

**WHO Global model regulatory framework for medical devices including in
vitro diagnostic medical devices (GMRF)**

NOTE:

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

The document is a revision of the initial GMRF, developed in 2015-2016 and published in 2017. This revision was developed based on the input, discussions and results of GMRF Working group meetings from September 2021 to April 2022, with the participation from 46 Member States and international harmonization groups in the field of medical devices. In June 2022 WHO convened two Consultative Meetings involving a broad representation from national regulatory authorities.

The text in its present form does not necessarily represent the agreed formulation of the ECBS. Written comments proposing modifications to this text MUST be received by 29 August 2022 using the Comment Form available separately and should be addressed to the Department of Health Products Policy and Standards, 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).

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117 **Acronyms and abbreviations**

118	AMDF	Africa Medical Devices Forum
119	ASEAN	Association of Southeast Asian Nations
120	CAB	conformity assessment body
121	CLSI	Clinical and Laboratory Standards Institute
122	EU	European Union
123	GBT	Global Benchmarking Tool
124	GDP	Good Distribution Practice
125	GHTF	Global Harmonization Task Force
126	GHWP	Global Harmonization Working Party (formerly Asian Harmonization Working
127		Party AHWP)
128	GMRF	WHO Global Model Regulatory Framework for medical devices including
129		IVDs
130	GRP	Good regulatory practices
131	GRelP	Good reliance practices
132	HMLW	Ministry of Health, Labour and Welfare (Japan)
133	IEC	International Electrotechnical Commission
134	IMDRF	International Medical Device Regulators Forum
135	ISO	International Organization for Standardization
136	ITU	International Telecommunication Union
137	IVD	in vitro diagnostic medical device
138	LIMC	Low and middle income country
139	NRA	National regulatory authority
140	QMS	Quality management system
141	SF	Substandard and falsified medical products
142	SUMD	Single-use medical device
143	TGA	Therapeutic goods administration
144	UDI	Unique device identification
145	UDI-DI	UDI- device identifier
146	UDI-PI	UDI – production identifier
147	UDID	UDI data base
148	USFDA	United States Food and Drug Administration
149	UN	United Nations

150 WHO World Health Organization

151 WHA World Health Assembly

152 1. Introduction and objectives

153

154 The regulation of medical devices including in vitro diagnostics is critical in assuring
155 their quality, safety and performance. In May 2014 the World Health Assembly (WHA) adopted
156 a Resolution regarding regulatory systems for medical products (WHA 67.20). [1] The
157 Resolution underscored the importance of an effective regulatory systems as an essential
158 component of health system strengthening and contribution to public health. WHO decided to
159 develop guidance to support member states that have yet to develop and implement regulatory
160 controls relating to medical devices.

161 The WHO Global Model Regulatory Framework for medical devices including in vitro
162 diagnostic medical devices (GMRF) was published in 2017 in English and was translated into
163 French and Russian. Since then, the GMRF served as background document in WHO
164 workshops on medical devices and is considered a standard in the development of the Global
165 Benchmarking Tool (GBT) [2] when adding medical devices as a product group to GBT+. [3]

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

178 In regulating medical devices multiple stakeholders are involved. The national
179 regulatory authority (NRA) has the authority under laws adopted by legislators and policy
180 makers to control and enforce regulatory requirements. The manufacturers, their authorized
181 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 on 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 regulatory controls – such as the publication of the law and resourcing the regulatory authority to undertake enforcement actions – then progresses to expanded-level regulatory 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 Purpose and scope

This revised Global Model Regulatory Framework for Medical Devices including IVDs (GMRF) 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 regulatory pathway for medical devices according to risk class, regulatory pathway with the mechanism of reliance, regulatory pathway for emergency use authorization, regulatory pathway for borderline products, regulatory pathway for donated medical devices, policy on medical devices testing, and local production of medical devices. It also addresses new topics such as software as a medical device (SaMD), combination products, and implementation topics on stakeholder involvement, regulatory capacity building and developing a road map for regulation of medical devices.

Despite expanding topics in the revised GMRF other medical device subjects have not been addressed e.g., orphan medical devices, off label use of medical devices, in-house developed medical device, 3D-printing of medical devices and medical device registries.

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 (GRP) and enabling conditions for effective regulation of medical devices. It then introduces essential tools for regulation, explaining the function of the regulatory entity and the resources required. Also, it provides information on when reliance and recognition approaches may be considered and the importance of international convergence of regulatory practice.

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.

Section 5 describes the regulatory pathways for different types of medical devices. It provides a clear 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.

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

1.2 Terminology

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. [4]

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. [4]

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. [5]

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. [6]

analytical performance. The ability of an IVD medical device to detect or measure a particular analyte. [7]

analytical validation. Measures the ability of a SaMD to accurately, reliably and precisely generate the intended technical output from the input data. [8]

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. [9]

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. [5]

authorized representative. Any natural or legal person established within a country or jurisdiction who has received a written mandate from the manufacturer to act on his or her behalf for specified tasks, with regard to the latter's obligations under that country or jurisdiction's legislation. [10]

certification. The term applied to third party attestation related to products, processes, systems or persons. [5]

clinical evaluation. Is a set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety, clinical performance and/or effectiveness of the medical device when used as intended by the manufacturer. [11]

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. [12]

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. [13]

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. [7]

clinical validation. Measures the ability of a SaMD to yield a clinically meaningful output associated to the target use of SaMD output in the target health care situation or condition identified in the SaMD definition statement. [8]

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. [14]

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*. [15]

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. [15]

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. [16]

corrective action. Action to eliminate the cause of a detected nonconformity or other undesirable situation. [17]

declaration of conformity. The manufacturer’s written attestation that it has correctly applied the conformity assessment elements relevant to the classification of the device. [15]

device identifier (UDI-DI). Is a unique numeric or alphanumeric code specific to a model of medical device and that is also used as the “access key” to information stored in a UDID. [18]

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. [10]

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. [19]

falsified. Medical products that deliberately/fraudulently misrepresent their identity, composition, or source. [20]

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. [21]

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. [22]

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. [23]

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. [24]

harmonization (regulatory). A process whereby the technical guidelines of participating authorities in several countries are made uniform. [16]

hazard: A potential source of harm. [24]

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. [25]

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. [10]

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. [26] .

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. [5]

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. [27]

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. [28]

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. [4]

IVD for self-testing. Any IVD medical device intended by the manufacturer for use by lay persons. [29]

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. [27]

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. [27]

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. [30]

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

lay person. Individual who does not have formal training in a specific field or discipline. [27]

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. [31]

machine learning-enabled medical device. A medical device that uses machine learning, in part or in whole, to achieve its intended medical purpose. [32]

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).

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. [10]

market surveillance. The activities carried out and measures taken by competent 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. To note: “Union harmonisation” deleted. [33]

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. [4]

medical products. A term that includes medicines, vaccines, diagnostics, and medical devices. [1] **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. [34]

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. All activities carried out by manufacturers in cooperation with other economic operators to institute and keep up to date a systematic procedure to proactively collect and review experience gained from devices they place on the market, make available on the market or put into service for the purpose of identifying any need to immediately apply any necessary corrective or preventive actions. [33]

production identifier (UDI-PI). Is a numeric or alphanumeric code that identifies the unit of device production. The different types of Production Identifier(s) include serial number, lot/batch number, Software as a Medical Device (SaMD) version and manufacturing and/or expiration date. [18]

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.

primary mode of action. The single mode of action of a combination product that makes the greatest contribution to the combination product's overall intended use(s). [35]

quality management system. The organizational structure, responsibilities, procedures, processes, and resources for implementing quality management. "Implementing quality management" is taken to include both the establishment and maintenance of the system. [36]

recall. Means any measure aimed at achieving the return of a device that has already been made available to the end user. [33]

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. [37]

reference regulatory authority. A national or regional authority or a trusted institution such as WHO prequalification (WHO PQ) whose regulatory decisions and/or regulatory work products are relied upon by another regulatory authority to inform its own regulatory decisions. [37]

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. [38]

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. [39]

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. [31]

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. [15]

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. [37]

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. [40]

risk. The combination of the probability of occurrence of harm and the severity of that harm. [24]

scientific validity. Refers to the extent to which the SaMD's output (concept, conclusion, measurements) is clinically accepted or well founded (existence of an established scientific framework or body of evidence) that corresponds accurately in the real world to the healthcare situation and condition identified in the SaMD definition statement. [8]

sameness. For the purpose of this document, sameness of product means that two products have identical essential characteristics (i.e. the product being submitted to the relying authority and the product approved by the reference regulatory authority should be essentially the same). [37]

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 foetal distress, foetal death or a congenital abnormality or birth defect. [6]

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. [26]

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. [27]

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. [41] **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. [42]

substandard. also called "out of specification", these are authorized medical products that fail to meet either their quality standards or specifications, or both. [20]

supply chain. A collective term for manufacturers, authorized representatives, importers, and distributors established internationally or domestically.

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. [15]

unique device identification (UDI). The 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-DI and UDI-PI.

Note: The word "Unique" does not imply serialization of individual production units. [18]

UDI database (UDID). The UDID contains identifying information and other elements associated with the specific medical device. [18]

user. The person, either professional or lay, who uses a medical device. The patient may be the user. [27]

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. [33]

World Health Assembly. The forum through which the World Health Organization is governed by its 194 Member States. [43].

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

2.1 Definition of medical device and IVD medical device¹

The GHTF developed a definition of the terms medical device and IVD medical device.

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 device² 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. [4]

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

¹ In vitro diagnostic medical device is a synonym of in vitro diagnostic and is abbreviated as IVD.

² Note from GHTF definition (<http://www.imdrf.org/docs/gh tf/final/sg1/technical-docs/gh tf-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 IVDs.

includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles.³⁴ [4] For relevant terms, see *Glossary*.

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 may be regulated as if they were medical devices. Examples include: personal protective equipment⁵ 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 such as dermal fillers (*see Section 6*).

2.2 Medical devices classification and classification rules⁷

The universe of medical devices is diverse with wide variations in potential severity of harm to the patient or user. The GMRF recommends that the regulatory authority allocates its resources and imposes controls proportional to the potential for harm associated with medical devices. [28] [29]

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 and the severity of that harm i.e., the risk 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, the useability of the medical device in realistic use cases, and if the medical device incorporates medicinal products, or human/animal tissues/cells. The risk class of an IVD is determined primarily by

³ Note 1 from GHTF definition (<http://www.imdrf.org/docs/ghrf/final/sg1/technical-docs/ghrf-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.

⁴ Definition of an IVD in the Asian Medical Device Directive (AMDD) <https://asean.org/wp-content/uploads/2016/06/22.-September-2015-ASEAN-Medical-Device-Directive.pdf>

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.bcg.co.uk/pages/index.cfm?page_id=29&title=medical_gases (accessed 14 October 2021)

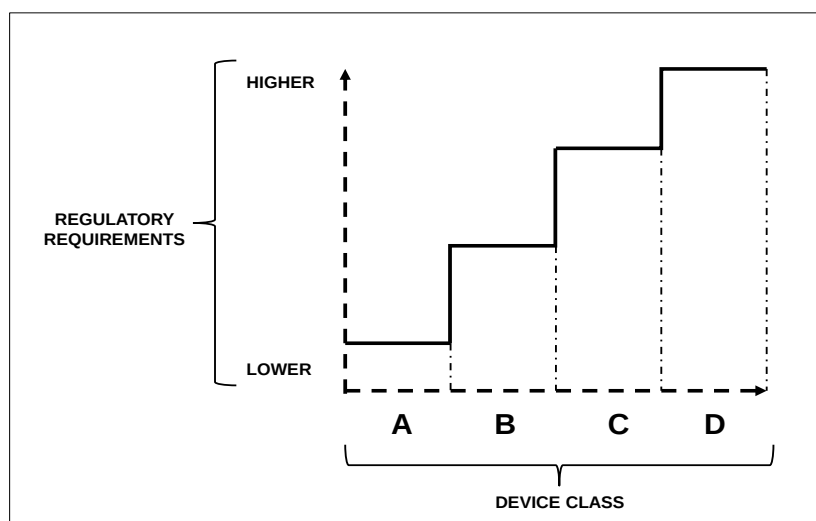
⁷ Medical devices classification is similar to medical devices risk classification

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 [28] and specifying separately the different conformity assessment procedures that should apply to each group of devices (Figure 2.1). A medical device can be classified to one risk class. If more than one risk class would apply, the highest shall be considered.

