

- *Used in source Jurisdictions*

Selection of a nomenclature system should consider the jurisdictions that are the source of purchased products. If UDI regulations are in place or proposed, consideration should be given to the nomenclature requirements associated with UDI for the source jurisdiction.

- *Language*

Selection of a nomenclature system should consider the availability of translations in multiple international languages, especially those of interest to the selection committee. If an appropriate translation is not available, then the committee should check if there is a possibility of translation.

- *Transferability*

Selection of a nomenclature system should consider whether the nomenclature can be shared with other public sources like national lists, procurement systems, inventory and maintenance systems, electronic health care records, relation with clinical interventions, traceability etc. (free interoperability).

The role of the selection committee is to select and propose to the Ministry of Health a nomenclature system to be adapted at the national level. The decision to adopt the proposed nomenclature system is vested to the Ministry who will then communicate the decision with all respective stakeholders for implementation.

How to implement a nomenclature system?

Successful implementation of a medical device nomenclature system requires significant planning and coordination. Below are a few steps to consider when developing and executing an implementation plan.

- Identify which stakeholders are responsible for which aspects of implementation and how actions of each stakeholder affect one another. For example, a manufacturer's ability to identify the correct term for a device impacts a healthcare provider's ability to input correct information into a medical record.
- Align the selected nomenclature system with the existing nomenclature systems used in your country.
- Develop a plan for which stakeholder is expected to use which aspects of the nomenclature system by what dates. This plan should balance the time required for each stakeholder to complete necessary tasks with the benefits of complete implementation.
- Obtain feedback from stakeholders on anticipated challenges with the proposed plan. Adjust plan as needed.
- Execute the plan, providing clear, consistent, and timely communication to all stakeholders.
- Evaluate effectiveness of implementation, making updates to implementation plan and policies as needed.

4.3.1.5 UDI

The UDI is comprised of two components: the Device Identifier (UDI-DI) and the production identifier (UDI-PI). Where a nomenclature identifies groups of medical devices, a UDI-DI identifies an individual medical device. Regulatory agencies accredit organizations to operate a system for assigning UDIs that complies with regulatory requirements.[33]

[33] Proprietary names for the UDI-DI issued by an accredited organisation include GS1 GTIN (Global Trade Item Number), HIBC-LIC (Labeller Identification Code), ISBT 128-PPIC (Processor Product Identification Code) and IFA GmbH PPN (pharmacy product number)

A UDI is one component of a UDI System. In addition to development of the UDI itself, the UDI System also includes the framework for the application of the UDI to the label and the submission of appropriate information to a public UDI database (UDID)

A UDI System must have three interrelated components:

1. UDIs must be based on global standards;

2. UDIs must be applied to the label of a medical device and its associated packaging; and

3. Information about the medical device must be submitted to a UDI database (UDID) for the purpose of making it public available and to promote data sharing between regulators and other healthcare stakeholders.

A UDI System provides a single, harmonized system for positive identification of medical devices. Healthcare professionals and patients no longer have to access multiple, inconsistent, and incomplete sources in an attempt to identify a medical device and its key attributes. The UDID is a designated source for additional information. The UDID contains identifying information and other elements associated with the specific medical device. It is critical to note that the benefits of UDI can only accrue if all stakeholders, from the manufacturer to healthcare providers and patients, use UDI throughout their workflow systems. Therefore, it is imperative that all stakeholders be educated about the development and use of a UDI System.

A globally harmonized and consistent approach to UDI is expected to increase patient safety and help optimize patient care by facilitating:

- traceability of medical devices throughout their lifecycle, especially for field safety corrective actions,
- adequate identification of medical devices through distribution and use,
- identification of medical devices in adverse events,
- reduction of medical errors,

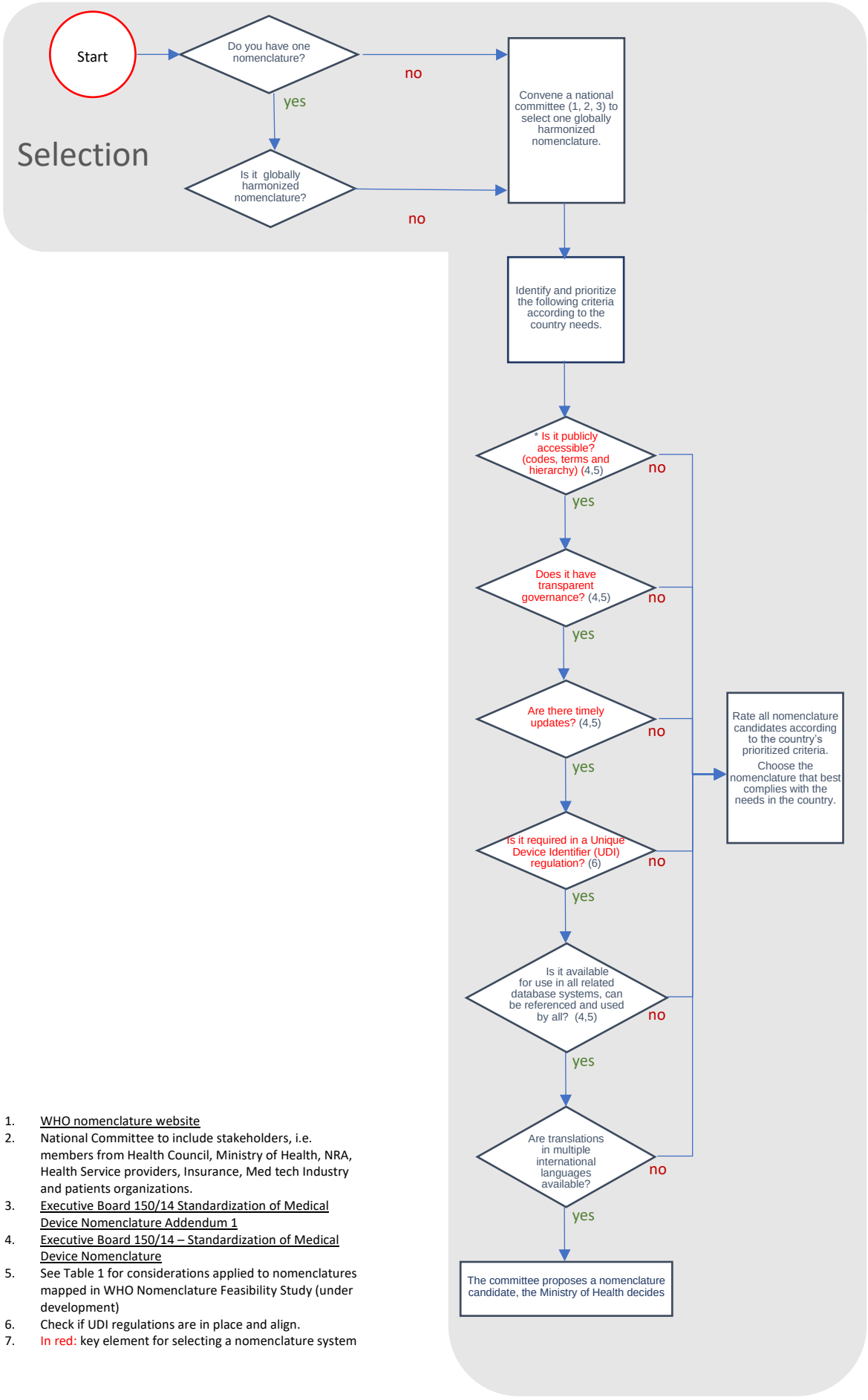
documenting and longitudinal capture of data on medical devices,

- Identification of falsified medical devices

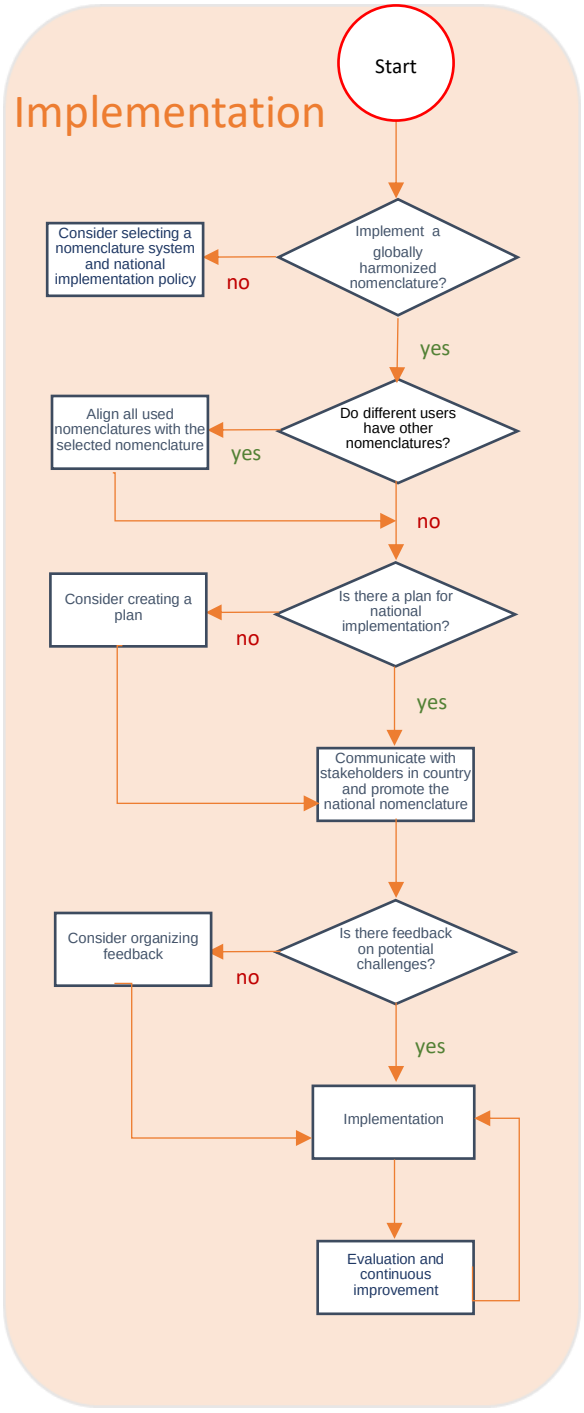
To ensure Unique Device Identification (UDI) as the means to increase the interoperability of device information, jurisdictions should follow international best practices when creating a jurisdiction-specific UDI System or in operating an existing UDI System. UDI Guidance: Unique Device Identification (UDI) of Medical Devices (IMDRF/UDI WG/N7) outlines the steps and considerations for implementing a UDI System and section 11.2 of the UDI System Application Guide (IMDRF/UDI/WG/N48 Final) includes a list of UDI implementation arrangements to address UDI adoption and use by all stakeholders

One key feature of UDI systems is the requirement to assign a specific medical device nomenclature for each UDI-DI record in a UDID. Section 9.2 of the IMDRF/UDI WG/N7 lists nomenclature as one of the core UDID data elements. Section 8.1 of the IMDRF /UDIWG/N48 refers to the expectations for including nomenclature as part of an effective UDID design, stating that regulators should "connect the device UDI-DI information with codes and terms of which would enable other stakeholders to: use the UDID data for activities like purchasing, stock handling, reimbursement, or research; find UDID information related to similar devices or to enable regulatory authorities to effectively assess the safety and performance of product groups in the field."

Figure XX: the diagram below illustrates the steps for selecting a harmonized nomenclature system



1. WHO nomenclature website
2. National Committee to include stakeholders, i.e. members from Health Council, Ministry of Health, NRA, Health Service providers, Insurance, Med tech Industry and patients organizations.
3. Executive Board 150/14 Standardization of Medical Device Nomenclature Addendum 1
4. Executive Board 150/14 – Standardization of Medical Device Nomenclature
5. See Table 1 for considerations applied to nomenclatures mapped in WHO Nomenclature Feasibility Study (under development)
6. Check if UDI regulations are in place and align.
7. In red: key element for selecting a nomenclature system



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, in all countries there should be a requirement that 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 should expand controls to include review of advertising and promotional material before it is placed on the market. At this time, the regulatory authority should 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. If preventative measures for regulating false, misleading or deceptive promotion fail, the regulatory authority may consider utilizing regulatory enforcement actions to intervene e.g. including issuance of warning letter, seizure, disposal, imposing a fine/penalties or pursuing a court order.

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 a regulation or ministerial decree that requires the regulatory authority to verify that a QMS appropriate to the medical devices under its control has been implemented by the manufacturer.

Although manufacturers of Class A medical devices are required to implement a QMS based on ISO 13485, 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 *()* CABs (*see Section 4.3.1.2*) to perform QMS audits or otherwise gather and assess evidence of the manufacturer's effective implementation of the QMS requirements *).*

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 *(*, The receiving country thereby relies upon the information from the QMS audit or recognizes the decision of the other jurisdiction regarding the QMS audit *()*. 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 post-market follow-up where appropriate *(* (10)*).*

At the basic level, assessing the safety and performance of medical devices depends primarily on an assessment by another regulatory authority supported by the manufacturer's declaration of conformity (See section 4.2.2.2). At the expanded level, the regulatory authority 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 web portal.

Internationally, harmonized formats for submission of technical documentation for conformity assessment purposes have been developed by various bodies, e.g. the IMDRF Table of Contents[34]. It describes a modular structure and format for such submissions in electronic form. Separate ToCs have been established for medical devices and IVDs The Association of

[34] The former harmonized format by GHTF was the Summary of Technical Documentation (STED) https://www.imdrf.org/sites/default/files/docs/ghtf/archived/SG1/technical-docs/ghtf-sg1-n011-2008-principles-safety-performance-medical-devices-080221.pdf, accessed 3 March 2022

Southeast Asian Nations (ASEAN) developed the Common Submission Dossier Template (CSDT) *()*. These formats provide guidance for the presentation of evidence that a medical device conforms to the regulatory requirements for safety and performance.