Figure 2.1

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*. [28]

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;

⁸ Some jurisdictions indicate the risk classes of medical devices differently such as class I, II, III, e.g. USFDA (<https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device>), 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), class I, II, III, and IV e.g. Health Canada (<https://laws-lois.justice.gc.ca/eng/regulations/sor-98-282/fulltext.html>), Schedule 1 (section 6) and China NMPA http://subsites.chinadaily.com.cn/nmpa/2019-10/11/c_415411.htm

- incorporates human or animal tissues or cells;
- is an active medical device;
- delivers medicinal products, energy or radiation;
- could modify blood or other body fluids;
- is used in combination with another medical device.

Classification of medical devices including IVDs also takes into account the technical, scientific and medical expertise of the intended user (lay person or health-care professional). The use of medical devices by laypersons puts specific requirements on the manufacturer to provide to provide necessary ergonomic features to ensure a high likelihood of correct use and 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. [29]

Classification may differ between jurisdictions. Rapid diagnostic tests may be classified as class B in one jurisdiction but as a class C in a country where a disease is endemic.⁹

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.¹⁰

⁹ Examples are available on <https://extranet.who.int/pqweb/vitro-diagnostics/risk-based-classification-ivds>

¹⁰ Reference: <https://www.fda.gov/about-fda/cdrh-transparency/reclassification>

Additionally, the regulatory authority may develop explanatory guidance to help a manufacturer apply the rules.¹¹ [44] [45] While the manufacturer has the primary obligation to classify its medical device, its decision may be challenged by the regulatory authority.

Table 2.2 shows examples of medical devices according to their risk class.

Table 2.2

Examples of medical devices by risk class¹²

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.

For IVDs a four-class system is recommended. An alphabetical system is used to identify risk-based classes for IVDs. Figure 2.3 indicates the four risk classes of devices. The examples given are for illustration only; the manufacturer must apply the classification rules to each IVD medical device according to its intended use.

¹¹ <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN>, Annex VIII

¹² 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 2.3

Examples of IVDs by risk class¹³ [29]

CLASS	RISK LEVEL	EXAMPLES
A	Low Individual Risk and Low Public Health Risk	Clinical Chemistry Analyser, general culture media
B	Moderate Individual Risk and/or Low Public Health Risk	Vitamin B12, Pregnancy self-testing, Anti-Nuclear Antibody, Urine test strips
C	High Individual Risk and/or Moderate Public Health Risk	Blood glucose self-testing, HLA typing, PSA screening, Rubella
D	High Individual Risk and High Public Health Risk	HIV Blood donor screening, HIV Blood diagnostic

2.3 Principles of safety and performance

Regulations should specify that a medical device should be safe and perform as intended as defined by the manufacturer when placed on the market. IMDRF has established a list of Essential Principles of safety and performance for medical devices including IVDs¹⁴. [46] [47] 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

¹³ 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.

¹⁴ 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

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 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.

Ensuring that a medical device conforms to all relevant Essential Principles [46] is the responsibility of the manufacturer. The GMRF recommends that the regulatory authority encourage manufacturers to utilize internationally recognized consensus standards to demonstrate conformance with the Essential Principles of safety and performance. 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 (*see Table 2.4*). The medical device regulation shall specify the extent of the regulatory authority's involvement with different classes of device [28] [29]. While retaining responsibility for the decisions it makes, the regulatory authority may appoint one or more conformity assessment bodies (CABs)¹⁵ to assist it in this task (*see Section 2.3*).

¹⁵ Certain technical elements of the regulatory framework may be delegated to "designated" or "recognized" CABs. For example, they may be approved to perform initial certification and surveillance audits of a device manufacturer's quality management system (QMS) and/or premarketing evaluation of device conformity with the Essential Principles. Satisfactory compliance with requirements is typically confirmed by the CAB issuing a design examination or QMS audit certificate. Based on the CAB's evaluation the regulatory authority may make final decisions on compliance. The CAB performs its evaluation under the oversight of the regulatory authority and may be subject to periodic assessments by that authority.

2.3.1 *Clinical evidence for non-IVD medical devices*

Clinical evidence [12] 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”. It is also recommended that manufacturers provide information on both the inherent risks and the benefits associated with using the device and the uncertainty associated with how accurately they can define the risks and the benefits. Clinical evidence is important to demonstrate compliance with 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 changed. For high-risk devices with new design, material or software, new evidence would be needed. 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*. [13]

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. [15]

Table 2.4

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 ¹⁶	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 2.2).	Review and verify compliance with requirements by the regulatory authority (see footnote to Table 2.2).	Review and verify compliance with requirements by the regulatory authority (see footnote to Table 2.2).

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

¹⁶ 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 nor routinely inspected by the NRA after the devices have been placed on the market. 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 Class B, C and D clinical evidence should be submitted. The amount and detail of clinical evidence required depends on various factors. This evidence is not required for Class B devices, but manufacturers should have this information available upon request. 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 file (risk management plan, risk assessment, and risk management report) [48] 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. [15]

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

2.4 Specific 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 risk presented by a particular device depends substantially on its intended use, indications for use and intended user. Regulatory controls should be proportional to the level of risk associated with a medical device. 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.

The classification of an IVD medical device is based on the following criteria:

- 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 physician
- the impact of the result (true or false) to the individual and/or to public health

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 [29] [49].¹⁷ Software as a Medical Device (SaMD) that processes output from an IVD should be classified based on the SaMD's intended diagnostic purpose. [50]

¹⁷ <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02017R0746-20170505&from=EN>, Annex VIII

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 *Essential Principles of safety and performance for IVDs*

The IMDRF has developed additional Essential Principles that apply to IVDs. [46] 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 order¹⁸

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;
- 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).

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

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. [51] [12] [7] 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. [46] [52] [53] 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* [13] 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* [54].

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 risk based 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 referral¹⁹ laboratory or other competent²⁰ laboratory that is assigned the overall responsibility for coordinating and conducting lot verification testing on its behalf.

3. Enabling conditions for effective regulation of medical devices 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. [37]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;
- science based.

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.

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>

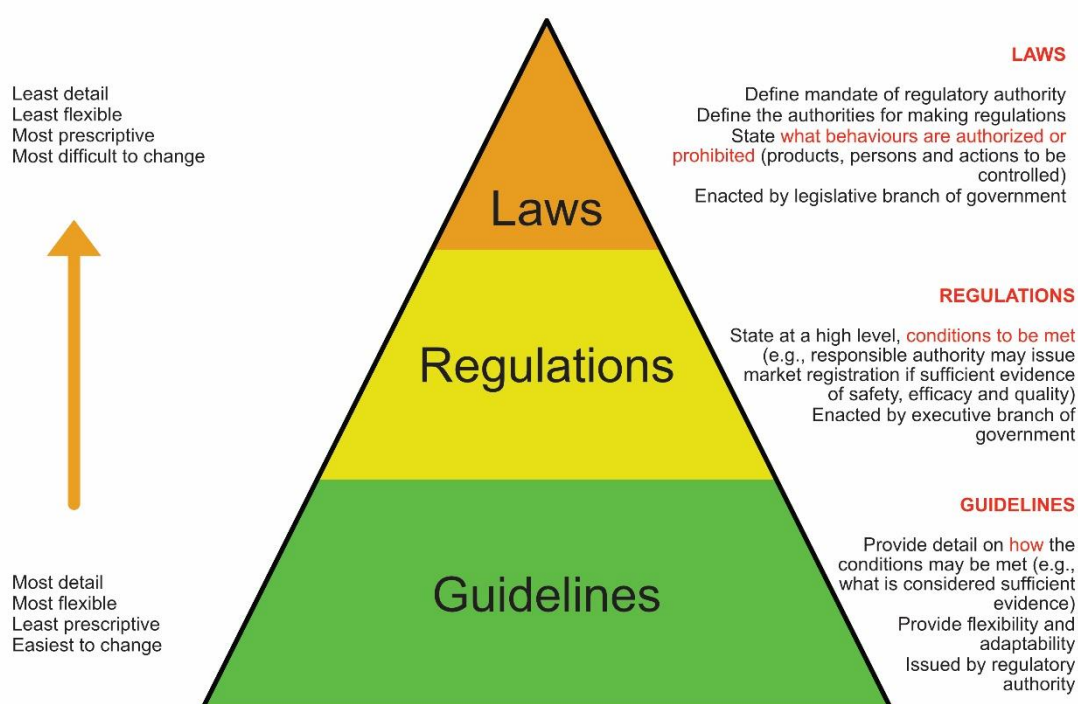


Fig 3.1. Architecture of a regulatory framework [16]

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 manufacturers, authorized representatives, importers, exporters, and distributors in the regulatory process. 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 and authorize the regulatory

960 authority to implement the principles of “reliance” and “recognition” within a set timeline (*see*
961 *also Section 3*). This provision will ensure the regulatory authority implements an effective
962 reliance and recognition pathway and leverages decisions, including but not limited to
963 assessments and regulatory decisions by authorities in other jurisdictions, CABs and trusted
964 institutions such as WHO. The law should let the regulatory authority establish approval
965 pathways for specific circumstances and categories. For example donated medical devices,
966 investigational use only and research only (not intended for diagnostic us) products, emergency
967 use authorization and personal use medical devices including IVDs. It should also allow the
968 regulatory authority to respond to public health emergencies in an appropriate and timely
969 manner. The law should accommodate a transition period from basic to expanded regulatory
970 controls to the extent that resources allow as experience is gained.

971 The authority should adhere to good regulatory practices such as creating opportunities to
972 obtain and review meaningful public comment on proposals, assessing regulatory impacts,
973 allowing reasonable transition periods for stakeholders and adopting requirements that are
974 proportionate and offer the least burdensome ways of achieving policy goals. Regular
975 interactions with stakeholders, including patient organizations, consumer organizations and
976 academic professional associations is key for support and commitment. Stakeholders should be
977 consulted in the development of new laws and regulations in order to receiving feedback on
978 proposed regulations and guidance. The provisions of laws, regulations and guidelines should
979 be as transparent, predictable and internally consistent as possible. (*see Section 7.1*) Measures
980 should be non-discriminatory, so that all similarly situated parties are treated in the same way
981 and that decisions are taken without regard to national or international origin of a medical device
982 or to the source of financing or the sector of the health-care system where it is used (e.g. whether
983 primary, secondary, tertiary or emergency health care; whether delivered through a public,
984 private or military facility).

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

987

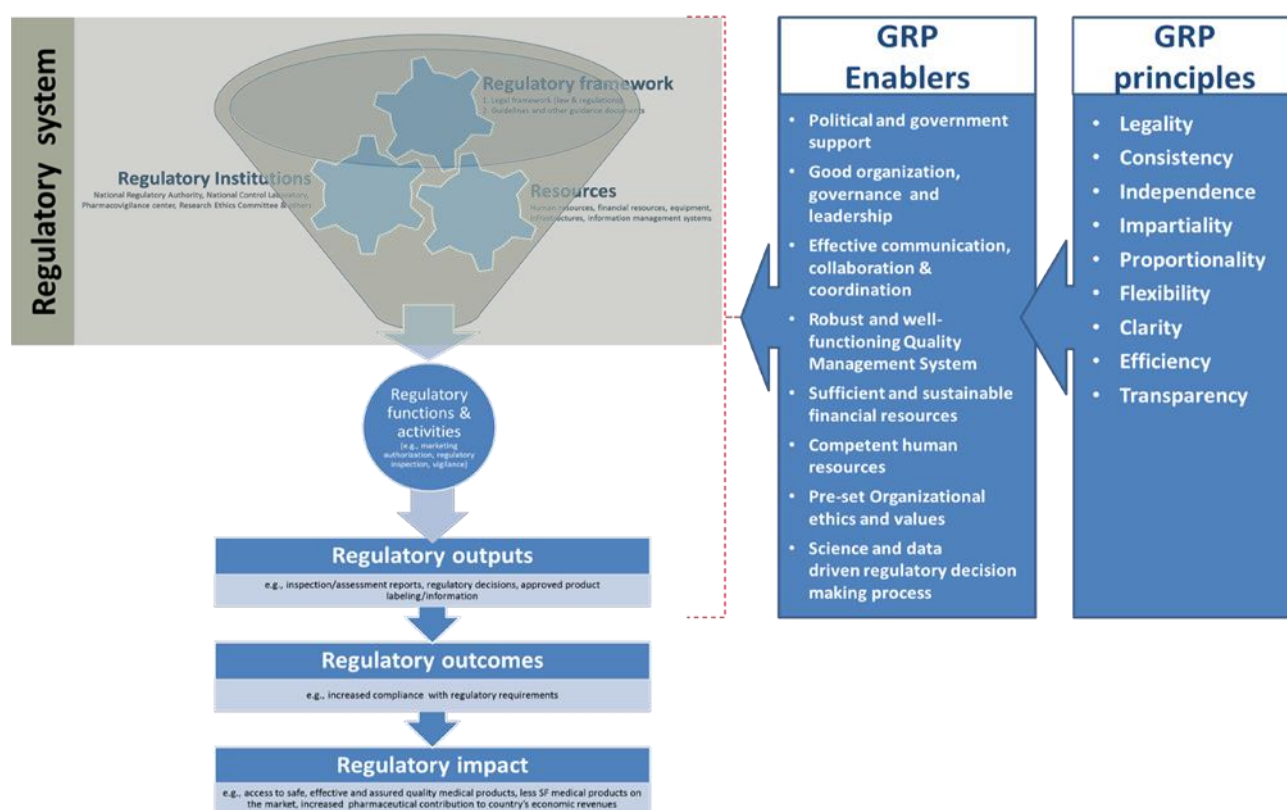


Fig. 3.2 Principles and enablers of good regulatory practices (GRP) and components of a regulatory system [16]

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, and industry 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 3.3 lists elements to be considered in a gap analysis.

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Box 3.3**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?
- Does the national authority observe good regulatory practices in drafting regulations?
- Has a regulatory impact analysis been performed?
- Is there a clear definition of the term “medical device” and does it match with the definition recommended by the GMRF?²¹
- What are the public health risks that exist in the country, and can those risks be mitigated by the use of medical devices? associated with medical devices including IVDs?
- Is there a system of registration and marketing authorization?
- Does the national regulatory authority use international standards or benchmarks in its regulatory process?
- Does the national regulatory authority use reliance or recognition mechanisms in its process?
- 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?
- Does the regulatory authority adopt codes of conduct to be observed by all its members?
- 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?

1007

1008 3.3 Implementation plan

1009 Once a national legislation on medical devices including IVDs has been adopted, the appointed
 1010 regulatory authority should adopt and publish a plan for its implementation. The plan will be
 1011 driven by public health priorities and needs and by the availability of resources, including
 1012 trained competent staff to implement legislation. Risk management should be an integral part
 1013 of management and decision-making and be integrated into the structure, operations, and

²¹ The definition used in the GMRF is from GHTF <http://www.imdrf.org/docs/ghrf/final/sg1/technical-docs/ghrf-sg1-n071-2012-definition-of-terms-120516.pdf>

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 Benchmarking Tool Revision VI (GBT) [2] i.e., national regulatory system, registration and marketing authorization, vigilance, market surveillance and control (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. [55] (*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+ [3] 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. [56] 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. The 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 (i.e., user fees). 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.

For each stage of implementing the regulatory system a sufficient transition period should be established. A transition period 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. Any transition period should be mindful of avoiding a disruption of the supply of medical devices to treat patients. 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. [57].

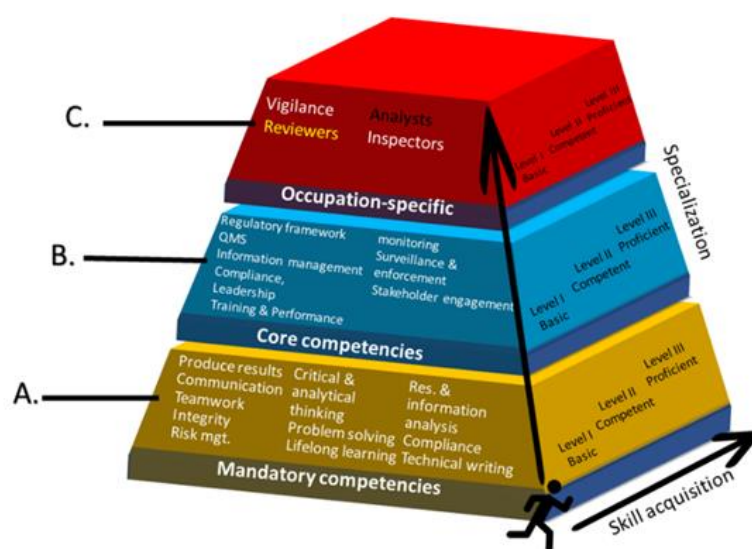


Fig. 3.4 Work functions (tasks/roles), underlying knowledge, and the skills or abilities. WHO Global Competency Framework [57]

In view of the importance of the manufacturer's QMS, the authority should recruit and train staff members with experience in that field. Such staff may inspect or audit manufacturers, authorized representatives, importers, and distributors. These skills should allow the regulatory authority to provide appropriate oversight and control throughout the life cycle of the medical device. When elements of the regulatory framework are delegated to designated or recognized third-party organizations (generally known as CABs (*see Section 4.3.1.2*)), authorities should have competent regulatory staff to assess compliance by the CAB with the relevant requirements. [9] [58]

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. [59] [52] 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 for advanced or well-resourced regulatory authorities it is 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 [3] 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). [37]

The law should establish to what extent the relying regulatory authority may reasonably use the assessment outcomes work of a reference regulatory authority, a CAB or trusted institution such as WHO 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. When relying on another regulatory authority, a relying national regulatory authority should only request additional information when required to meet legislative requirements. While reliance approaches are widely used for the initial authorization of medical devices, they may also be used for vigilance and other post-authorization activities (e.g. post approval changes, inspections) in view of the substantial regulatory resources required for evaluating safety and post-approval changes during a product's life cycle. If a relying authority has relied on another regulator, CAB or trusted institution such as WHO for its initial approval, use of similar reliance measures for post approval changes and vigilance activities is beneficial, as long as the sameness of the product from the initial authorization is maintained.

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.

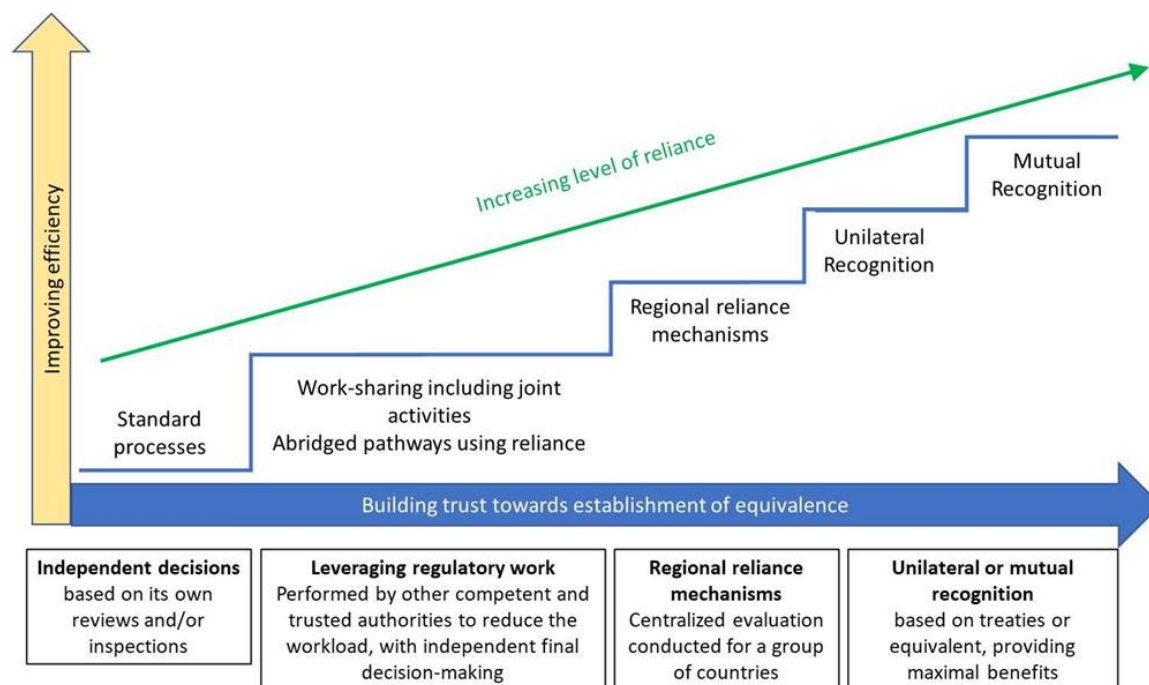


Fig. 3.5 Key concepts of reliance. [37]

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, based on defined criteria, for example WHO-Listed authorities²² or as determined by maturity level from the GBT+ tool, 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.²³ This places responsibility on the regulatory authority of the importing country and may make reliance and recognition inappropriate. Reliance and recognition are not

²² <https://www.who.int/initiatives/who-listed-authority-reg-authorities>

²³ Double standards whereby standards for some jurisdictions set lower requirements for certain jurisdictions are considered unacceptable

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 same²⁴ 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) [49] 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 2025²⁵. 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.²⁶ 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, if applicable, reach agreement on the exchange of confidential information.²⁷ The same considerations apply to the outsourcing of any activities, for example to CABs and third-party parties [60] or experts (locally or internationally based). An example of a specific pathway in reliance is the CRP abridged assessment²⁸, whereby the relying regulatory authority may take into account the output of work performed by reference

²⁴ Sameness of product means that two products have identical essential characteristics (i.e. the product being submitted to the relying authority and the product approved by the reference regulatory authority should be essentially the same).

²⁵ Transition period EU IVDR https://ec.europa.eu/health/sites/default/files/md_newregulations/docs/timeline_ivdr_en.pdf

²⁶ 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.

²⁷ An example of reliance between mature jurisdictions: Australia and the EU. <https://www.tga.gov.au/medical-devices-reforms-mutual-recognition-agreements-mra>

²⁸ 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>

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, 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 incidents²⁹ 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.

4. Establishing a stepwise approach to regulating medical devices

4.1 Stepwise approach

This GMRF 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 and 3.2) The regulatory framework must be sustainable,

²⁹ 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

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 GMRF encourages countries to adopt the principles recommended in internationally harmonized technical guidance into their legislation [61] [62]

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. The implementation of expanded pre-market controls does not mean that a regulator should discontinue existing regulatory reliance practices. 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 GMRF 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-

1303 market activities of the regulatory authority would include a system to ensure that
1304 manufacturers act proportionately to reports of quality, safety or performance problems
1305 associated with use of a medical device.