Regulatory authorities 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 trends to be associated with an excessive number of incidents, including use errors;
- the device incorporates innovative or potentially hazardous materials;
- the device type raises specific public health concerns (particularly for IVDs);
- if the medical devices class by the relying regulatory authority is different from the manufacturers' assigned classification;
- the imported medical device had not been assessed and approved by another regulatory authority;
- the device type will be used by laypersons to support or sustain the life;
- IVDs for self testing;
- the device type raises specific public health concerns.

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

The regulatory authority may be assisted in reaching its decision on premarket assessment (or any other regulatory decision) by advice from an expert medical device

committee, which may include experts from outside the regulatory authority. Where advice from external experts is sought, the regulatory authority should ensure that the necessary agreements for the exchange of confidential information are in place and a signed declaration of interest. The final regulatory decision rests at all times with the regulatory authority.

4.3.3 Expanded-level controls – post-market

4.3.3.1 Establish within the regulatory authority processes for post-market surveillance and incident reporting

At the basic level a system for reporting incidents involving medical devices to the regulatory authority, in particular those resulting in death or serious injury, is established (*see Section 4.2.4.1*). At the expanded level, this may be extended to post-market surveillance system by the manufacturer or its authorized representative and a capacity to monitor a manufacturer's investigation of serious incidents and serious public health threats . Manufacturers undertake post-market surveillance activities including review of user feedback to determine reporting of certain categories of incidents to the regulator. Manufacturers should review the risk/benefit profile associated with the on-going use of devices. Manufacturers may implement corrective actions may be taken to reduce the likelihood of recurrence. Properly structured post-market 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*).*

Regulators should ensure that manufacturers have a system for post-market surveillance including collection of user feedback, reporting certain incidents to the regulator and evaluating the need for corrective actions encompassing:

- incident reporting and complaint handling systems with clear responsibilities for the regulator, manufacturer, authorized representative, importer and distributors;
- collecting and reviewing incident reported by the manufacturer;
- maintenance by parties in the distribution chain (importers and distributors) of appropriate records of complaints and actions taken;
- reviewing implementation of corrective actions and preventive actions, including FSCA, by the manufacturer or its authorized representative, 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 all user feedback and quality problems to the manufacturer for investigation and possibly corrective action.

4.3.3.2 Require mandatory reporting of incidents and serious public health threats

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 incidents and serious public health threats associated with medical devices in the jurisdiction. It should define the threshold for reporting (i.e. what kinds of incidents should be reported), reporting time limits, required information and which party (or parties) shall report. In general, those criteria should be consistent with WHO and IMDRF guidance on incident reporting

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 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, servicing and disposal. 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, traceability of record keeping and disposal;

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

Collection of customer feedback and implementation of correction and corrective actions, post-market 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 global trade, new suppliers entering the field often without much relevant qualifications, including the supply of SF medical products.[35] 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 13485:2016 . The Asian Harmonization Working Party (AHWP) has published guidance on the application of ISO 13485:2016 in an organization that distributes or imports medical devices.

4.3.3.3.2 Local production

Local production of quality medical devices can contribute to better access, and affordable products which is critical in provision and quality health services. Governments can have legitimate policy interests in promoting and encouraging the development of local development and manufacturing capacity, as well as ensuring the safety, quality, and performance of medical devices. Local production can potentially offer a cost-effective pathway to improving access to health care and medical devices. While local production is one method to increase access to medical devices, additional research or tech-transfer is needed to create an environment that will benefit public health. It requires multisectoral approach to put in place policies to ensure manufacturing of quality products. The government will play crucial roles in local production of medical devices including policies, mobilization of all relevant government sectors, stakeholders, conducive business environment engaged in the local productions of medical devices and establishment of a strong regulatory authority. The government should appropriately regard transparency, predictability, non-discrimination, consistency of requirements, impartiality, and respect for proprietary confidential information (i.e. Good Regulatory Practices).

The national regulatory authority shall be well equipped to:

[35] http://www.who.int/entity/mediacentre/factsheets/fs275/en/ (accessed July 2021).

- Advise the government in preparation of appropriate policies to facilitate local production of medical devices.
- Ensure public availability of international standards including a list of national standards required for production, and handling of quality medical devices to local manufacturers.
- Provide proportionate and stepwise technical support to local manufacturers. Whether domestic or foreign manufacturers, appropriate consultation mechanisms encourage compliance with regulatory requirements because they can address misunderstandings. This may enable them achieve proficiency in production of quality and safe medical devices using a dedicated team considering possible conflict of interest.
- Ensure public availability of concise regulations, guidelines and standard operating procedures for assessment, market authorization, post market surveillance, and market surveillance of quality and safe medical devices equally applicable to local and international applicants.
- Implement risk based and timely regulatory assessment and issue market authorization for both local and imported manufactured of medical devices
- Mobilize regional initiative for implementation of reliance and recognition. mechanisms to ensure expanded market of local produced medical devices

In order to ensure quality, safety and performance for all medical devices, the regulatory framework and regulatory controls shall equally apply to locally manufactured medical devices and imported products. However, because the local manufacturer is physically located in the jurisdiction of the national regulatory authority, that regulatory authority, in the pre-market phase, would provide clear guidance on the legal requirements for local manufacturers specially and how to submit technical documentation for the different risk classes of medical devices. Support from regulatory authorities to local manufacturers shall be made available at the point of request. Manufacturer will differ, due to the different medical devices, the different risk class and different levels of development of the manufacturer. A pre-submission meeting between the NRA and manufacturer may be a good starting point to discuss the requirements for an application . The pre-submission meeting provides the opportunity for a manufacturer to obtain NRA feedback prior to an intended premarket submission, which may include information about national requirements and is entirely voluntary on the part of the manufacturer.

For placing on the market the national regulatory authority, dependent on the risk class (*See Section 2*) assesses the technical documentation, and, conducts QMS inspections of the manufacturer's plant(s) and warehouse(s), or designate a CAB to act on its behalf.

In the post market phase the regulatory authority undertakes market surveillance and imposes measures, if appropriate. The vigilance system is similar for locally manufactured medical devices as for imported medical devices, differing in the manner how to act when serious public health threats occur. For locally manufactured medical devices the national regulatory authority enforces the manufacturer to act; for imported medical devices it is the authorized representative.

In the case of inspections to investigate suspected noncompliance or problems with products, the national regulatory authority is likely to undertake the inspection.

Based on the outcomes of the inspection/audit, the regulatory authority or third-party certification body can either allow the local manufacturer to continue with existing operation or issue citations for non-conformance activities. According to the significance of the non-conformance, a warning letter, product recall or even plant shutdown of the local manufacturing site are possible.

Activities by the national regulatory authority such as assessing the technical dossier, performing on-site inspections and enforcing post market requirements require specific capacity building. Oversight of the required expertise and competencies is key for staff of the NRA to perform these tasks effectively and responsibly.

4.3.3.4 Regulatory Testing of Medical Devices

Laboratory testing of medical devices including IVDS may be considered as an important regulatory assessment function. To implement this function, the national regulatory authority should establish legal provisions, regulations, and guidelines required to define the mandate of the NRA and testing laboratories in regulating medical devices.

Given the diversity of medical devices, it is unlikely that a national regulatory authority will have capacities to test all categories of medical devices including IVDs. Testing of medical devices can be conducted by the national control laboratory which is usually located within the national regulatory authority, by the National Reference Laboratory(s) or other external testing laboratories within or outside the country. Therefore, the legal provisions shall include the option to outsource testing to competent laboratories to perform testing and officially issue results of the same to the national regulatory authority as part of the regulatory controls. The competency of the testing laboratories should be evaluated by an accreditation body and the national regulatory authority should further verify that evidence before entering into the agreement. The legal provision shall therefore define organizational and governance structure, have clear communication and define responsibilities of entities responsible for laboratory

testing activities in a form of signed memorandum of understanding with all stakeholders involved. The policy should also emphasize provision of adequate funding for human resource and infrastructure for the testing laboratories. Countries that do not have well-resourced and accredited testing laboratories, are encouraged to implement the mechanism of reliance of laboratory testing from other regulatory authorities or expert laboratories.

Implementation of testing of medical devices by national reference laboratories, national control laboratories and other testing laboratories.

Testing of medical devices is an essential element in both the basic level and expanded level regulatory controls. Medical devices are usually not tested pre-market by the national regulatory authority as part of pre-market evaluation. Authorities accept testing evidence held or submitted by the manufacturer. As with all other evidence of conformity held or submitted by the manufacturer, that testing evidence is subject to review or audit/inspection by the regulatory authority. Considerations for pre-market testing may include the reliability of the source of a medical device, performance history of the medical device and post shipment lot verification of IVDs. Post market, the application of testing would be with a tiered approach that would allow the regulatory authority to respond to national public health priorities and to progressively develop capacity, taking into account that knowledge and experience required by having an independent and accredited testing laboratory with qualified personnel and equipment including testing of medical devices with a risk approach, or working through a post-market testing program for imported devices according to specific public health risks. In the post market phase, the testing laboratory will conduct reactive testing (for cause testing), with due cause when a public health threat presents, by investigating devices following a serious incident, suspected substandard or falsified products (SF) etc. Pro-active testing may be performed according to a testing policy plan established in collaboration with the national regulatory authority and the reference laboratory.

Tasks that may be undertaken by an appropriately qualified and equipped testing laboratory include:

- testing of medical devices as part of pre-market evaluation (routing testing is not recommended; accept testing reports from the manufacturer);
- examination and testing of medical devices that are suspected as SF (*see Section 6.5*);

- institution of a program of post-market testing of specific imported and locally manufactured devices according to specific national public health risks based on a risk assessment approach;
- testing for investigation of devices allegedly involved in a serious incident;
- investigation of devices sent to the regulatory authority by laypersons; and
- post-shipment lot verification testing of IVDs.

The NRA shall establish criteria for selection of testing laboratories. These criteria will include, having competent staff, adequate testing facilities, analyte specific accreditation to publicly available international standards such as ISO/IEC 17025: General Requirements for the competence of testing and calibration laboratories or ISO 15189:2012 Medical laboratories- Requirements for quality and competence or equivalent and access to testing specimens . The integrity of laboratory testing shall be maintained through effective implementation of an established quality management system including, policies and procedures for validation and verification of test methods and transfer of validated test methods, established standard procedures for receipt, handling, storage and retention of samples received for quality testing and a management system of all laboratory records.

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.

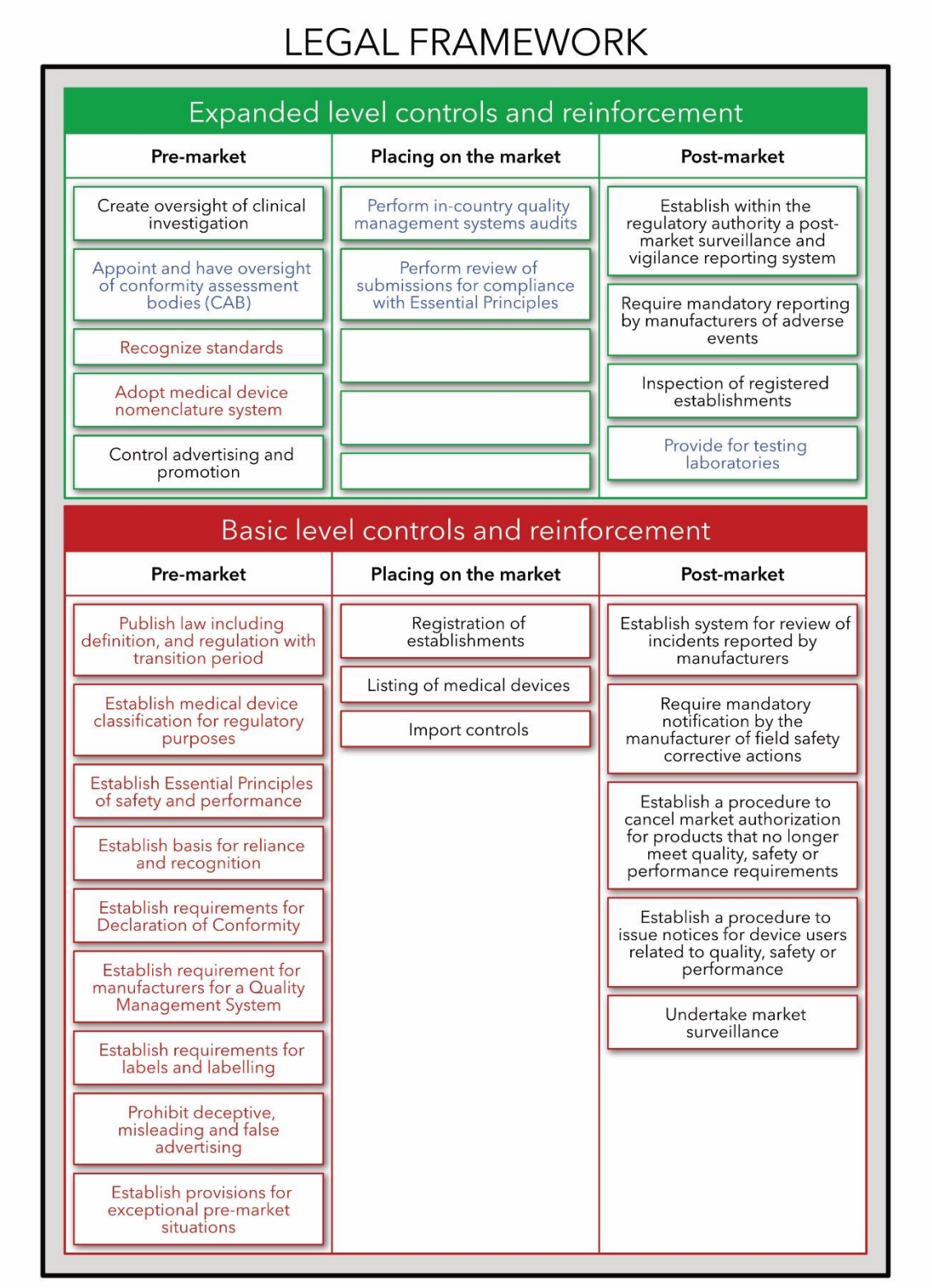
WHA Resolution 67.20 also urges Member States to "engage in global, regional and subregional networks of national regulatory authorities, as appropriate, recognizing the importance of collaboration to pool regulatory capacities to promote greater access to quality,

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

Element for regulatory controls for which international regulatory guidance has been developed and those that may be implemented through reliance or recognition

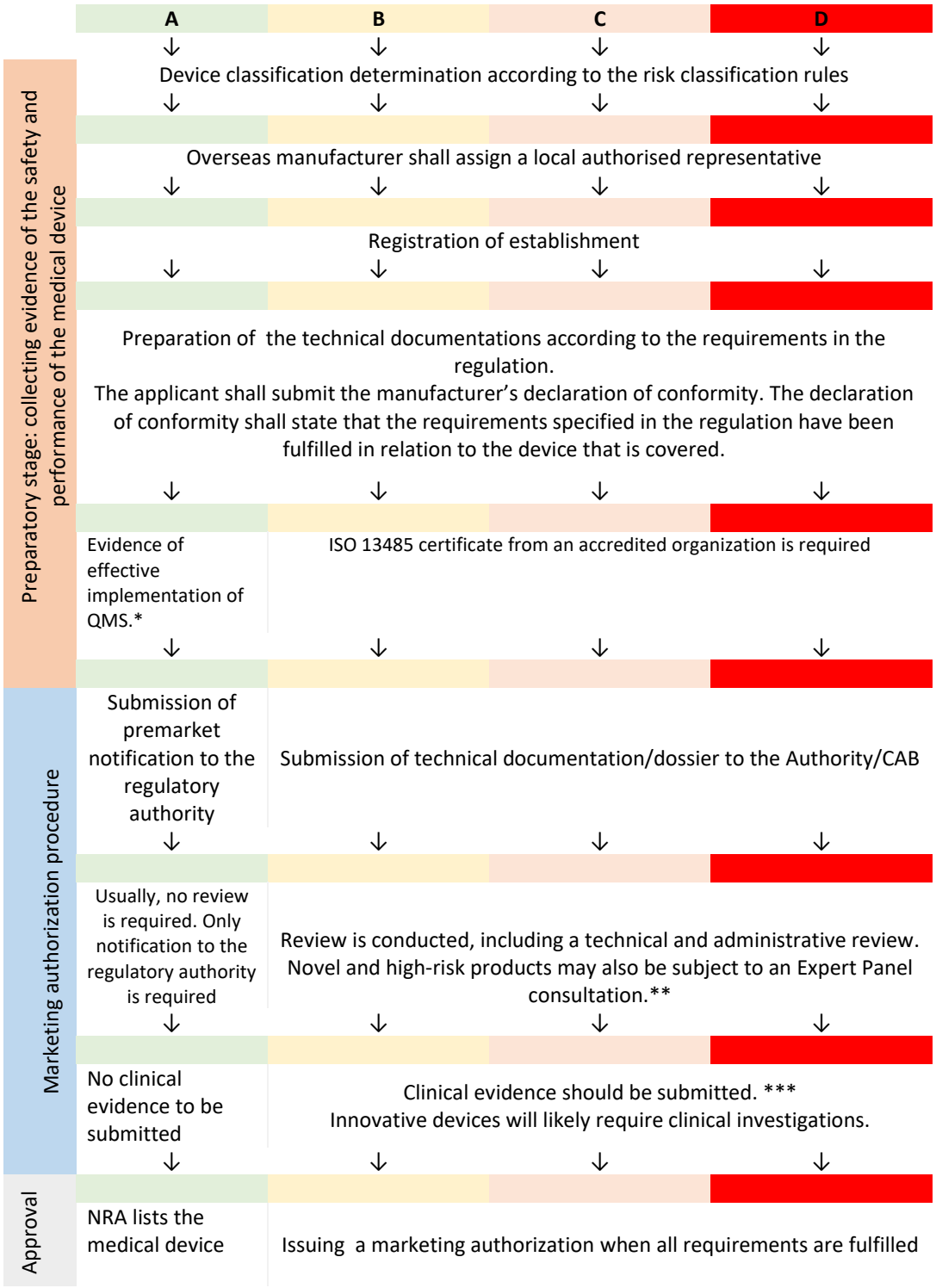


Note: The elements indicated in red are those for which international regulatory harmonization guidance documents have been developed. Elements that may be implemented through reliance or recognition are in blue.

5. Regulatory pathways.

5.1 Regulatory pathway for premarket conformity assessment of medical devices according to risk class.

The regulatory pathway in the diagram below describes the steps required for routine assessment to obtain marketing authorization for a medical device according to its risk class. The first step of determining the risk class of a medical devices is the responsibility of the manufacturer, however that may always be challenged by the regulatory authority. The scrutiny of the assessment by the regulatory authority depends on the risk class of the medical device. This is without prejudice to the obligation of the manufacturer to comply with legal requirements, regardless of the risk class and regardless of the approval process


A
B
C
D
Preparatory stage: collecting evidence of the safety and performance of the medical device
Device classification determination according to the risk classification rules
Overseas manufacturer shall assign a local authorised representative
Registration of establishment
Preparation of the technical documentations according to the requirements in the regulation.
The applicant shall submit the manufacturer's declaration of conformity. The declaration of conformity shall state that the requirements specified in the regulation have been fulfilled in relation to the device that is covered.
Evidence of effective implementation of QMS.*
ISO 13485 certificate from an accredited organization is required
Marketing authorization procedure
Submission of premarket notification to the regulatory authority
Submission of technical documentation/dossier to the Authority/CAB
Usually, no review is required. Only notification to the regulatory authority is required
Review is conducted, including a technical and administrative review. Novel and high-risk products may also be subject to an Expert Panel consultation.**
No clinical evidence to be submitted
Clinical evidence should be submitted. ***
Innovative devices will likely require clinical investigations.
Approval
NRA lists the medical device
Issuing a marketing authorization when all requirements are fulfilled

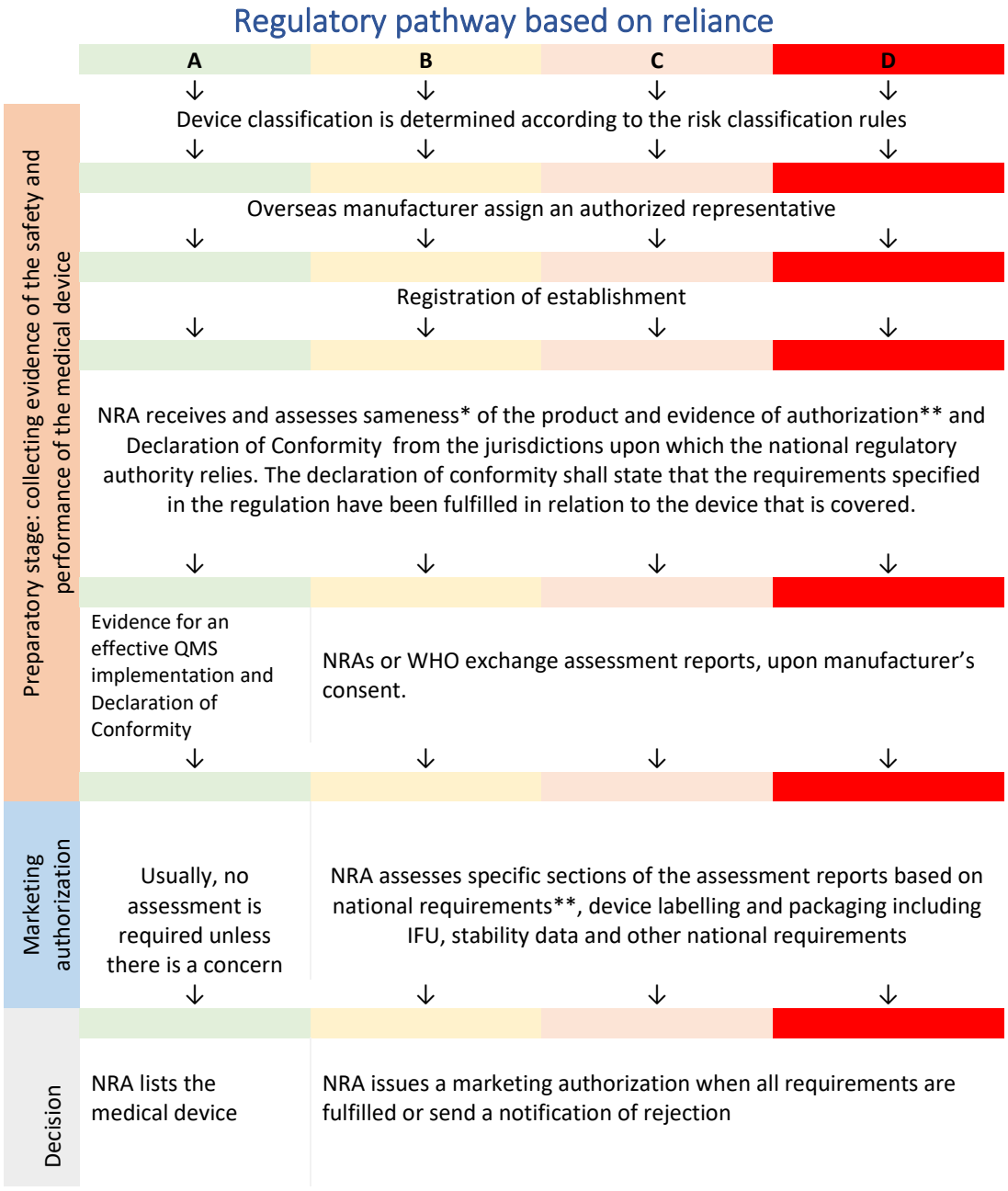
1984

Durations of the approval process are providing guidelines based on best practice. The national regulatory authority might consider different timeframes. Renewal period are indicative and may not be applicable when jurisdictions do not apply a renewal requirement.

Device classification	A	B	C	D
How long you should expect to wait after submission until approval is granted	< 1 month	1-3 months	2-6 months	2-6 months
Validity period for device registrations		3-5 years	3-5 years	3-5 years
Registration renewal should be started this far in advance		6 months	6 months	6 months

5.2 Regulatory pathway for premarket conformity assessment of medical devices with reliance mechanism.

Reliance is a process that may apply to several regulatory decisions and activities. Examples are reliance on inspection reports from inspections performed by another regulatory authority, recognition of the accreditation of a conformity assessment body and the evaluation of incidents by another jurisdiction where an incident occurred that also affects the domestic market of the national regulatory authority. Collaborating and relying on the test results may also be considered reliance. The diagram below illustrates the steps for marketing authorization for a medical device based on reliance.



* For sameness check at a minimum name of the product, regulatory version, product code, design, labelling and packaging, intended use, IFU manufacturing site and QMS certificate ISO 13485.
** Certificate or letter from the authorizing entity

Durations of the approval process are providing guidelines based on best practice. The national regulatory authority might consider different timeframes. Renewal period are indicative and may not be applicable when jurisdictions do not apply a renewal requirement.

Device classification	A	B	C	D
How long you should expect to wait after submission until approval is granted	< 1 month	1-2 months	1-2 months	1-2 months
Validity period for device registrations		3 years	3 years	3 years
Registration renewal should be started this far in advance		6 months	6 months	6 months

5.3 Regulatory pathway for emergency use authorization or derogation

Public health emergencies often stress the entire healthcare system, including regulatory authorities, which play an important role in tackling the public health emergency by enabling timely, appropriate and adequate access to essential medical devices.

This model recommends that the regulatory authority establish policies and processes to allow emergency authorization of medical devices or derogation from the routine assessment procedure which are considered essential in managing public health emergencies, enabling regulatory agility in responding to an emergency that may pose serious health threat to people. The adoption of such mechanisms shall be a critical component of national emergency preparedness.

When the regulatory authority requires that medical devices must be reviewed and approved under an established regulatory pathway for use legally in their jurisdiction, an emergency authorization or derogation procedure strategy can be designed based on the adoption of reliance practices and risk-based assessments, which enable regulatory authority to make the best use of available resources and expertise.

The main purpose of setting up emergency regulatory authorization mechanism or derogation procedure is to allow the use of medical devices which have not been approved under a traditional, established regulatory pathway in a public health emergency crisis, where some minimal criteria have been met.

The key concept for emergency regulatory authorization or derogation procedure mechanism is making risk-calibrated regulatory decision, weighing the potential benefits against the potential risks caused by the public health emergency, based on the available evidence submitted to support the authorization request supplementing with post authorization monitoring and continued safety and performance evidence to adjust the regulatory decisions as necessary.

A medical device may be designated by the regulatory authority as authorized for emergency use where:

a) The medical device is needed:

- to treat or diagnose any medical condition resulting from a public health emergency,
- to prevent the spread or possible outbreak of an infectious disease,
- to treat or diagnose an infectious disease or any medical condition associated with an infectious disease, where the medical condition or infectious disease is potentially serious or life-threatening.

b) In the understanding of the regulatory authority, there is:

- preliminary scientific evidence that the medical device has the potential:
    - to treat or diagnose the medical condition resulting from the public health emergency,
    - to prevent the spread or possible outbreak of the infectious disease,
    - to treat or diagnose the infectious disease or any medical condition associated with the infectious disease.
- ongoing scientific evidence that the potential benefits of the medical device outweigh the known risks of the medical device, to a person on whom the medical device is used,

and

- strong post-market structure and market surveillance to monitor not only product safety and performance, but also to reduce the chances that substandard or counterfeit products reach the market.
- The applicant is required to provide more evidence as it becomes available.

In order to develop and establish the minimum criteria for evaluating the safety and performance of medical devices before the products are placed on the market, it is important that the regulatory authority performs consultations with experts at the national, regional, or even global level, before the products are placed on the market.

Any emergency regulatory authorization strategy adopted must allow a transparent disclosure of the requirements and criteria adopted for a medical device to receive emergency authorization.. Likewise, it is important to establish a validity period for such measures during the emergencies as well as for the authorized medical devices so that the evidence assessed during the emergency period may be proven or strengthened.