Table 4.2

Basic-level controls and enforcement for medical devices within the legal framework³⁰

LEGAL FRAMEWORK

EXPANDED

Basic level controls and reinforcement		
Pre-market	Placing on the market	Post-market
Publish law including definition, and regulation with transition period	Registration of establishments	Establish a system for incident reporting
Establish medical device classification for regulatory purposes	Listing of medical devices	Require mandatory notification by the manufacturer of field safety corrective actions
Establish Essential Principles of safety and performance	Import controls	Establish a procedure to cancel market authorization for products that no longer meet quality, safety or performance requirements
Establish basis for reliance and recognition		Establish a procedure to issue safety alerts to users
Establish requirements for Declaration of Conformity		Undertake market surveillance
Establish requirement for manufacturers for a Quality Management System		
Establish requirements for labels and labelling		
Prohibit deceptive, misleading and false advertising		
Establish provisions for exceptional pre-market situations		

1314
1315 *4.2.1 Publish law, including definition, and regulations with transition period*

1316 The national law for medical devices will set out principles and broad requirements and delegate
1317 authority to the regulatory authority (*See 3.1*). In particular it includes:

- 1318 • define the products and parties within its scope, in particular the terms medical device
1319 and IVD, using harmonized definitions [4].
- 1320 • ensure the regulatory framework is capable of adapting to new technologies and
1321 treatment modalities;
- 1322 • designate the regulatory authority, its enforcement powers, market oversight
1323 responsibilities, powers to issue implementing regulations and to take action where the
1324 health of patients or users is compromised, and the responsibility for publishing guidance
1325 documents to aid understanding of legal requirements;
- 1326 • provide the regulatory authority with administrative and enforcement discretion for
1327 reliance upon and recognition of the work or decisions of regulatory authorities in other
1328 jurisdictions (*see Section 3.9*);
- 1329 • require that only safe medical devices that perform as the manufacturer intends may be
1330 placed on the market;
- 1331 • specify market entry requirements for medical devices;
- 1332 • establish record keeping, registration and reporting requirements for all parties within
1333 the scope of the law, including the regulatory authority;
- 1334 • create the option of appeal to a regulatory decision;
- 1335 • specify a transition period sufficient to allow parties affected by the law to comply with
1336 its requirements and ensure minimal disruption to the continuing supply of medical
1337 devices to health facilities and other users;
- 1338 • specify that after the transition period manufacturers shall comply with the regulatory
1339 requirement
- 1340 • specify regulatory approaches during special situations such as public health
1341 emergencies.

1342
1343 To allow progressive adoption and implementation of the stepwise approach
1344 recommended in the Model, the law should foresee and include provisions covering the

³⁰ The expanded level regulatory controls are listed in 4.3

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. In part, the length of the transition 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. [29] [28] 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 or at any appropriate moment for class A devices that do not require pre-market approval. To avoid this situation, it is recommended that the regulatory authority establishes a consultation process whereby manufacturers can gain regulator input on the proposed classification of the device. (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) [46]. Failure to make such a declaration of conformity (see below) ([15] 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 standards³¹ 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.

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. [37]

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 instruction of the manufacturer in the intended purpose statement;

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.

- 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 13485:2016³² *Medical devices Quality management systems – Requirements for regulatory purposes* and ISO 14971:2019: *Medical devices – Application of risk management to medical devices* [63]

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. Information on contra-indications, precautions and warnings should be place. 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 lay persons, and set language(s)

³² The latest version of the ISO Standards apply.

requirements.³³ To begin establishing regulatory controls, regulatory authorities must provide specific guidance on the labelling and language requirements for medical devices and fully describe any exceptions to these requirements. Regulatory authorities should ensure that labelling is in an official language or in a language acceptable for the jurisdiction. The authority should also consider whether instructions for use may be provided in addition to or instead of the printed instructions in alternative media such as via the Internet or connected devices. However, printed instructions for use shall be provided if requested by the user and be available for medical devices for use at home.

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. Guidance may be provided indicating if specific devices require a UDI information as authorized representative, registration information, specific marking, environmental information could be provided electronically (e-labelling).

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.

³³ 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) This standard includes IVD specific symbols.

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).

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
- 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, or for individual patients with exceptional circumstances, 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. [10] [64]

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, distributor, authorized representative or importer should be provided on the medical devices or on the outer packing of medical devices. Specific information may be made available by e-labelling. (see 4.2.2.4) 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. [31]

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. [64]

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, e.g., IFU and labels;
- ensure that all information received from its clients or customers is brought up to the manufacturer/authorized representative as appropriate;
- 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. [64] There are circumstance where one entity performs multiple activities: that entity can identify all activities in a single registration.

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. [31] Among other elements, the listing should provide the standardized generic descriptive names of those medical devices, where possible using an internationally recognized 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, so that the customs service and other relevant government officials have appropriate training to accept the application of medical device-specific rules e.g. labelling and 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

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 including serious public health threats³⁴.

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 user feedback (including complaints) involving medical devices, including malfunction at the device level and incidents at the patient level. 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
 - Death, serious deterioration in state of health of patient, user or another person occurred
 - No death or serious deterioration in health of a user, patient/client or other person occurred, but the failure, malfunction, improper or inadequate design, manufacture, labeling, or user error of the medical device could lead to death or serious deterioration in health of a user, patient/client or other person. [26]

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. To expedite review of reportable events, it is recommended to user or healthcare provider report such incidents directly to the manufacturer or in the case of a non-domestic company, to the authorized representative. 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

³⁴ Note: Depending on jurisdictions, the term adverse event (in its post-market meaning) and incident can typically be used interchangeably

public safety is immediately protected. NRAs should exchange information, if they possess any information that indicates the consequences of using a medical device: [21]

- 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 .

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. Manufacturers often possess additional information regarding perceived safety issues. By requesting such information and consulting the manufacturer before issuing a public alert, the regulator can more thoroughly investigate the issue and provide important context regarding the issue in any public alerts. 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 (see also 4.3.3.2)

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 user feedback (including complaints and incidents), and information from the post-market surveillance systems of medical device manufacturers and their authorized representatives.

1690

1691 **4.3 Expanded-level regulatory controls**

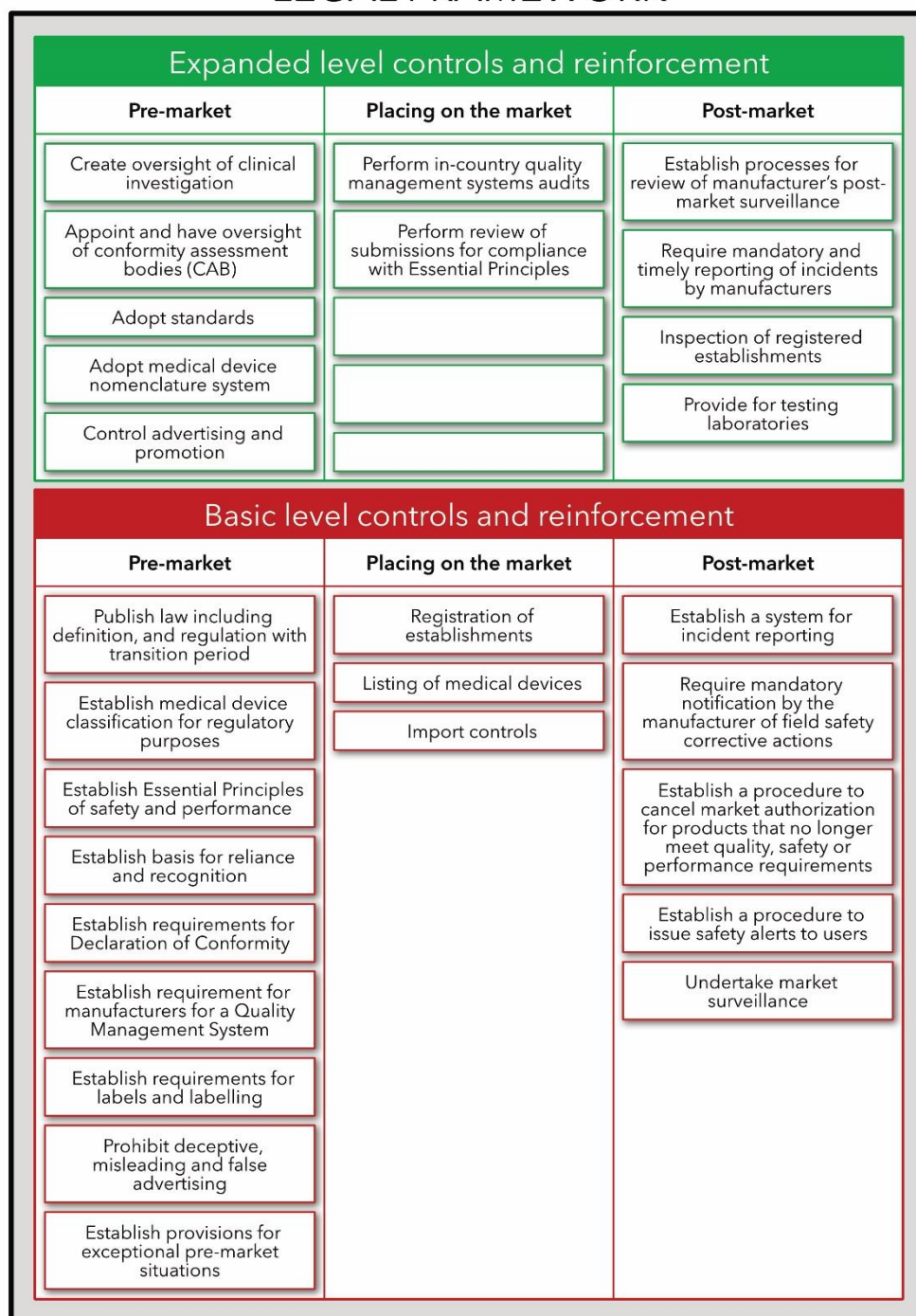
1692 Once the basic-level controls have been implemented effectively and efficiently, the regulatory
1693 authority may consider implementing more advanced controls. To do so, the law should provide
1694 the legal basis for such expanded controls, the regulatory authority must have effectively
1695 enforced the basic controls, and additional resources (e.g., financial and technical expertise)
1696 must be available to it. Building on the basic-level controls, expanded-level controls are
1697 intended to be more comprehensive. In adopting expanded-level controls, the regulatory
1698 authority may choose to implement one or more of the controls described below according to
1699 the priorities of the country. A stepwise approach is recommended for the implementation of
1700 individual elements of expanded controls depending on the availability of technical expertise
1701 and resources (*Table 4.3*). Implementation should always be consistent with available
1702 resources: enforcing a limited set of requirements and publishing them is preferable to covering
1703 a large area of regulatory controls without properly enforcing them. This requires a flexible
1704 response system to serious incidents and violations of legal requirements (*see 3.4*).

1705

Table 4.3

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.

LEGAL FRAMEWORK

4.3.1 Expanded-level controls – premarket

4.3.1.1 Create oversight of clinical investigations

In-country clinical trials may not be needed, especially if the jurisdiction has implemented Good Reliance Practices. However, there may be situations where a country performs clinical trials if the domestic population is unique (e.g., Companion Diagnostics). In these cases 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 pre-market clinical investigations of unauthorized devices 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- h investigations should also be conducted under the oversight of a local ethics committee or institutional review board.³⁵ 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* [13]

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

³⁵ 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/>)

registration, should generally not be required, unless there is a compelling and sound scientific reason.

4.3.1.2 Appoint and have oversight of CAB

Certain technical elements of the regulatory framework may be delegated to designated or recognized 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). [60] Satisfactory compliance with requirements is typically documented with a CAB certificate [58]. 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. [65]

4.3.1.3 Recognition of standards³⁶

Conformity with internationally accepted 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 lifecycle.