In order to avoid abuse of the emergency authorization or derogation procedure of a medical device, the validity period of the data assessed for authorization that allows the circulation and use of such product must be clearly disclosed in such a way that health services and professionals do not purchase or use products for which authorizations have expired or cancelled.

As part of post market monitoring, manufacturers should continuously provide additional evidence on the safety and performance of the medical devices which have been given emergency use authorization as such evidence becomes available. Meanwhile, the NRA should review the safety and performance requirements for market authorization. When adequate supporting data have been found to meet the safety and performance requirements, complete assessment of the product using routine assessment procedure of the product can be conducted by the NRA, followed by formal market authorization.

One important approach for international action in terms of emergency authorization is regulatory reliance (*see 4.1.1*), which is a mechanism to strengthen regulatory capacity, to improve health systems nationally and internationally, to increase the availability of medical devices, to save financial resources and to use human resources more strategically.

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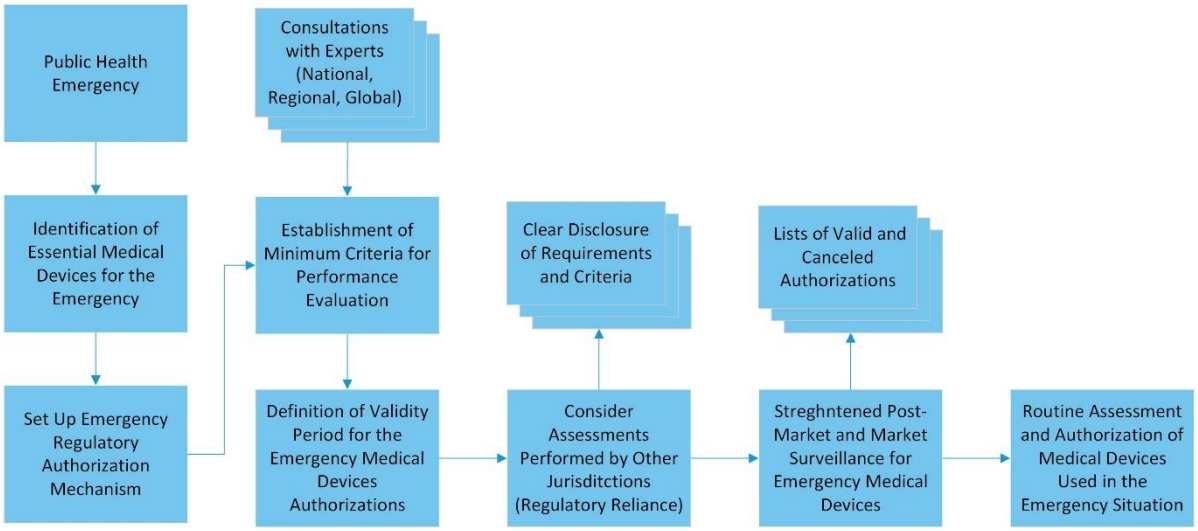


5.4 Regulatory pathway for borderline products

The field of borderline products[36] is becoming more and more complex due to conflicting regulatory decisions and changing regulations. 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 even exists. It is in the public interest to ensure the safety, quality and performance of all "borderline" products through appropriate regulatory controls either those for medical devices or for other regulated products sectors.

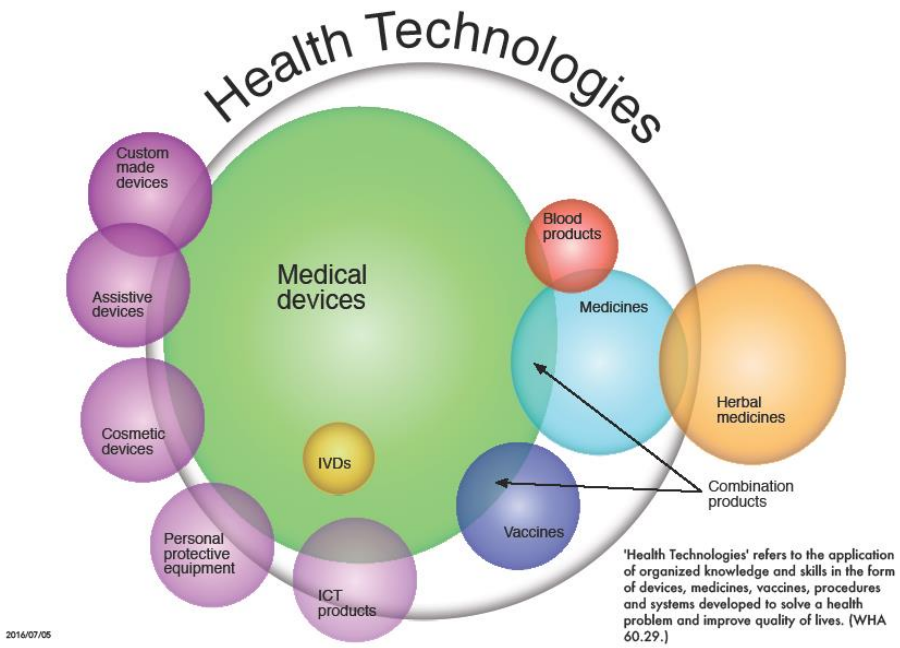
Background information and approaches to improve regulation of borderline products

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". Nowadays, an increasing number of products are characterized as borderline, an ambiguity that exists due to either innovative products that do not fall under current regulations or overlaps in existing regulations. It is important to have established demarcation and identification of an appropriate regulatory path with applicable legislation for these products.

Borderline products are considered to be those products where it is not clear from the outset whether a given product is a medical device or not. These products pose a challenge to regulators of medical devices across the world.

[36] Borderline products are generally (medical) products for which it is unclear which legislation applies. Borderline products are not combination products. Please view section X.

Examples of borderline products cosmetic articles including esthetic implants, air purifiers, personal protective equipment (PPE), biocidals, blood products, herbal products, food supplements, information and communication technology (ICT products), custom made devices, assistive devices, medical gases, and products for general laboratory use, products used for hospital support or infrastructure, products for personal or home use or products for common use employed as parts or accessories of healthcare products.[37]



A product considered a medical device in some countries, does not necessarily be considered as such in another country. Manufacturers should always refer to the definitions of a medical device and other relevant regulations in the country in which the application is submitted.

To be predictable and transparent, the National Regulatory Authority (NRA) should develop criteria and mechanisms for determining the appropriate regulatory regime for borderline products through an established guidance**.** It should describe considerations and the process whereby an applicant may obtain an advisory opinion from the NRA. Where necessary, that process should allow for consultation with subject matter experts as well as with regulatory authorities from other product sectors and with the manufacturers concerned. It may also take into account regulatory decisions by regulatory authorities of other jurisdictions. After appropriate review and consultation, a product may be deemed to be subject to regulation as a medical device even though it may not clearly fall within the statutory definition of "medical

[37] This is not an exhaustive list of borderline products, but a number of examples

device" e.g. cosmetic contact lenses, based on their documented potential for adverse health effects in wearers. NRAs may take decisions on a case-by-case basis, considering all the characteristics of the product or a medical purpose. A committee or working group on borderline products may be appointed to advise the regulatory authority on deciding on the regulatory status of a product.

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.

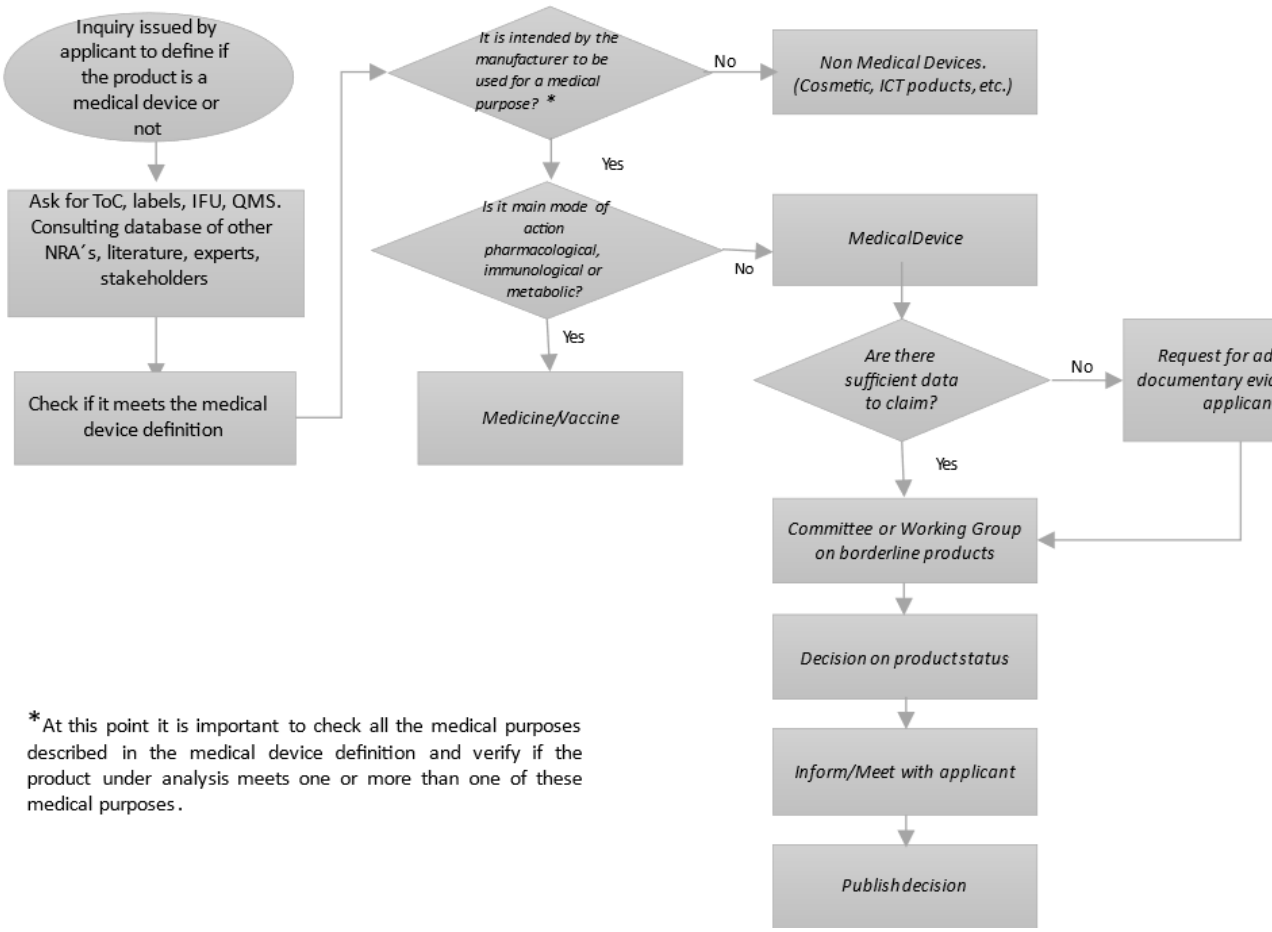
How to decide if a product is a medical device?

NRAs should always firstly refer to medical device definition when making any borderline product determinations.

In order to decide if a product is a medical device, NRAs should consider the following aspects:

- How the product is presented to regulatory authority and to the market: labelling, packaging, promotional literature and advertisements, including websites.
- The primary intended purpose of the product including the claims about on what the product is and what it does (explicit and implicit). Medical devices must have a 'medical purpose', which is guided by the definition of a medical device.
- The mode of action: medical devices do not attain their primary intended mode of action through pharmacological, immunological of metabolic means, but which may be assisted by such means.
- Whether there are any similar products on the local market and how they are being regulated. This can be through consulting databases of regulatory authorities of other product categories in the jurisdiction.

It is important to note that not all equipment used in healthcare settings or used by a healthcare professional.



5.5 Regulatory pathway for combination products

There is no internationally harmonized definition of a combination product. As such, the definition may vary in scope across regulatory jurisdictions, especially as the field continues to progress. A combination product is defined by many jurisdictions as a product comprised of two or more different types of medical products (i.e., a combination of a medicine, device, and/or biological product with one another). The medicine, devices, and biological products included in combination products are referred to as constituent parts of the combination product..[38] Depending on the applicable regulations, the medicine component of a combination product may be a pharmaceutical, radiopharmaceutical, natural health product, biologic, cell, tissue, organ, gene therapy, or human blood and its components.

Some jurisdictions have distinct definitions for a medicine and a biologic. As such, they also include in the definition of a combination product a medicine-biologic and a biologic-device.

[38] Examples are from Health Canada https://www.canada.ca/en/health-canada/programs/consultation-issue-identification-paper-drug-device-combination-products-draft/document.html and from USFDA https://www.fda.gov/combination-products

The evolution of medicines and medical technologies worldwide has created a broad spectrum of medicine-device combination products that range from relatively simple in nature to highly complex. These products have the potential to provide enhanced health benefits to patients, and it is in the public interest for regulatory authorities to ensure their safety, quality, and performance through appropriate regulatory controls.

The regulatory requirements for combination products arise from the statutory and regulatory requirements applicable to medicine, devices, and biological products, which retain their discrete regulatory identities when they are constituent parts of a combination product. At the same time, combination products comprise a distinct category of medical products that can be subject to specialized regulatory requirements, where appropriate. Specialized regulatory requirements for combination products generally are designed to address the overlaps and distinctions between the statutory and regulatory requirements applicable to the drug, device, and biological product constituent parts that comprise them. (26) (27)

Globally, examples of medicinal product-device combination products include drug-eluting stents, pre-filled syringes, transdermal medicine patches, metered dose inhalers, heparin coated vascular catheters, or orthopaedic bone cement containing antibiotics.

Considerations for regulating combination products

In the interest of consistency, transparency and predictability, the national regulatory authority should adopt and publish guidance on how to:

1) determining what qualifies as a combination product

2) determining an appropriate regulatory pathway; and

3) establishing suitable pre- and post-authorization requirements.

It is recommended that the designation of a product that combines a medicine and a device as a combination product be decided by the national regulatory authority. Some combination products will be designated as primarily subject to the regulatory requirements for medicines; and some to the requirements for medical devices. This may require development of a single product-specific “hybrid” pathway, combining elements of both sets of requirements.

To be predictable and transparent in their decision, the regulatory authority is best advised to employ a single regulatory pathway and develop criteria for determining the appropriate regulatory regime for combination products. Creating such a single regulatory pathway for combination products helps streamline their effective review, while taking into account the particulars of each component and protecting the health and safety of the public. A single regulatory pathway also helps avoid overlapping administrative requirements.

This pathway determines both the type of application and the type of marketing authorization for the combination product. The designation may be based on the principal mechanism of action by which the product achieves its intended therapeutic or diagnostic purpose. Where this is achieved by pharmacological, immunological, or metabolic means, the combination product should be primarily subject to medicine regulatory controls. Where the principal action is not achieved by pharmacological, immunological, or metabolic means, but may be assisted in that action by pharmacological, immunological, or metabolic means, the combination product should be primarily subject to medical device regulations.[39] In some situations, elements of both medicine and device regulations may be applicable. (28) (29)

In addition to designating the combination product into the appropriate regulatory pathway, the regulatory authority would also need to decide on the extent of requirements to apply to the ancillary component(s) of a combination product. For example, the safety and performance of the medical device that contains a medicinal substance should be verified as a whole, as well as the identity, safety, quality and efficacy of the medicinal substance in its intended function in the specific combination product.

Regulators may also describe considerations and a process by which an applicant may obtain a designation decision from the regulatory authority. Where necessary, the process may allow for consultation with subject matter experts as well as with regulators from other product sectors and with the manufacturers or authorized representatives concerned. Regulators may also take into account determinations made by regulatory authorities of other jurisdictions. National authorities may take decisions on a case-by-case basis, taking account of all the characteristics

[39] if a medicine is incorporated in a medical device, according to the IMDRF classification rules, it is always a class D medical device. https://www.imdrf.org/sites/default/files/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n15-2006-guidance-classification-060627.pdf, accessed 17 April 2022

of the product. A decision by the regulatory authority on the regulatory status of a product will always have the option of appeal in case the applicant does not agree with the decision.

Reliance and recognition of medicine-device combination product may be a challenge due to the diversity and complexity of drug-device combination products. Because regulatory controls for drugs and medical devices may be different in different jurisdictions, it will be challenging to seek alignment with more than one regulator. Furthermore, a lack of clarity within regulations in different jurisdictions may lead to overlapping or conflicting regulatory requirements for a product. As there is no international harmonization guidance on combination products, national regulatory authorities using reliance or recognition may consider which requirements in other benchmark jurisdictions would best serve their country's needs.

5.6 Regulatory pathway for donated medical devices.

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 pose health risks if the donated medical devices' safety and performance are not verified. Another potential challenge is a lack of clear documentation, label and labelling of the donated medical device, its state, its origin and history and the responsibilities of donors. (30)

Quality problems associated with donated medical devices have been reported in many countries (31) (32). They include short expiry dates, defective equipment[40] and gifts or donation 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"[41] on a receiving country (31) (33) (32) For these reasons, some countries have banned donations of used equipment. Before donating medical devices including IVDs, WHO advocates that core principles be taken into account. They include:

- address a validated request from the end-users, corresponding to a real clinical need;
- be authorized by regulatory authorities of the receiving country and/or meet current

[40] Donated used durable medical equipment often is not accompanied by documentation of the calibration, service and maintenance or refurbishment history. Whereas a device may have conformed to relevant safety, quality, and performance standards at the time it left the original factory, its continued conformity may no longer be assured or presumed..
[41] Dumping' of obsolete equipment by high-income countries (HICs) has been described as 'morally reprehensible'*(1)*

international safety standards;

- have all its parts and accessories, be functional, and be safe to use on arrival;
- be accompanied by documentation in a language understood in the receiving setting;
- be adapted to the local context such as electrical power, language of the instruction manual (if possible); and
- match the operating and maintenance human resource capacities, be imported with a plan for its disposal when it can no longer be used in the recipient's country.[42]

Authorities from countries from which donations originate are urged to develop policies, regulations and guidelines on exportation of donated medical devices to other countries.

A national policy for donations in the receiving country is key to guide all parties involved so that they can develop their own institution-level operational donation guidelines and standard operating procedures by drawing inspiration from this document. Policy on donations should address three phases. The key features include:

- Pre-donation phase: Assessment and identificaton of country needs, familiarization of requirements, specifications and application to import/export.
- Donation phase: Importation, document verification, physical inspection, sample collection (where applicable) and verification studies (where applicable).
- Post-donation: Installation, commissioning, verification of functioning status and, post market surveillance[43] . This implies feedback to the donor on performance and post market surveillance data.

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. It is the responsibility of the donor - a (charity) organization, a private person or a (medical devices) company - in consultation with the recipient and vice versa, to ensure that medical devices intended to be donated are in compliance with the regulatory requirements of the receiving country. This also applies to

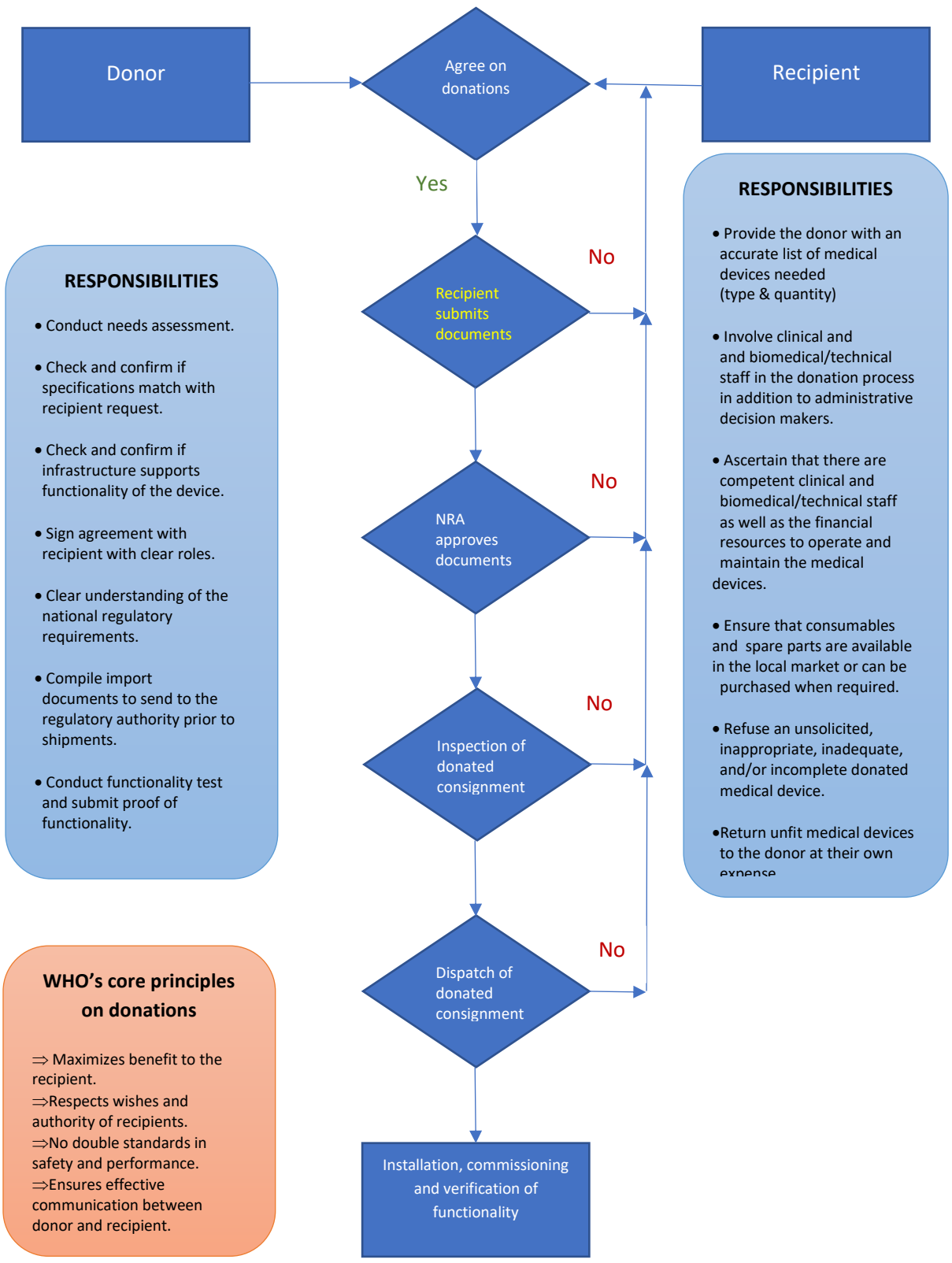
[42] Upon arrival the medical devices specifically IVDs, the remaining shelf life should be reasonable and according to the specifications set between donor and recipient. 17150-Manual for procurement of diagnostics.pdf (who.int)

[43] Donated devices may (probably will) be beyond their manufacturer warranty period. Importers should be informed of, and take into consideration, that fact and the possible expenses associated with repair and maintenance and lack of spare parts

donation *within* a jurisdiction. In case of emergency public safety prevails and the recipient should take action according to guidance on donations.

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. To avoid delay and additional expense, importation documents as well as supporting documents for the device's technical requirements must be submitted to the regulatory authority of the recipient's country for assessment and authorization decision by the authority before shipment of the consignment. These documents will typically include but are not limited to: a list of products to be donated, each product's (package) label, name and address of manufacturer(s) of the products, evidence that the products are approved/authorized in the donor's country or the manufacturer's QMS certificate (for high risk medical devices), expiry dates (if applicable), and a commitment letter that confirms the safety and performance of the devices to be donated. (33)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. Annex X shows typical regulatory pathway for donated medical devices.

Figure XX below shows the steps for responsible donations including the responsibilities of stakeholders



6. 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.

6.1 Disposal

A medical device that reaches the end of its intended life-cycle must be disposed of safely according to the manufacturers recommendations and local regulations. In some cases it may be necessary to dispose of and destroy a device before the end of its life and ensure that the device will not be re-used 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 agents, hazardous waste, toxic or radiological materials, electronic components and pathological products (e.g. human organs, unused blood products). Medical device labelling and instructions for use should include information on proper decontamination and disposal at the end of device 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)[44]. This will ensure that such substandard or falsified 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 or in vitro diagnostic medical devices, decontamination and proper waste management practices according to the manufacturer's instructions should be required based on national and international standards[45]. 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

[44] An example of specific guidance on disposal of unfit products: https://trade.tanzania.go.tz/media/THE%20TANZANIA%20FOOD,%20DRUGS%20AND%20COSMETICS(%20medical%20device)%20regulation.pdf

[45] E.g. WEEE https://ec.europa.eu/environment/topics/waste-and-recycling/waste-electrical-and-electronic-equipment-weee_en

high-technology and complicated products in order to decide the best way to dispose of them Separate guidance is to be provided to the health care system by the Ministry of Health to dispose of hospital waste management.

6.2 Reprocessing of single-use medical devices

In general, regulatory and public health concerns about reprocessing of SUMDs include : responsibilities for reprocessing are not established, variability in reprocessing methods, risk assessment has not been performed, and reprocessing is not performed under a QMS, thereby not controlling cross-infection, contamination, residues of disinfectants, mechanical failure, endotoxins, labelling and ethical considerations.

The perceived 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 could pose a risk to patients, 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 safety, quality or performance 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 in that the entity that reprocesses a medical device becomes the new manufacturer with the associated responsibilities, and economic in that to reprocess a SUMD using a validated process raises the costs and the perceived savings may therefore not be realized.

A device designated by the original manufacturer and labelled as ‘single-use’ should not be reused. It should only be used in or on an individual patient during a single procedure and then discarded. It is not intended to be reprocessed and used again, even for the same patient . Single-use medical devices (SUMDs) do not come with appropriate instructions for cleaning, disinfecting, or sterilizing after use and the manufacturer generally has not investigated safety or deterioration in performance if they are subject to reprocessing. A patient

or user may be endangered when SUMDs are reprocessed and used more than once, because device conformity to their its original standards for safety, quality, and performance cannot be assured.

Exceptional situations: manufacturers reprocessing SUMDs

Regulatory authorities, after considering all potential risks and benefits, may opt to allow the reprocessing of SUMDs in limited circumstances. (34) (35) (36) (37)In extremely rare and dire situations, like a global pandemic, reprocessing may be permitted, even if the devices does not fully meet the specifications of the original manufacturer. The conditions applicable for these situations are restricted to specific medical devices for example such as single-use surgical masks and respirators,[46]for a limited period of time and only after performing a validation of the reprocessing process. In such circumstances the national regulatory authority may develop specific guidance that describes conditions for reprocessing of SUMDs, whether it is a manufacturer or a health care facility.

Entities reprocessing SUMDs: requirements

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. The entity placing reprocessed SUMDs on the market is considered to be manufacturer I and assumes all the obligations of a 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 equivalent requirements of safety, quality, and performance as manufacturers of new devices such as risk management (including the analysis of the construction and material, related properties of the device and procedures to detect changes in the design of the original device as well as of its planned application after reprocessing), validation of the reprocessing process, and established QMS, product release and traceability (38) (39)The original manufacturer should be identified in the technical dossier submitted to the regulatory authority. The label of the reprocessed SUMD does not necessarily

[46] https://www.cebm.net/covid-19/extended-use-or-re-use-of-single-use-surgical-masks-and-filtering-facepiece-respirators-a-rapid-evidence-review/ (accessed 17 February 2022)

carry the name of the original manufacturer, however, should carry the name of the entity reprocessing the SUMD and should clearly indicate that the SUMD has been reprocessed. (40)

Reprocessing SUMDs: health care facilities

Requirements for reprocessing may equally apply to a healthcare facility fully reprocessing SUMDs for reuse within its own facility, without the obligation of a manufacturer. The reprocessing of a SUMD in a health care institution is performed in accordance with the requirements that ensure the safety, quality, and performance of the reprocessed medical device. This would include performing risk assessment (analysis of the construction and material, and procedures to detect changes in the design of the original device), the validation of procedures for the entire process, including cleaning steps, the product release and performance testing, the quality management system, the reporting of incidents involving devices that have been reprocessed, and the traceability of reprocessed devices.[47] If a healthcare facility is not able to meet these conditions, it shall refrain from reprocessing SUMDs. (41)

Post market surveillance of SUMDs

Post market surveillance requirements and vigilance apply equally to all medical devices, also reprocessed SUMDs. When investigating complaints and adverse events, the entity that reprocesses the SUMD – whether this is the manufacturer or the health care facility and, if appropriate, the regulatory authority should consider the possibility that reprocessing of SUMDs may have contributed to their occurrence. The regulatory 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.