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 [36], risk management system [63], clinical investigation [13];
- 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.

³⁶ 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.

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

Preference for recognition should be given to international standards, e.g., those of the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC), other international Standards Development Organizations (SDOs). If there are no standards available from international SDOs, NRAs may wish to look to standards from regional or national SDOs. It is also important that national members of SDOs, such as ISO and IEC, participate in standards development and in the adoption of international standards by the national SDOs in a timely manner. It is also important that national standards correspond to the current version of international standards. As international standards are periodically revised, national adoptions of updated edition will have to take place 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 rather 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

A internationally recognized medical device nomenclature system [66] 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 devices³⁷.

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;

³⁷ 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 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 an internationally recognized nomenclature 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 an internationally recognized nomenclature supports information being aggregated and analyzed not only within a given jurisdiction but also internationally. [67] An internationally recognized nomenclature system is particularly relevant for low- and middle-income countries (LMICs) who are recipients to medical devices from developed economies. [68] [69] If economies have their own nomenclature systems that are jurisdiction-specific, accessibility of a tracking system of those devices in health system is significantly hindered. Fig. 4.4 provides suggested processes for selecting and implementing an internationally recognized nomenclature. It is important to convene 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 an internationally recognized nomenclature system that is best suited to national requirements.

WHO recognizes 3 most used nomenclatures by Member States:

- European Medical Device Nomenclature (EMDN);
- Global Medical Device Nomenclature (GMDN);
- Universal Medical Device Nomenclature System (UMDNS).

1838 Considerations in selecting a nomenclature system include:

1839 - *Harmonization*

1840 Selection of a nomenclature system should consider whether the system is harmonized between
1841 various countries, regionally or internationally to allow for pooling of data and exchange of
1842 information worldwide. Currently, several nomenclature systems are available. Selection
1843 should first be limited to those nomenclature systems that are internationally recognized,
1844 meaning that the nomenclature agency is actively contributing their terms and codes toward
1845 ongoing harmonization efforts (e.g. mapping of codes and terms with other nomenclature
1846 systems) and the nomenclature contains a hierarchical structure grouped into categories and
1847 subcategories to meet stakeholder needs.

1848 - *Accessibility and Ease of Use*

1849 Selection of a nomenclature system should balance the needs of all stakeholders in the
1850 healthcare landscape to enable consistent implementation. Access to the codes and terms
1851 should be free to users.

1852 - *Governance*

1853 Selection of a nomenclature system should consider whether the system is managed in a
1854 transparent manner with a process for obtaining feedback from all stakeholders and a quality
1855 system for managing changes to terminology. Organizational and review structures should be
1856 in place to ensure that all stakeholders from different regions are able to provide feedback
1857 according to global needs. Processes for the classification should have a transparent
1858 methodology of coding, and establishment of nomenclature terms.

1859 - *Timely Updates*

1860 Selection of a nomenclature system should consider the mechanism and periodicity of updates
1861 to medical device terms e.g., once per year. The frequency of updates should balance rapid
1862 innovation of new types of medical devices with the need for clear, consistent implementation
1863 of the nomenclature across all stakeholders.

1864 - *Used in source jurisdictions*

1865 Selection of a nomenclature system should consider the jurisdictions that are the source of
1866 purchased products. If UDI regulations are in place or proposed, consideration should be given
1867 to the nomenclature requirements associated with UDI for the source jurisdiction.

1868 - *Language*

1869 Selection of a nomenclature system should consider the availability of translations in multiple
1870 international languages, especially those of interest to the selection committee. If an appropriate

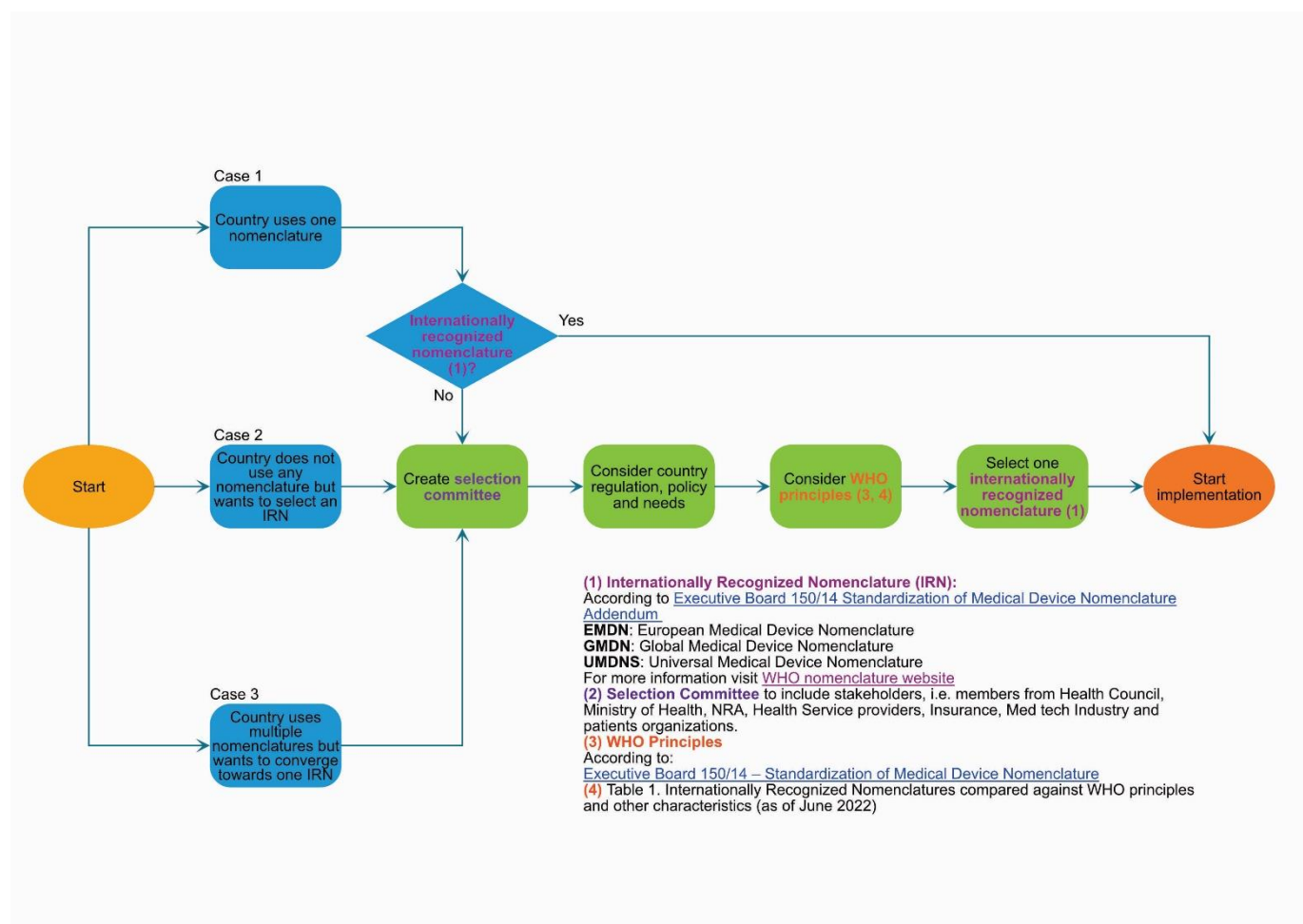
translation is not available, then the committee should check if there is a possibility of translation.

- *Transferability*

Selection of a nomenclature system should consider whether the nomenclature can be shared and fully used with other public sources like national lists, procurement systems, inventory and maintenance systems, electronic health care records, relation with clinical interventions, traceability etc. (open source, interoperability) and be accessible through simple and intuitive search. The nomenclature system should support an unique identification (UDI) system.

The role of the selection committee is to select and propose to the Ministry of Health a nomenclature system to be adopted 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.

Fig. 4.4 Selection of internationally recognized nomenclature (IRN)



How to implement a nomenclature system?

Successful implementation of a medical device nomenclature system requires significant planning and coordination. Below are 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.

- Map the selected nomenclature system with the existing nomenclature systems used in your country. Provide map to stakeholders to enable adoption.

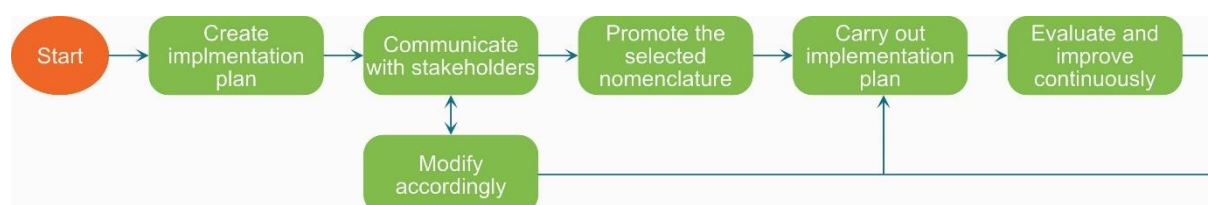
- Define a transition plan to have only one nomenclature in the country. The plan describes which stakeholder is expected to use which aspects of the nomenclature system by what dates. This plan should balance the time required for each stakeholder to complete necessary tasks with the benefits of complete 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.

Fig. 4.5 Country implementation of nomenclature for medical devices



4.3.1.5 UDI

The UDI is comprised of two components: the Device Identifier (UDI-DI) and the production identifier (UDI-PI) and is assigned to a medical device by the manufacturer. The UDI-DI is a

1917 unique numeric or alphanumeric code specific to a model of medical device. The production
1918 identifier (PI) is a numeric or alphanumeric code that identifies the unit of device production.
1919 The different types of production identifier(s) include serial number, lot/batch number,
1920 Software as a Medical Device (SaMD) version and manufacturing and/or expiration date.

1921 The UDI is part of the regulatory requirements for placing a medical device on the market.
1922 Regulatory agencies accredit organizations to operate a system for assigning UDIs that
1923 complies with regulatory requirements. The government usually recognizes the issuing agency
1924 such as GS1, HIBCC. [18] [70]

1925
1926 A UDI is one component of a UDI System. In addition to development of the UDI itself, the
1927 UDI System also includes the framework that requires manufacturers of a device to apply the
1928 the application of the UDI to the device label and to submit data elements associated with the
1929 UDI-DI to a public UDI database (UDID).

1930 A UDI System must have three interrelated components:

- 1931 1. UDIs must be based on technical specifications of DI issuing agencies;
1932 2. UDIs must be applied to the label of a medical device and its associated packaging; and
1933 3. UDI-Dis with specific information about the medical device must be submitted to a UDI
1934 database (UDID) for the purpose of making it public available and to promote data sharing
1935 between regulators and other healthcare stakeholders.

1936 A UDI System provides a single, harmonized system for positive identification of medical
1937 devices. Healthcare professionals and patients no longer have to access multiple, inconsistent,
1938 and incomplete sources in an attempt to identify a medical device and its key attributes. The
1939 UDID is a designated source for additional information. The UDID contains identifying
1940 information and other elements associated with the specific medical device. It is critical to note
1941 that the benefits of UDI can only accrue if all stakeholders, from the manufacturer to healthcare
1942 providers and patients, use UDI throughout their workflow systems. Therefore, it is imperative
1943 that all stakeholders be educated about the development and use of a UDI System.

1944 A globally harmonized and consistent approach to UDI is expected to increase patient safety
1945 and help optimize patient care by facilitating:

- 1946 - traceability of medical devices throughout their lifecycle, especially for field safety
1947 corrective actions,
1948 - adequate identification of medical devices through distribution and use;
1949 - identification of medical devices in adverse events;

1950 - reduction of medical errors, documenting and longitudinal capture of data on medical
1951 devices;

1952 - detection of falsified medical devices.