6.3 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.

[47] EU MDR 2017/745 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN

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. 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 may considered as a change to the medical device and assessed accordingly.

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 *(*

6.4 New Medical Device Technologies: Software as a Medical Device (SaMD) and Software in a medical device (SiMD)

Medical devices and healthcare are increasingly incorporating emerging technologies, including implementing computing platforms, connectivity, software, and sensors in diverse and interoperable systems. These hold the promise of improved safety, performance, and reliability; smaller size; energy efficiency; remote use by less-skilled operators; and new therapeutic and diagnostic powers. Current examples include stand-alone software for medical purposes, networked systems, machine learning, and artificial intelligence. Whether software is regulated as a medical device depends whether it meets the requirements of the statutory definition of a medical device in the jurisdiction.

The International Medical Device Regulators Forum (IMDRF) defines "medical purpose software" to generally include:

(1) software as a medical device (SaMD)

(2) software in a medical device (SiMD), sometimes referred to as "embedded" or "part of" (42)

SaMD may have requirements and limitations defined by the platforms on which they are intended to be deployed and the broader, connected systems in which they may be used.

SiMD may have similar considerations as SaMD but may also have functional requirements that are driven by the relationship between the software and hardware components of the device.

Artificial Intelligence (AI) is a branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviors such as learning, making decisions and making predictions. (43) (44)Machine Learning (ML) is a subset of AI that allows ML models to be developed by ML training algorithms through analysis of data, without models being explicitly programmed. Where a machine or software uses ML, with the intention to treat, diagnose, cure, mitigate or prevent disease or other conditions (in other words, for a medical purpose), it is termed a machine learning-enabled medical device (MLMD). Unlike traditional medical devices where manufacturers would plan for changes ahead, collect data before performing a change request, the MLMD will be continuously exposed to new data and performance may change as it learns and adapt over time. (45)

Because of their many possible implementations, when establishing a regulatory approach for SaMD, it is important to clearly define the scope and characteristics that:

- meet the definition of a medical device,
- should be the focus of regulatory oversight,
- and require specialized approaches to their review and oversight that may differ from hardware medical devices. (46)

While medical device software, may provide significant potential benefit to improving patients' access and quality of healthcare, these technologies may also present different regulatory challenges than those seen for hardware medical devices.

For example:

- Medical device software might behave differently when deployed to different hardware platforms.
- Often an update made available by the manufacturer is left to the user of the medical device software to install. Device software functions are often modified or updated more frequently than hardware medical devices or hardware components. The option to provide or push updates remotely may lead manufacturers to place more responsibility on device-users than may generally be the case with hardware devices.
- Due to its non-physical nature (a key differentiating characteristic), medical device software may be duplicated in numerous copies and widely spread, often outside the control of the manufacturer. A plan for clear and timely communication between manufacturers

and device-users over the life of the software's use may be a critical consideration when evaluating the safety and effectiveness of device software functions in their context of use.

In addition to the general considerations of medical device safety, quality and performance, device software functions must also be secure to ensure continued, safe functionality. The need for effective cybersecurity to ensure medical device functionality and safety has become more important with the increasing use of wireless, Internet, and network-connected devices. Cybersecurity incidents have rendered medical devices and hospital networks inoperable, disrupting the delivery of patient care across healthcare facilities.

Regulatory systems must have the capacity to accommodate that diversity and assure high levels of device safety, quality, and performance. Consistent with good regulatory practices, regulatory controls should be proportionate to risks and benefits, including those arising from the technologies incorporated in devices.

Using a risk-based approach based on the intended use of a SaMD, IMDRF published a framework for risk categorizing SaMDs. The intended use of a SaMD can generally be described by two factors: "A. Significance of the information provided by the SaMD to the healthcare decision, and B. State of the healthcare situation or condition." Based on these two axes, the framework suggests that SaMDs can then be categorized into categories I-IV, with category IV devices considered to be of "very high impact"

State of Healthcare situation or condition	Significance of information provided by SaMD to healthcare decision		
	Treat or diagnose	Drive clinical management	Inform clinical management
Critical	IV	III	II
rious	III	II	I
Non-serious	II	I	I

While applicable to device software functions broadly, the IMDRF notes that, "like other high-quality products, a SaMD manufacturer implements on-going lifecycle processes to thoroughly evaluate the product's performance in its intended market".

It is important that all devices software functions demonstrate:

- Scientific validity – showing with evidence on the association of the SaMD output to a clinical condition/physiological state;
- Analytical validity – showing with evidence the technical performance related to accuracy, reliability, repeatability and reproducibility; and if necessary
- Clinical performance – showing evidence of the ability of a SaMD to yield a clinically meaningful output associated to the target use of SaMD output in the health care situation or condition . (47)

The manufacturing of SaMD, which is a software-only product, is primarily based on the development lifecycle activities often supported by the use of automated software development tools. However, the principles in a QMS that provide structure and support to the lifecycle processes and activities are still applicable and important to control the quality of SaMD. (48) (49)

Increasingly, medical devices that employ SaMD and SiMD or MLMD are being made available in regions with more limited regulatory systems and capacity, often those with little domestic manufacturing, that are primarily dependent on imported products.

Policy makers and national regulatory authorities jurisdictions with limited regulatory systems should consider:

Regulatory priority-setting: A detailed in-country pre-market assessment of the summary technical dossier for a medical device that is already authorized for marketing in countries or regions with mature regulatory systems may not be the most appropriate use of limited local resources. The authority in countries with less developed regulatory systems should consider whether reliance may be used to provide evidence for underlying questions of

SaMD and SiMD safety, performance, and quality. Local review should focus on, for example, include applicability of the device in jurisdiction's population(s) and burden of disease, the assessment of regular updates, adequacy and appropriateness of labelling and promotional materials in local language, local distribution practices, appropriateness for local conditions of use and maintenance, user training, and local post-market surveillance requirements. SaMD can be deployed at scale, at pace, meaning effective requirements for post-market surveillance, clinical evaluation, and risk management must be in place (21) (50) (51) (52). Regulators should require incident reporting by manufacturers as a minimum and may design specialized protocols for market surveillance of SaMD, SiMD and MLMD that may incorporate real-world evidence [13].

Recognized international standards: As part of the pre-market conformity assessment process, the national regulatory authority should verify the extent to which the manufacturer and/or applicant have applied recognized international standards in design, development, verification, and manufacture [13]. This is especially important in software (either as a stand-alone device, or incorporated in a device, SiMD) and networked device systems, as they generally cannot be verified by inspection or testing alone.

Appropriateness to local populations and conditions: In medical devices that incorporate machine learning (MLMD), the regulatory authority should consider whether clinical study participants and data sets adequately reflect the intended patient populations (age, gender, sex, race and ethnicity), disease prevalence, and local standards of medical practice. If it is expected that a device's performance will change over time as it "learns", then the authority should examine how its continued safety, risks, and benefits will be assured under local conditions. The expertise of an IT specialist or a biomedical engineer may be required to perform this assessment of risks.

Health care professional intervention: In some cases, MLMD are intended to supplement or take the place of a health care professional. The regulatory authority should evaluate whether that is appropriate in the local context and the possibility, if any, for intervention in device diagnostic or therapeutic actions by a health care professional.

Data handling and network safety: The regulatory authority should assess the extent to which user or patient data is generated and processed in the device itself or is imported from, exported to, or processed in locations outside the authority's jurisdiction. The regulatory risk assessment should include evaluation of safety in the event of network failure or degradation.

This may require coordination with the national telecommunications, privacy, and cybersecurity authorities.

Advances in the technology state of the art: As much of the technical expertise in these device fields may lie outside the jurisdiction, the national regulatory authority should consider how to develop regulatory knowledge and experience, either at national or regional level, perhaps through consultation with local academic institutions. The authority should also follow the development of new international standards (e.g., IEC, ISO, ITU, and IEEE) and/or evolving harmonized regulatory guidance (e.g., IMDRF, EU, US FDA, TGA, Health Canada, Japan MHLW).

6.5 Substandard and falsified medical devices.

SF medical devices 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. WHO publishes and regularly updates a list of medical products alerts including SF medical products[48]. Falsified diagnostic tests, facemasks and COVID test kits and other products for the management of COVID. have been reported[49],[50] *()*. 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 may be required to distinguish the SF product from the genuine version.

The established approach is one of prevention, detection and response . 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

[48] https://www.who.int/teams/regulation-prequalification/incidents-and-SF/full-list-of-who-medical-product-alerts, accessed 3 August 2021

[49] https://www.cbp.gov/newsroom/local-media-release/cbp-baltimore-field-office-seizes-nearly-59000-counterfeit-covid-19 , accessed 3 August 2021.

[50] https://www.gov.uk/government/news/uk-medicines-and-medical-devices-regulator-investigating-14-cases-of-fake-or-unlicensed-covid-19-medical-products, accessed 3 August 2021.

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

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. International collaboration, 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.

6.6 WHO Prequalification of IVDs and male circumcision devices.

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 of IVDs provides countries with the appropriate technical support, tools and guidance on the provision of IVDs and laboratory services; it also included the prequalification of male circumcision devices. [51] In addition to relying upon the work of other authorities, for some medical devices the regulatory authority may choose to rely upon assessments conducted by the WHO Prequalification of IVDs and male circumcision devices. The focus is on IVDs for priority diseases such as HIV/AIDS, malaria, hepatitis C, and others, and their suitability for use in resource-limited settings [52]*(.*

The WHO Prequalification of IVDs and male circumcision devices undertakes an assessment of individual IVDs and male circumcision devices through a standardized procedure

[51] WHO is extending the prequalification of medical devices to other categories soon.
[52] The criteria for IVDs eligible for prequalification are listed on the page through the link https://extranet.who.int/pqweb/vitro-diagnostics/eligibility

aimed at determining whether the product meets WHO prequalification requirements. The process includes three components:

- review of the technical documentation (product dossier) ;
- independent performance evaluation for IVDs/ evaluation of clinical studies for male circumcision devices;
- inspection of manufacturing site(s).

Prequalification requirements are based on best international practices 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 Standards , Clinical & Laboratory Standards Institute (CLSI) and IMDRF/GHTF, to ensure compliance with the Essential Principles. Like other WHO listed authorities[53] 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 and male circumcision devices, together with the report summarizing the assessment findings, is made publicly available by WHO

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

6.7 Collaborative Registration Procedure

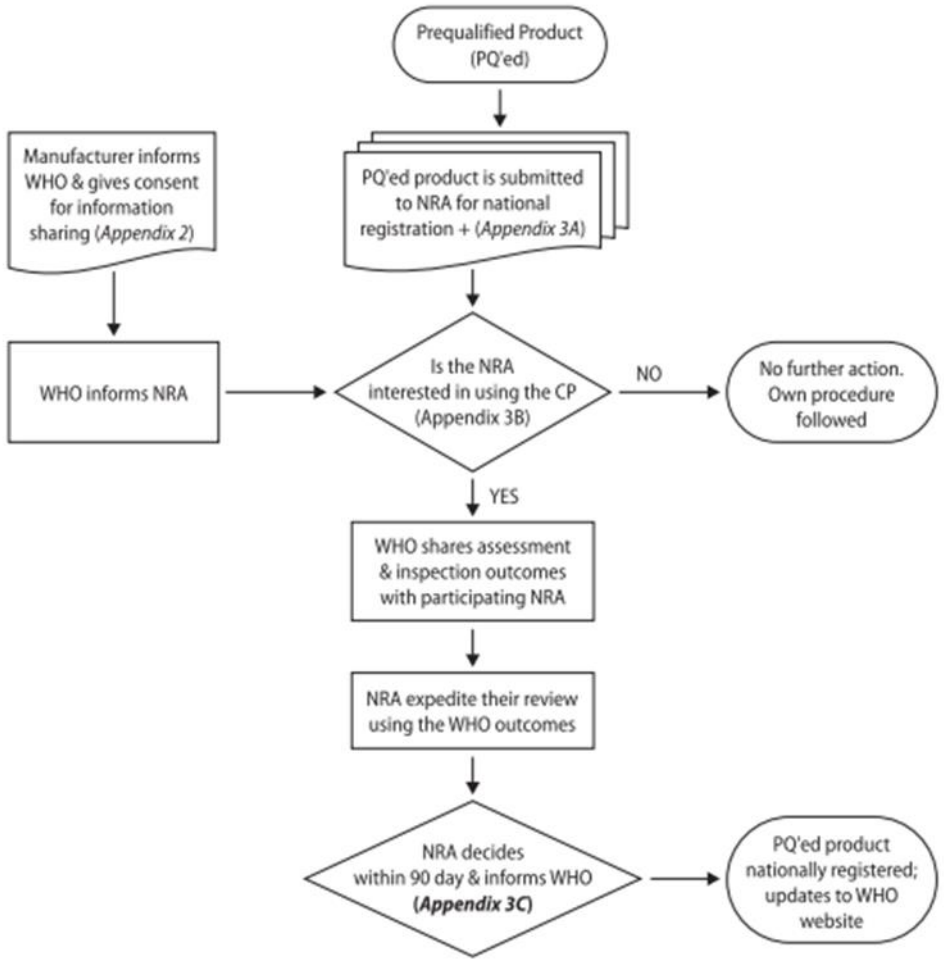
The collaborative registration procedure (CRP)[54] was introduced to accelerate registration of medical products i.e. in member states through information sharing between WHO and national regulatory authorities upon the consent of a manufacturer of the respective prequalified medical product. Collaborative Procedure for in vitro diagnostics was successfully piloted in 2019 and

[53] https://www.who.int/initiatives/who-listed-authority-reg-authorities
[54] Reference https://apps.who.int/iris/handle/10665/341239

was rolled out in May 2020 after approval of the guidelines on the Collaborative procedure between the World Health Organization and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified in vitro diagnostics by the expert committee and official publication through the WHO technical report series 1030 .By The collaborative procedure for in vitro diagnostics incorporates elements of capacity building and regulatory harmonization. Successful application of the procedures is highly dependent on the ability and willingness of manufacturers (the applicants), regulatory authorities, and WHO to work together to meet public health goals. In vitro diagnostics that have been prequalified by WHO undergo thorough evaluation (dossier assessment and laboratory performance evaluation) and quality audit of the manufacturing facilities according to international standards to confirm their quality, safety, and performance. Such products need to be approved for use by the NRAs of the countries for which market entry is sought. Repeating assessment, performance evaluation, and quality audits of those products consumes scarce regulatory resources and unnecessarily prolongs the issuance of market authorization and the time needed to make them available to patients.

leveraging assessment and inspection outputs already produced by WHO prequalification, and thereby eliminating duplicative regulatory work, it speeds up in-country registration of quality-assured products and contributes to their wider availability. The CRP is a typical reliance mechanism with the three key principles, regulators and manufacturers participation is on voluntary basis, confirmation on the sameness of the product of interest and confidentiality of information. NRAs are expected to issue its national regulatory decision on registration of a given WHO-prequalified product (whether positive or negative) within 90 calendar days of regulatory time. Below is a diagram figure that illustrates the steps in joining the CRP.