1953 To ensure Unique Device Identification (UDI) as the means to increase the interoperability of
1954 device information, jurisdictions should follow international best practices when creating a
1955 jurisdiction-specific UDI System or in operating an existing UDI System. UDI Guidance:
1956 Unique Device Identification (UDI) of Medical Devices [18] provides a framework for
1957 regulatory authorities that intend to develop their UDI systems that achieves a globally
1958 harmonized approach to the UDI. The UDI System Application Guide [70] provides the details
1959 and specifications necessary to ensure consistency for enabling a harmonized approach in the
1960 application of the requirements.

1961 One key feature of UDI systems is the requirement to assign a specific medical device
1962 nomenclature for each UDI-DI record in a UDID. Section 9.2 of the IMDRF/UDI WG/N7 lists
1963 nomenclature as one of the core UDID data elements. Section 8.1 of the IMDRF /UDIWG/N48
1964 refers to the expectations for including nomenclature as part of an effective UDID design,
1965 stating that regulators should “connect the device UDI-DI information with codes and terms of
1966 which would enable other stakeholders to: use the UDID data for activities like purchasing,
1967 stock handling, reimbursement, or research; find UDID information related to similar devices
1968 or to enable regulatory authorities to effectively assess the safety and performance of product
1969 groups in the field.” Where the UDI identifies an individual device, the nomenclature
1970 assignments to UDI-DI records enable grouping of products with the same or similar
1971 nomenclature assignments and therefore the UDI System complements and helps to achieve the
1972 goal of a nomenclature system – the accurate identification of medical devices with similar
1973 characteristics.

1974

1975 *4.3.1.5 Control advertising and promotion*

1976 As part of their market development efforts, manufacturers, importers and distributors generally
1977 seek to promote medical devices to health-care professionals, users and/or patients. At a
1978 minimum, in all countries there should be a requirement that advertising and promotion should
1979 not be false, misleading or deceptive. In countries where the presence of misleading and
1980 inaccurate advertisements is a particular problem, the regulatory authority may expand controls
1981 to include review of advertising and promotional material before it is placed on the market. At
1982 this time, the regulatory authority should also contemplate a role for preclearance agencies,
1983 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 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, in most countries with established NRAs, they are generally 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 2.4 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. [36] 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 adopted 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. [5] [46] [52] [15]

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 or may rely on an assessment by another regulatory authority. 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 Contents³⁸. It describes a modular structure and format for such submissions in electronic form. Separate ToCs have been established for medical devices and IVDs. [48] [71] The Association of Southeast Asian Nations (ASEAN) also developed a template, the Common Submission Dossier Template (CSDT). [72] These formats provide guidance for the presentation of evidence that a medical device conforms to the regulatory requirements for safety and performance.

³⁸ The former harmonized format by GHTF was the Summary of Technical Documentation (STED) <https://www.imdrf.org/sites/default/files/docs/ghdf/archived/SG1/technical-docs/ghdf-sg1-n011-2008-principles-safety-performance-medical-devices-080221.pdf>, accessed 3 March 2022

Regulatory authorities are encouraged to adopt such harmonized and electronic formats if they require submission of technical documentation. E-submission will enhance the exchange of documentation for regulatory reliance purposes.

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, i.e., a new or improved product or process whose technological characteristics are significantly different from before;
- an existing compliant device is being used for a new intended use;
- the device type is new to the manufacturer;
- the device type tends to be associated with an excessive number of 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 lay persons to support or sustain the life;
- IVDs for self-testing.

Considerations (or “triggers”) for notification to the regulatory authority after initial approval could include change of manufacturing facility, specifications, change in mode of action on the human body or any change to the device intended use including change in intended population. Regulatory authority shall provide clear guidance and timelines on changes based on risk, and allow for an exemption or simplified process for changes which do not affect safety and performance.

Once medical devices have been granted market authorization the manufacturer may introduce changes to the product, its manufacturing process or location, or the quality management system (QMS) under which it is produced. Such changes may range from minor, with little potential to impact the quality, safety and/or performance of the medical device, to substantial, and likely to affect the quality, safety and/or performance of the medical device.

Significant change means a change that could reasonably be expected to affect the safety or effectiveness of a medical device. It includes a change to any of the following:

- the manufacturing process, facility or equipment;
- the manufacturing quality control procedures, including the methods, tests or procedures used to control the quality, purity and sterility of the device or of the materials used in its manufacture;
- the design of the device, including its performance characteristics, principles of operation and specifications of materials, energy source, software or accessories; and
- the intended use of the device, including any new or extended use, any addition or deletion of a contra-indication for the device, and any change to the period used to establish its expiry date.

The manufacturer should establish, maintain and apply a procedure for categorizing and documenting any changes to the device design/type (including software) and/or quality system as either “substantial” or not substantial.

The NRA shall establish a guidance on changes including definition and tools and processes to handles these changes. The NRA should when possible, implement reliance and recognition principle when handling changes.

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.

2114 4.3.3 Expanded-level controls – post-market

2115

2116 *4.3.3.1 Establish within the regulatory authority processes for review of manufacturer's post-*

2117 *market surveillance and incident reporting*

2118 At the basic level a system for reporting incidents involving medical devices to the regulatory
2119 authority, in particular those resulting in death or serious deterioration in health of a user,
2120 patient/client or other person, is established (*see Section 4.2.4.1*). At the expanded level, the
2121 role of the regulator may be extended to review the post-market surveillance system of the
2122 manufacturer or its authorized representative, and to review and monitor manufacturer's
2123 investigation of user feedback. Manufacturers undertake post-market surveillance activities
2124 including review of user feedback to determine reporting of certain categories of incidents to
2125 the regulator. Manufacturers should review the risk/benefit profile associated with the on-going
2126 use of devices. Manufacturers may implement corrective actions may be taken to reduce the
2127 likelihood of recurrence. Properly structured post-market surveillance can identify serious
2128 problems in the safety, quality or performance of a medical device that may not have been
2129 foreseen or detected during product development or premarket evaluation, and provide for
2130 corrective actions. This may include exchange of alerts internationally in a standardized
2131 manner.

2132 Regulators should ensure that manufacturers have a system for post-market surveillance
2133 (e.g., through an ISO 13485 inspection) including collection of user feedback, reporting certain
2134 incidents to the regulator and evaluating the need for corrective actions encompassing:

- 2135 • incident reporting and user feedback (including complaints) handling systems with clear
2136 responsibilities for the regulator, manufacturer, authorized representative, importer and
2137 distributors;
- 2138 • collecting and reviewing incident reported by the manufacturer;
- 2139 • maintenance by parties in the distribution chain (importers and distributors) of appropriate
2140 records of user feedback (including complaints) and actions taken;
- 2141 • reviewing implementation of corrective actions and preventive actions, including FSCA, by
2142 the manufacturer or its authorized representative, when appropriate.

2143 Where the manufacturer is located outside the jurisdiction of the regulatory authority
2144 there should be an agreement between the manufacturer and its authorized representative
2145 defining who fulfils the national regulatory requirements and maintains records of the
2146 distribution of the device. The agreement should require the authorized representative to report

2147 all user feedback including complaints and quality problems to the manufacturer for
2148 investigation and possibly corrective action.

2149 To the extent that investigation and information management resources allow, the regulatory
2150 authority should establish a mandatory requirement for the timely reporting, by the authorized
2151 representative or manufacturer, of incidents and serious public health threats associated with
2152 medical devices in the jurisdiction. It should define the threshold for reporting (i.e. what kinds
2153 of incidents should be reported), reporting time limits, required information and which party
2154 (or parties) shall report. In general, those criteria should be consistent with WHO and IMDRF
2155 guidance on incident reporting. [26] [73]

2156 *4.3.3.2 Develop a system for market surveillance (see also 4.2.4.5)*

2157 In addition to the incident reporting by the manufacturer the regulatory authority may develop
2158 a system of market surveillance. The system includes receiving feedback from users and
2159 patients, analyzing data from regulatory controls and considering testing of medical device
2160 post-market. The NRA assesses the reports from users and may forward these reports to the
2161 manufacturers or the authorized representative in case the NRA requires them to follow up on
2162 the reports. For a systematic approach of market surveillance the NRA may develop a risk-
2163 based market plan for surveillance based on data from regulatory controls on medical devices
2164 already on the market. Sampling and testing may be part of the market surveillance if applied
2165 in a focused manner: considering the resources to acquire expertise and maintain testing
2166 facilities covering the broad spectrum of medical devices, is not within reach of most testing
2167 laboratories. A focused approach on why to test and what to test may assure an efficient
2168 approach. Collaborating with laboratories on a national or regional level promotes building
2169 expertise and better use of resources. [26]

2170

2171 *4.3.3.3 Inspections of registered establishments*

2172 The regulatory authority may inspect periodically, scheduled or unannounced, all registered
2173 organizations to confirm they have the facilities, procedures and records in place to allow them
2174 to comply with the attestations made when they were registered. Regulators are encouraged to
2175 rely on inspections performed by other regulatory authorities, CABs or trusted institutions such
2176 as WHO. However, the regulator should maintain the right to inspect periodically, scheduled
2177 or unannounced, all registered organizations based on a risk-based approach (e.g., inspect

higher risk products first, those manufacturers with recent audit findings, or those manufacturers that have not yet been inspected) 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 it performs 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);
- where appropriate, 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.³⁹ 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,

³⁹ <http://www.who.int/entity/mediacentre/factsheets/fs275/en/> (accessed July 2021).

2209 now GHWP) has published guidance on the application of ISO 13485:2016 in an organization
2210 that distributes or imports medical devices. [64]

2211

2212 4.3.3.3.2 *Local production*

2213 Local production of quality medical devices can contribute to better access, and affordable
2214 products which is critical in provision and quality health services. [74] [75] [76] Governments
2215 can have legitimate policy interests in promoting and encouraging the development of local
2216 development and manufacturing capacity, as well as ensuring the safety, quality, and
2217 performance of medical devices. Local production can potentially offer a cost-effective
2218 pathway to improving access to health care and medical devices. While local production is
2219 one method to increase access to medical devices, additional research or technology-transfer
2220 is needed to create an environment that will benefit public health. It requires a multisectoral
2221 approach to put in place policies to ensure manufacturing of quality products. The
2222 government should appropriately ensure transparency, predictability, non-discrimination,
2223 consistency of requirements, impartiality, and respect for proprietary confidential information
2224 (i.e. Good Regulatory Practices). The government will play crucial roles in local production
2225 of medical devices including policies, mobilization of all relevant government sectors,
2226 stakeholders, conducive business environment engaged in the local productions of medical
2227 devices and establishment of a strong regulatory authority.

2228 The national regulatory authority shall be well equipped to:

- 2229 • Advise the government in preparation of appropriate policies to facilitate local
2230 production of medical devices.
- 2231 • Ensure adoption of international standards including a list of national standards required
2232 for production, and handling of quality medical devices to local manufacturers;
- 2233 • Provide proportionate and stepwise technical support to local manufacturers. Whether
2234 domestic or foreign manufacturers, appropriate consultation mechanisms encourage
2235 compliance with regulatory requirements because they can address misunderstandings. This
2236 may enable manufacturers in achieving proficiency in production of quality and safe medical
2237 devices using a dedicated team considering possible conflict of interest;
- 2238 • Ensure public availability of concise regulations, guidelines and standard operating
2239 procedures for assessment, market authorization, post market surveillance, and market
2240 surveillance of quality and safe medical devices equally applicable to local and international
2241 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 the interest of safeguarding public health, and to ensure quality, safety and performance, local manufacturers shall be subject to the same regulatory controls as manufacturers and distributors of imported medical devices. Those controls should be consistent, non-discriminatory, and impartial regardless of the origin of medical devices. The regulatory authority, in the pre-market phase, would provide clear guidance on the legal requirements for both foreign and 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.