Steps in the Procedure for national registration of a WHO-prequalified IVD product



6.8 Emergency Use Listing Procedure

The WHO Emergency Use Listing Procedure (EUL) (formerly the Emergency Use Assessment and Listing procedure (EUAL)) is a risk-based procedure for assessing and listing in vitro diagnostics (IVDs) (as well as medicines and vaccines) that have not (yet) undergone stringent regulatory assessment and that are intended for use primarily during public health emergencies of international concern (PHEICs), or in other public health emergencies. *(see Section 5.3 and 6.8)* During such times communities and public health authorities may be willing to tolerate less certainty about the quality, safety and performance of products, given the morbidity and/or mortality of the disease, and the need for diagnostics. The EUL process is based on an essential set of available quality, safety and performance data. The EUL procedure includes the following:

- Quality Management Systems Review and Plan for Post-Market Surveillance: desktop review of the manufacturer's Quality Management System documentation and specific manufacturing documents.
- Product Dossier Review: assessment of the documentary evidence of safety and performance. This evaluation of limited scope is to verify critical analytical and performance characteristics.

7. Implementation

7.1 Implementation: involving stakeholders in the regulatory process

In order to ensure that regulatory processes meet the objectives for which they are designed, it is important to determine the effects (benefits and costs) in terms of public health, economic and social effects that they might generate. (53)

Likewise, these processes must take into consideration the limited resources of regulatory authorities and the importance of ensuring that the process does not duplicate or restrict the objective of the regulatory system. A key element is engaging stakeholders[55] in all stages of the process those groups that may be affected by the regulatory system such as manufacturers, authorized representatives, importers, distributors, health care sector, patients and users. (54)

Working with stakeholders can define which regulatory controls are the best option to solve a public health problem: can the objectives be achieved best through laws (statutes and regulations), or through economic instruments (e.g. market-based instruments such as taxes, fees, user charges, etc.), self-regulation, standards and other forms of voluntary actions, information and education campaigns.

Introduction of medical device regulation should be accompanied by the participation of the stakeholders involved. This will enable the implementation and may prevent delays or threats to this process. It is therefore essential to involve stakeholders in the development and implementation of regulation of medical devices.

To include the relevant stakeholders for a specific process, the regulatory authority should establish a multidisciplinary team with experience in each of the stages of the life cycle of the medical device, by posing questions such as:

1. How and who can be impacted by the regulatory controls, the implementation process, policy, etc.?
2. Who has or may have influence over the regulatory controls, the implementation , process, policy, etc.?
3. Who has or may have an interest in the regulatory controls the implementation, process, policy, etc., either being successful or unsuccessful? (55)

Subsequently, a list should be made of the stakeholders according to the stage of the life cycle: the pre-market, placing on market and post-market stages.

[55] ISO 26000: defines a stakeholder as an "individual or group that has an interest in any decision or activity of an organization" https://iso26000.info/definitions/

According to Schmeer (56) the multidisciplinary team must define the characteristics that each stakeholder must have, considering the following:

- *Position and organization.*
- *Internal/external: internal stakeholders work within the organization promoting or implementing the policy; all other stakeholders are external.*
- *Knowledge of the policy: the exact level of knowledge that the actor has about the policy under analysis, and how each actor defines the policy in question.*
- *Position: whether the stakeholder supports, opposes or is neutral with respect to the policy, which is key to establishing whether it will block the implementation of the policy.*
- *Interest: the stakeholder's interest in the policy, or the advantages and disadvantages that implementing the policy may bring to the stakeholder or their organization. Determining stakeholders' vested interests helps policymakers and managers better understand their position and address their concerns.*
- *Alliances: organizations that collaborate to support or oppose policy. Alliances can strengthen a weak stakeholder or provide a way to influence several stakeholders by dealing with a key stakeholder.*
- *Resources: the number of resources (human, financial, technological, political and others) available to the actor and its capacity to mobilize them. This is an important characteristic that is summarized in a power indicator and will determine the level of strength with which the actor can support or oppose the policy.*
- *Power: the stakeholder's ability to affect the implementation of health reform policy.*
- *Leadership: the willingness to initiate, convene or lead an action for or against pro-health reform policy.*

The following diagram provide a non-exhaustive list of stakeholders in the three phases of regulation:

After the characterization of the stakeholders, the regulatory authority's multidisciplinary team must develop a "stakeholder map", in order to evaluate their expertise, positions, importance in the process, interests, impact and alliances. This will allow the regulator to interact appropriately with the stakeholders and increase their support in the implementation of the regulatory controls, while avoiding potential misunderstandings and delays.

Public consultation may help to improve both the quality of regulation and governments' responsiveness to citizens and businesses. At the technical level, the use of consultation mechanisms and the introduction of the Regulatory Impact Analysis (12) in particular – is pivotal for collecting empirical information, measuring expectations, assessing costs and benefits and identifying alternative policy options. At the policy level, stakeholder involvement enables a transparent policy-making process and increases the level of social acceptance of decisions and, therefore, compliance. Stakeholder consultation is usually considered to be an integral part of regulatory quality. The stakeholders should be involved when deciding, developing, reviewing, amending or getting feedback on the following regulatory factors.

- Legislation
- Regulatory Strategy, Roadmap and policy

- Status of the NRA
- Regulations and Guidelines
- Requirements for registration, licencing, and post market surveillance
- Transition period for implementing specific regulatory processes
- Regulatory fees and timelines
- and other factors as may be determined.

The importance of involving or informing the stakeholders on the above factors will lead into among other things;

- Transparency and access to information: Stakeholder consultation can increase the transparency of the rule-making process because stakeholders have access to the process itself. Additionally, consultation enables policy makers to make use of the stakeholder's precious experience and knowledge. Stakeholder engagement in rule making can raise support for mentioned regulatory factors, as they feel connected to the policy-making process which therefore enhances alienation and connectivity.
- Increased compliance and regulatory literacy: Engaging the stakeholders and striving for consensus can help to increase the social acceptance of mentioned regulatory factors. It can contribute to greater compliance and, therefore, reduce enforcement costs. Stakeholder engagements promotes stakeholder education on rule making, and provides stakeholders with a chance to increase their regulatory literacy.
- Managing conflict and Legitimacy: Stakeholder consultation provides a mechanism to manage conflicts at an early stage. Greater stakeholder engagement has the potential to create a source of legitimacy and proof of successful governance.
- Credibility, confidence and social cohesion: Stakeholder consultation can help to re-establish stakeholder trust and government credibility by means of creating new and better ways to communicate with stakeholders. Stakeholder consultation can promote stakeholder confidence which in turn contributes to greater social cohesion and buy-inn in the whole regulatory circle.

It is important to define the stages in which the different parties will be involved. The success of involving all stakeholders in the corresponding phases will allow the development not only of policies, but also of processes, avoiding reprocesses, and leading to the placing on them market and making available medical devices that meet the regulatory requirements.

Within the strategies of active and objective participation of stakeholders, it is possible to make use of:

- Initial creation of an multidisciplinary team to evaluate which stakeholders are interested in the regulation process to be carried out.
- Generate questionnaires for stakeholders, allowing the multidisciplinary team identifying those that would have a greater or lesser impact, and a greater or lesser influence.
- Establish neutral spaces that allow collaboration among stakeholders, so that those involved can listen to, discuss and learn from each other.
- Workshops.
- Send documents for consultation and comments.
- Specific technical roundtables for each stage of the life cycle, allowing the appropriate stakeholders to be involved for each topic.

As part of Good Regulatory Practice it is important to control the influence that stakeholders may have during the process, so that the development and implementation of the regulatory controls it is not prejudiced or biased by one of the stakeholders.

7.2 Implementation: developing a road map

A road map is visual way to quickly communicate a plan or strategy. The establishment of a new, or significant changes to an existing, national medical device regulatory system requires thorough and careful planning. A comprehensive outline, or 'roadmap', will be helpful in planning, communicating, and implementing those plans.

In preparing a roadmap, the first step would be to carry out a gap analysis (*see Section 3.2*) where the current local situation is compared with established medical devices regulatory system (benchmark), based on the WHO recommendations (53) (12) (18) (16) and international harmonization consensus guidance documents. (20) It is important to consider the views of country stakeholders at the local level, including patient representatives. In addition, it is recommended to consider public health needs, characteristics of the national medical devices market, national burden of disease, demographic trends, level and characteristics of economic development, size of the country, supply chain and the nature of the medical devices in the market.

Based on the findings of the gap analysis, it is important for the national regulatory authority to identify priorities and the regulatory functions to be implemented, in the pre-market, placing on the market and post-market stages.

It is generally not feasible to make the transition from an unregulated market to a highly regulated market in one go or in a very short time. This type of process requires a significant increase in the size and knowledge of the regulatory authority, education of the regulated industry and health product purchasers and users, as well as a high level political commitment and long-term financial support.

To achieve the above, the WHO recommends that the implementation of the regulation be carried out progressively or in stages. At each stage, the international principles of Good Regulatory Practices for medical products should be applied. The GMRF outlines basic regulatory controls which should be effectively implemented first. As resources permit, and according to national policy priorities, expanded level controls may be implemented on the foundation of the basic controls.

The general and specific objectives that the regulatory authority must meet in the implementation of a new or changed regulatory system must be outlined in an implementation plan and identify possible regulatory, institutional and/or technical changes in the processes of the regulatory authority.

The objectives must be set out in such a way that they can be evaluated for meeting these objectives. For example, the SMART method outlines that the objectives must be Specific, Measurable, Achievable, Relevant and within an established Time.

The development of a prioritization matrix in which the consequences of risks [56]are mapped to the probability of a risk occurring (57) makes it possible to prioritize the identified objectives and the necessary actions to comply with the regulatory processes of the regulatory authority.

[56] ISO 31000: risk is the "effect of uncertainty on objectives"

	Very low consequences	Low consequences	Medium consequences	High consequences	Very high consequences
Very low probability	Low risk	Low risk	Low risk	Low risk	Medium risk
Low probability	Low risk	Low risk	Low risk	Medium risk	Medium risk
Medium probability	Low risk	Low risk	Medium risk	Medium risk	Critical risk
High probability	Low risk	Medium risk	Medium risk	Critical risk	Critical risk
Very high probability	Low risk	Medium risk	Critical risk	Critical risk	Critical risk

An example of the "probability – impact" matrix for risk ranking. (57)

At this point, the necessary resources (human, technical or economic) must be estimated. A realistic execution timeline must be established for the stepwise implementation of the plan in the short, medium and long terms. Based on the proposed prioritization, detailed work plans must be prepared. A road map should lay out outcomes, responsibilities and timelines.

The implementation plan requires continuous monitoring and evaluation of compliance with its objectives. To enable this, it is recommended to develop guides, technical documents or other guidance documents, which make the established guidelines known to the stakeholders involved. It is recommended that these documents be based on international regulatory guidance, being adapted to the local context.

Based on the above, it is recommended to establish a roadmap in which the activities are listed, considering the established priorities, which should be carried out to advance with the implementation plan. The defined roadmap must be communicated with stakeholders. An *example* of a road map is described below . (17)

The road map must be updated on a regular basis.

Objective	Responsible	Outcome/indicator	Information source	Interested stakeholder	Comm
General					
Adopt law and regulations	MoH	Adopted legislation	Parliament	Manufacturers, importers, patients, health care sector	
Premarket					
Define premarket conformity	NRA	Guidance for stakeholders	NRA	Manufacturers, importers, authorized persons.	Meet work interr
Placing on the market					
Oversight: Registration of establishments	NRA	Number of establishment registrations	NRA	Importers, distributors.	Meet maili
Oversight: Listing of medical devices	NRA	Number of medical devices	NRA	Importers, distributors, authorized persons	Meet maili
Post market					
Establish system for review of incidents reported by manufacturers.	NRA	Number of reports of incidents reviewed compared to neighbouring countries	NRA	Manufacturers, authorized representatives	Meet maili
Establish procedure to issue notices for device users related to quality, safety or performance	NRA	Number of notices issued compared to neighbouring countries	NRA	Manufacturers, authorized representatives, health care, patients	Interr medi

7.3 Implementation: regulatory capacity building

National Regulatory Agencies (NRA) should ensure the quality of the regulatory processes through continuous capacity building for its staff.

Capacity building generally includes increasing organizational capacity, physical and communication infrastructure, and individuals' knowledge and skills. Regulatory capacities are related to the technical and scientific competence necessary to adapt to developments in

national and international regulatory standards. Regulatory capacities should also sufficiently support regulators in implementing legal framework, guidelines and procedures.