Where premarket conformity assessment of both foreign and locally produced higher risk class medical devices is necessary, the regulatory authority would generally conduct its own evaluations, but may take into consideration similar evaluations conducted by other authorities, if any. Because the local manufacturer is physically located in the jurisdiction of the authority, the regulatory authority would conduct its own QMS inspections/audits of the manufacturer's plant(s) and warehouse(s). Reliance and recognition mechanisms would generally not apply in such cases. Requirements for registration of local manufacturers and distributors would be similar to those for foreign manufacturers, authorized representatives, importers, and distributors, as would the requirement for listing of devices for which a pre-market assessment is not required.

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

2275 enforces the manufacturer to act; for imported medical devices it is the authorized
2276 representative.

2277 In the event of vigilance reports or FSCA involving locally produced devices exported to other
2278 countries, the national regulatory authority may be called upon to investigate the
2279 manufacturer/exporter and/or to coordinate with foreign authorities. Local vigilance reports or
2280 FSCA involving locally produced devices would be investigated and monitored by the national
2281 regulatory authority but may also involve coordination with others.

2282 In the case of inspections to investigate suspected noncompliance or problems with products,
2283 the national regulatory authority is likely to undertake the inspection.

2284 Based on the outcomes of the inspection/audit, the regulatory authority or CAB can either allow
2285 the local manufacturer to continue with existing operation or issue citations for non-
2286 conformance activities. According to the significance of the non-conformance, a warning letter,
2287 product withdrawal or even plant shutdown of the local manufacturing site is possible.

2288 Activities by the national regulatory authority such as assessing the technical dossier,
2289 performing on-site inspections and enforcing post market requirements require specific
2290 capacity building. Oversight of the required expertise and competencies is key for staff of the
2291 NRA to perform these tasks effectively and responsibly.

2292

2293 *4.3.3.3.3 Regulatory Testing of Medical Devices*

2294 In general, routine testing of medical devices by the NRA, either imported or locally produced,
2295 is not a cost-effective use of limited resources and is not recommended. The manufacturer has
2296 the primary responsibility for demonstrating that a device conforms to the essential principles
2297 of safety and performance, quality requirements, and all applicable national laws and
2298 regulations. Under the manufacturer's quality management system, this includes any testing
2299 and documentation, all of which is subject to auditing and review by the NRA or CAB, either
2300 before market introduction or upon demand. As with all other evidence of conformity held or
2301 submitted by the manufacturer, that testing evidence is subject to review or audit/inspection by
2302 the regulatory authority.

2303 The manufacturer is also responsible for any testing that may be required as part of the
2304 investigation of product complaints or adverse event reports or testing to verify corrective and
2305 preventive actions. All such testing is covered by, and forms part of the basis for, the
2306 manufacturer's declaration of conformity.

2307 As directed by the NRA, an appropriately qualified and equipped testing laboratory may
2308 undertake tasks such as:

- 2309 • Examination and testing of medical devices that are suspected as SF (*see Section*
2310 *6.5*);
- 2311 • Investigation of devices allegedly involved in a serious adverse event;
- 2312 • Investigation of devices sent to the regulatory authority by laypersons;
- 2313 • Systematic post market testing of specific devices, imported or locally produced,
2314 according to specific national public health priorities;
- 2315 • Post-shipment lot verification of IVDs; or
- 2316 • Support for law enforcement investigations.

2317
2318 Given the diversity of medical devices, and the large volume of many medical devices in
2319 circulation, it is unlikely that a national regulatory authority will have the necessary resources
2320 to test all categories of medical devices including IVDs. The work of the regulatory authority
2321 may benefit from, and be supplemented by, having access to an independent, accredited test
2322 laboratory(ies) when testing is deemed necessary to verify the safety or performance of a
2323 device. Testing of medical devices can be conducted by the national control laboratory which
2324 is usually located within the national regulatory authority, by the National Reference
2325 Laboratory(s), other external testing laboratories within or outside the country or by the
2326 medical device manufacturer - in accordance with appropriate internationally adopted standards
2327 and appropriate performance testing - that demonstrates conformance to the essential principles.
2328 Therefore, the legal provisions shall include the option to outsource testing to competent
2329 laboratories to perform testing and officially issue results of the same to the national regulatory
2330 authority as part of the regulatory controls. The legal provision shall therefore define
2331 organizational and governance structure, have clear communication, and define responsibilities
2332 of entities responsible for laboratory testing activities in a form of signed memorandum of
2333 understanding with all stakeholders involved.

2334
2335 The competency of the testing laboratories should be evaluated by an accreditation body and
2336 the national regulatory authority should further verify that evidence before entering into the
2337 agreement. The policy should also emphasize provision of adequate funding for human resource
2338 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.

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 sub-regional 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 sub-regional 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”.

2370 Harmonization, recognition and reliance contribute to more effective regulatory
2371 systems. They are an essential component of health system strengthening and contribute to
2372 better public health outcomes (*Table 4.4*).

2373

2374

Table 4.4

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**.

LEGAL FRAMEWORK		
Expanded level controls and reinforcement		
Pre-market	Placing on the market	Post-market
Create oversight of clinical investigation	Perform in-country quality management systems audits	Establish processes for review of manufacturer's post-market surveillance
Appoint and have oversight of conformity assessment bodies (CAB)	Perform review of submissions for compliance with Essential Principles	Require mandatory and timely reporting of incidents by manufacturers
Adopt standards		Inspection of registered establishments
Adopt medical device nomenclature system		Provide for testing laboratories
Control advertising and promotion		
Basic level controls and reinforcement		
Pre-market	Placing on the market	Post-market
Publish law including definition, and regulation with transition period	Registration of establishments	Establish a system for incident reporting
Establish medical device classification for regulatory purposes	Listing of medical devices	Require mandatory notification by the manufacturer of field safety corrective actions
Establish Essential Principles of safety and performance	Import controls	Establish a procedure to cancel market authorization for products that no longer meet quality, safety or performance requirements
Establish basis for reliance and recognition		Establish a procedure to issue safety alerts to users
Establish requirements for Declaration of Conformity		Undertake market surveillance
Establish requirement for manufacturers for a Quality Management System		
Establish requirements for labels and labelling		
Prohibit deceptive, misleading and false advertising		
Establish provisions for exceptional pre-market situations		

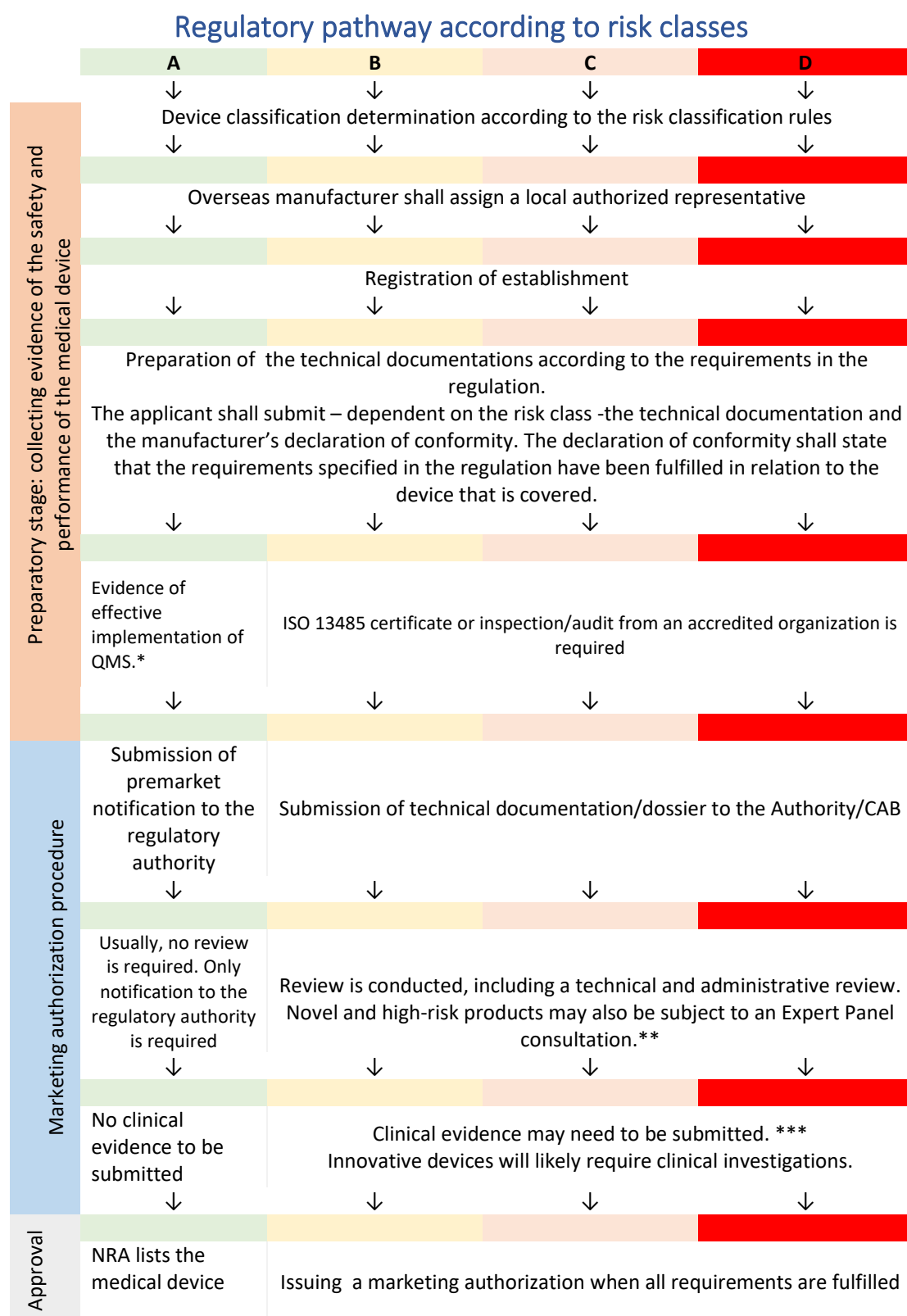
5. Regulatory pathways

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 can always be disputed by the regulatory authority. The scrutiny of the regulatory assessment depends on the risk class of the medical device. This is without prejudice to the manufacturer's obligation to comply with legal requirements, regardless of the risk class and regardless of the approval process.

2412

2413 *Fig. 5.1 Regulatory pathway according to risk class*



* Class A sterile and with measuring function: regulatory audit can be considered

**Some countries may require national verification for medical devices and IVDs

***Clinical evidence includes the clinical data and its evaluation pertaining to a medical device (see Glossary).

2414

The durations of the approval process provides guidance based on best practices. The national regulatory authority may consider different time limits. The renewal period is indicative and may not apply when jurisdictions do not apply a renewal requirement.

Fig. 5.2 Duration of approval process regulatory pathway based on risk class.