An array of technical and scientific knowledge and skills of regulatory staff contribute to the development, implementation and maintenance of an effective regulatory system for medical products. Policies and measures for personal and career development (e.g. training programs, competitive remuneration schemes) are critical for regulatory authorities to attract competent staff and retain them in the service. (1a)

Medical Devices including in vitro diagnostic (IVD) medical devices, take on special relevance due to the complexity of their classification as well as the wide range of product categories. The NRA should be able to assess the quality, safety, and performance of all the product categories of medical devices and IVDs.

The staff that works in this area must be composed of multidisciplinary profiles that allows the NRA to assess medical devices for compliance with the national regulatory requirements during non – emergency situations, emergency situation and when utilizing other approaches such as reliance or recognition.

The development of regulatory capacities should begin by establishing the regulatory processes and the associated required competencies and skills that the personnel involved in the regulatory processes of medical devices must have. Regulatory capacities should be strengthened through institutional programs for the development and monitoring of these competencies and skills.

The WHO global competency framework for regulators of medical products describes competencies and underlying knowledge and skills. (15) Each NRA should specify the functions conferred to the jobs, based on the differentiation of responsibilities, in the most concise and detailed way possible, as defined in the institutional organizational chart.

Training plan for the staff of the regulatory authority

The training of staff in regulatory functions must be aligned and maintained to the competencies that have to be developed and those that must be implemented in the NRA. The NRA generates annual programs, based on the mapping of the training needs including training on specific topics.

Based on the mapping, it is recommended to establish annual training plans for each staff member. The training plans should address specific issues for the training of the staff member involved. The annual training plans should be reviewed at least once every year.

The International Medical Device Regulators Forum (IMDRF) states that the NRA should establish procedures for the formal selection, training, approving, and assigning personnel involved in regulatory reviews. In the same way that it is the responsibility of the NRA to establish mechanisms to provide evidence that the personnel involved in the regulatory processes meet the required skills and competencies The exchange of experiences with regulatory experts from other regulatory agencies enables harmonization of regulatory processes and may improve reliance practice.

Competencies, skills, and expertise

Eight blocks of competencies as described below may be considered having a broader vision on the collaborator's skills. The competencies to be evaluated will depend on the objectives of the established programs. The NRA should establish continuous evaluation and monitoring programs of these competencies, skills and expertise of its staff.

Table 2. Core competencies for regulators (ref.xx)

Competence	Characteristics
Context Analysis	• Understanding of the role of regulation as a tool of Government • Ability to work within the wider regulatory framework • Ability to work towards your organization's regulatory objectives • Ability to work with the legislation relevant to your regulatory function(s) • Ability to work within your organization's regulatory policies and procedures • Understanding of the role and responsibilities of partner organizations
Risk assessment	• Ability to assess regulatory risks • Ability to gather, analyze, use and share data to inform risk assessment • Ability to use risk assessment to guide your activities • Understanding of risk management in a business context

Understanding those you regulate	● Understanding of the current business environment and the business sector(s) regulated ● Understanding of how regulation and the way it is enforced can impact on the business communities and individual businesses regulated ● Understanding of the factors that affect business approaches to compliance ● Ability to engage constructively with business ● Ability to tailor your approach to businesses and individuals that you interact with
Planning of Activities	● Ability to act within your role and area(s) of responsibility ● Ability to make appropriate intervention choices, drawing on your understanding of the context in which you operate, of those that you regulate, and of the use of risk-based approaches so as to have the greatest impact ● Ability to work effectively with other organizations ● Ability to plan your work, and that of your team, so as to deliver your responsibilities efficiently
Compliance	● Ability to prepare appropriately for checks on compliance ● Ability to conduct checks in a proportionate manner ● Ability to be responsive to the circumstances encountered ● Ability to make informed assessments of compliance and risk ● Ability to follow-up on checks on compliance in an appropriate manner
Support for compliance	● Understanding of the need for compliance support amongst those you regulate ● Ability to promote the importance of compliance, and your organization's role in supporting compliance ● Ability to communicate in appropriate ways to suit the circumstances ● Ability to provide the information and guidance that is needed by those you regulate ● Ability to provide the tailored advice that is needed by those you regulate, where appropriate
	● Ability to select proportionate responses to non-compliance and potential non-compliance ● Ability to communicate effectively with businesses that have failed to comply

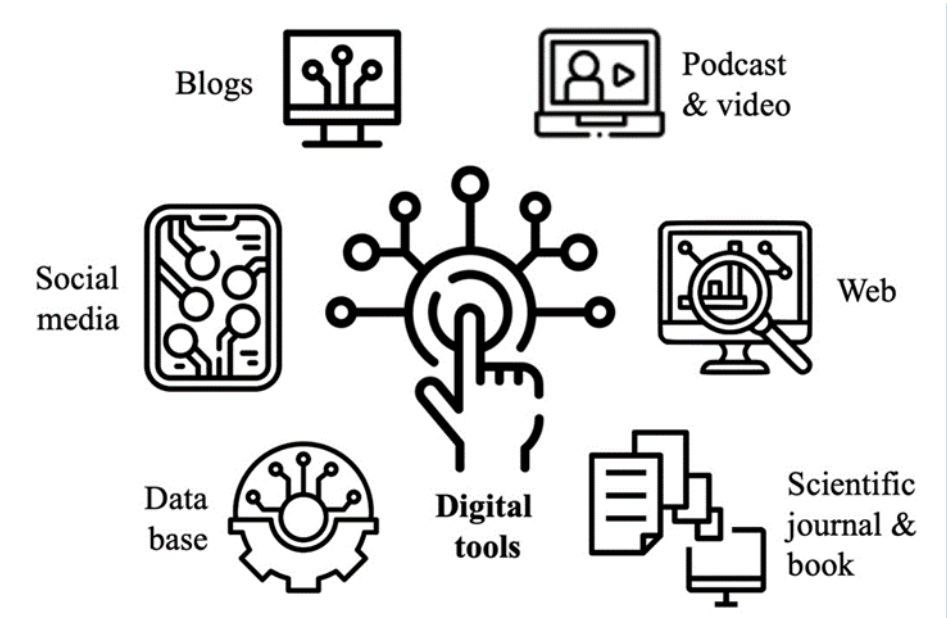
Management of non-compliance	• Ability to conduct thorough investigations of non-compliance and allegations of non-compliance • Ability to prepare and implement effective responses to non-compliance • Ability to provide appropriate support for those adversely affected by non-compliance
Evaluation	• Ability to monitor and report on your activities and performance • Ability to evaluate your activities in relation to your regulatory objectives and your organization's strategic priorities • Understanding of the value of feedback from those you regulate, and the beneficiaries of regulation in informing future activities

Exploring training opportunities.

Options for training are workshops, courses, webinars, worktables, and discussion, as well as evaluations of regulatory processes that shows improvements to be made in a specific area.

E- learning and digital information resources will facilitate access to updated training options. Examples of digital sources of information are shown in the diagram below

Fig. 2 Digital sources to strengthen regulatory capacities.



The NRA may choose to create alliances in terms of capacity development with institutions that can support the strengthening and development of regulatory capacities, both at national and international level. Regulators through a Regional Harmonization Initiative or regional

collaboration may opt to create regional Centers of Excellence (CoEs) to facilitate training of regulators.

Several institutions and regulatory authorities have generated programs that do not only focus on the regulator, but are also applicable to the regulated public, through innovation centers for educational purposes through organizing virtual courses, cooperation agreements and inter-institutional trainings e.g., on building capacities.

The implementation of internal policies can be useful to address the limitations of the NRA in terms of regulatory capacities as well as to put right the specialization needs required by the NRA.

To access experts the following options may be considered:

- External Experts Policy
- CABs
- International Organizations e.g. WHO,
- Regional Harmonization initiatives e.g IMDRF. GHWP, AMDF
- WHO listed Authorities
- Internal portfolio of national and international experts
- Academic Institutions

The creation of these instruments allows the entry of non-binding opinions from external experts that can guide the actions of regulators within the NRA and serve as support to achieve a greater understanding regarding medical devices including IVD, innovative or therapeutic devices of recent creation.

2990 # References

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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 *(5).*

audit. Process for obtaining relevant information about an object of conformity assessment and evaluating it objectively to determine the extent to which specified requirements are fulfilled *(2).*

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 evidence. The clinical data and its evaluation pertaining to a medical device. Clinical evidence is an important component of the technical documentation of a medical device, which along 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. It should be cross-referenced to other relevant parts of the technical documentation that impact on its interpretation. *(8)*

clinical investigation. Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety, clinical performance and/or effectiveness of a medical device. *(9).*

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)*.

conflict of interest. As occurring when a public official has private-capacity interests which could improperly influence the performance of their official duties and responsibilities *(10).*

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 (11)*.

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 *(11).*

convergence (regulatory). A voluntary process whereby the regulatory requirements in different countries or regions become more similar or "aligned" over time. Convergence results from gradual adoption of internationally recognized technical guideline documents, standards, and scientific principles, common or similar practices and procedures or the establishment of appropriate domestic regulatory mechanisms that align with shared principles to achieve a common public health goal *(21).*

corrective action. Action to eliminate the cause of a detected nonconformity or other undesirable situation *(13).*

declaration of conformity. The manufacturer's written attestation that it has correctly applied the conformity assessment elements relevant to the classification of the device *(11).*

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 *(14).*

falsified. Medical products that deliberately/fraudulently misrepresent their identity, composition, or source *(15).*

field safety corrective action (FSCA). An action taken by a manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device. Such actions should be notified via a field safety notice. *(16).*

field safety notice (FSN). A communication sent out by a manufacturer or its representative to the device users in relation to a Field Safety Corrective Action *(17).*

unique device identifier (UDI). Is a series of numeric or alphanumeric characters that is created through a globally accepted device identification and coding standard. It allows the unambiguous identification of a specific medical device on the market. The UDI is comprised of the UDI-device identifier (DI) and UDI-Production identifier (PI) *(18).*

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. *(19).*

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 *(20).*

harmonization (regulatory). A process whereby the technical guidelines of participating authorities in several countries are made uniform *(12; 21).*

hazard: A potential source of harm *(20).*

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 *(22).*

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).*

incident. Malfunction or deterioration in the safety, quality or performance of a device made available on the market, any inadequacy in the information supplied by the manufacturer and undesirable side-effects.

Note: Depending on jurisdictions, the term adverse event (in its post-market meaning) and incident can typically be used interchangeably *(23).*

inspection. examination of a product, process, service, or installation or their design and determination of its conformity with specific requirements or, on the basis of professional judgment, with general requirements

Note 1: Inspection of processes can include personnel, facilities, technology or methodology.

Note 2: Inspection procedures or schemes can restrict inspection to examination only.

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 *(24).*

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 *(25).*

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 *(26).*

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 *(24).*

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 *(24).*

laboratory.
Body that performs one or more of the following activities: testing; calibration; sampling, associated with subsequent testing or calibration

Note 1 to entry: In the context of this document, "laboratory activities" refer to the three above-mentioned activities *(40).*

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

layperson. Individual who does not have formal training in a specific field or discipline *(24)*.

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 *(27).*

machine learning-enabled medical device. A medical device that uses machine learning, in part or in whole, to achieve its intended medical purpose *(28).*

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 competent authorities (regulatory authorities) to check and ensure that devices comply with the requirements set out in the relevant legislation and do not endanger health, safety, or any other aspect of public interest protection *(29).*

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 *(30)*.

personal protective equipment. Protective clothing, helmets, gloves, face shields, goggles, facemasks and/or respirators or other equipment designed to protect the wearer from injury or the spread of infection or illness. PPE is commonly used in health care settings such as hospitals, doctor's offices, and clinical labs *(31)*.

personalized medical device. A generic term to describe any of the types of medical devices that are intended for a particular individual, which could be either a custom-made, patient-matched, or adaptable medical device *(32)*.

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.

post market 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.

post market surveillance. Systematic process to collect and analyse experience gained from medical devices that have been placed on the market *(34)*.

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 thesystem *(34).*

recall. Means any measure aimed at achieving the return of a device that has already been made available to the end user *(29).*

recognition. Acceptance of the regulatory decision of another regulator or other trusted institution. Recognition should be based on evidence that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement (*36)*

referral laboratory. External laboratory to which a sample is submitted for examination

Note 1 to entry: A referral laboratory is one to which laboratory management chooses to submit a sample or sub-sample for examination or when routine examinations cannot be carried out. This differs from a laboratory that may include public health, forensics, tumour registry, or a central (parent) facility to which submission of samples is required by structure or regulation *(36).*

refurbishing. Reconditioning medical devices for safety and effectiveness with no significant change in their performance, safety specifications or service procedures as defined by the manufacturer and their original intended use *(37).*

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 *(27).*

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 *(11).*

reliance. The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible, and accountable for the decisions taken, even when it relies on the decisions, assessments, and information of others. *(35).*

reprocessing. A process carried out on a used device in order to allow its safe reuse including cleaning, disinfection, sterilisation and related procedures, as well as testing and restoring the technical and functional safety of the used device *(38).*

risk. The combination of the probability of occurrence of harm and the severity of that harm *(20).*

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 public health threat. Any event type or device deficiency which could result in imminent risk of death, serious deterioration in the state of health, serious injury, or serious illness of more than one patient, user or other person that requires prompt remedial action *(23).*

single-use device. A medical device or IVD medical device that is intended to be used on an individual patient during or for a single procedure and then disposed of. It is not intended to be reprocessed and used again *(24).*

software as a medical device. is defined as software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device. *(33)*

standard. 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 *(39)*.

substandard. also called "out of specification", these are authorized medical products that fail to meet either their quality standards or specifications, or both *(15)*.

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 *(11)*.

user. The person, either professional or lay, who uses a medical device. The patient may be the user *(41)*.

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.

withdrawal. Means any measure aimed at preventing a device in the supply chain from being further made available on the market *(29)*.

World Health Assembly. The forum through which the World Health Organization is governed by its 194 Member States *(45)*.

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