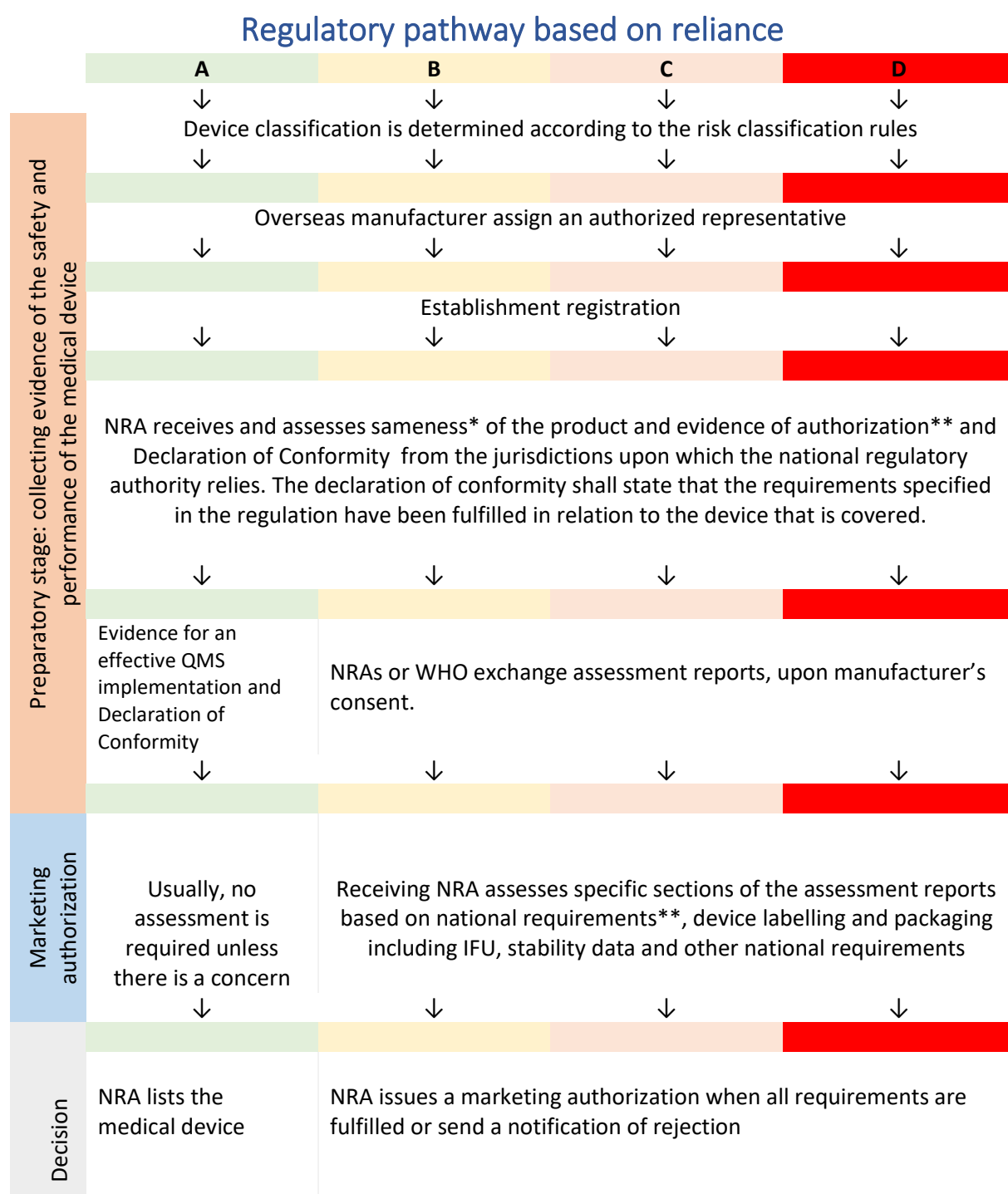
Device classification	A	B	C	D
How long you should expect to wait after submission until approval is granted	< 1 month	1-3 months	2-6 months	2-6 months
Validity period for device registrations		3-5 years	3-5 years	3-5 years
Registration renewal should be started this far in advance		6 months	6 months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

2439

2440 *Fig. 5.3 Regulatory pathway with reliance mechanism*



* 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. Reference: Good Regulatory Practice
<https://apps.who.int/iris/bitstream/handle/10665/340323/9789240020900-eng.pdf>

** Certificate or letter from the authorizing entity

2441

The durations of the approval process provide guidance based on best practices. The national regulatory authority may consider different timelimits. The renewal period is indicative and may not apply when jurisdictions do not apply a renewal requirement.

Fig.5.4 Duration of approval process with reliance mechanism

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.

2466 The key concept for emergency regulatory authorization or derogation procedure mechanism
2467 is making risk-calibrated regulatory decision, weighing the potential benefits against the
2468 potential risks caused by the public health emergency, based on the available evidence
2469 submitted to support the authorization request supplementing with post authorization
2470 monitoring and continued safety and performance evidence to adjust the regulatory decisions
2471 as necessary.

2472 A medical device may be designated by the regulatory authority as authorized for emergency
2473 use where:

2474 a) The medical device is needed:

- 2475 • to treat or diagnose any medical condition resulting from a public health emergency,
- 2476 • to prevent the spread or possible outbreak of an infectious disease,
- 2477 • to treat or diagnose an infectious disease or any medical condition associated with an
2478 infectious disease, where the medical condition or infectious disease is potentially
2479 serious or life-threatening.

2480 b) In the understanding of the regulatory authority, there is:

- 2481 • preliminary scientific evidence that the medical device has the potential:
 - 2482 ○ to treat or diagnose the medical condition resulting from the public health
2483 emergency,
 - 2484 ○ to prevent the spread or possible outbreak of the infectious disease,
 - 2485 ○ to treat or diagnose the infectious disease or any medical condition associated
2486 with the infectious disease.
- 2487 • ongoing scientific evidence that the potential benefits of the medical device outweigh
2488 the known risks of the medical device, to a person on whom the medical device is
2489 used,

2490 and

- 2491 • strong post-market structure and market surveillance to monitor not only product
2492 safety and performance, but also to reduce the chances that substandard or counterfeit
2493 products reach the market.
- 2494 • The applicant is required to provide more evidence as it becomes available.

2495 In order to develop and establish the minimum criteria for evaluating the safety and
2496 performance of medical devices before the products are placed on the market, it is important
2497 that the regulatory authority performs consultations with experts at the national, regional, or
2498 even global level, before the products are placed on the market.

2499 Any emergency regulatory authorization strategy adopted must allow a transparent disclosure
2500 of the requirements and criteria adopted for a medical device to receive emergency
2501 authorization. Likewise, it is important to establish a validity period for such measures during
2502 the emergencies as well as for the authorized medical devices so that the evidence assessed
2503 during the emergency period may be proven or strengthened.

2504 In order to avoid abuse of the emergency authorization or derogation procedure of a medical
2505 device, the validity period of the data assessed for authorization that allows the circulation and
2506 use of such product must be clearly disclosed in such a way that health services and
2507 professionals do not purchase or use products for which authorizations have expired or
2508 cancelled.

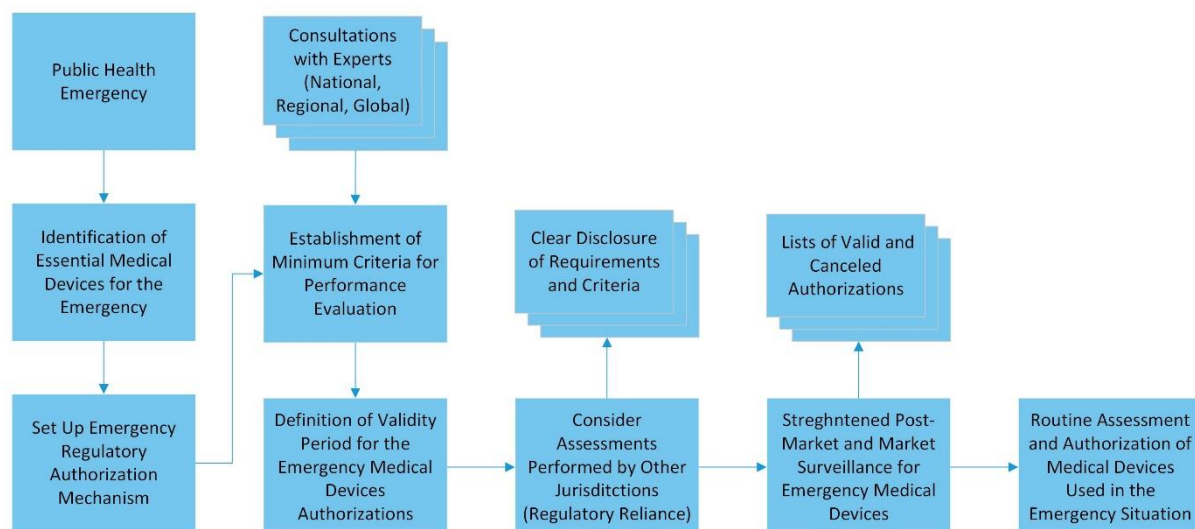
2509 As part of post market surveillance, manufacturers should continuously monitor post-market
2510 data on the safety and performance of the medical devices which have been given emergency
2511 use authorization as such evidence becomes available. Meanwhile, the NRA should review the
2512 safety and performance requirements for market authorization. When adequate supporting data
2513 have been found to meet the safety and performance requirements, complete assessment of the
2514 product using routine assessment procedure of the product can be conducted by the NRA,
2515 followed by formal market authorization.

2516 One important approach for international action in terms of emergency authorization is
2517 regulatory reliance (*see 4.1.1*), which is a mechanism to strengthen regulatory capacity, to
2518 improve health systems nationally and internationally, to increase the availability of medical
2519 devices, to save financial resources and to use human resources more strategically. It is
2520 important that regulators implement recognition or reliance mechanisms to foster data sharing
2521 and product authorization, particularly during a public health emergency when resources are
2522 the most strained and urgency is most needed.

2523

2524

Fig. 5.5 Flow chart for emergency use authorization



5.4 Regulatory pathway for borderline products

The field of borderline products⁴⁰ 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

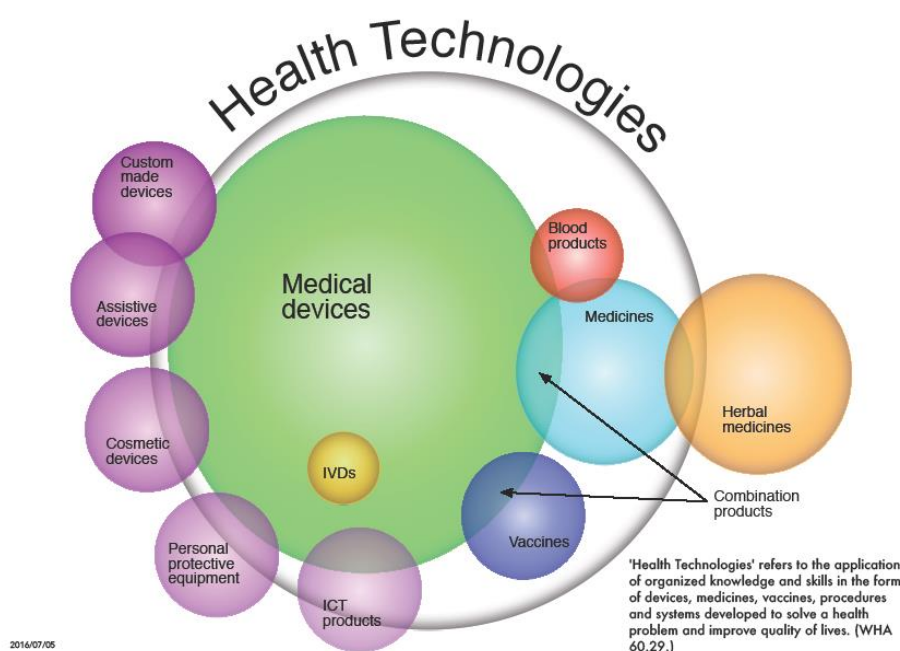
Many products are used in the delivery of health care, yet not all fit comfortably within an existing definition for a medical product, more specifically the term “medical device”. Nowadays, an increasing number of products are characterized as borderline, an ambiguity that exists due to either innovative 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.

⁴⁰ Borderline products are generally (medical) products that offer combined characteristics that are covered by at least two legislations (e.g., both medical device and medicinal product), whose lead legislation within a jurisdiction may be unclear. Borderline products are not combination products. Please see Section 5.6.

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.

Examples of borderline products include cosmetic articles such as 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.⁴¹

Fig. 5.6 Examples of borderline products.



A product considered a medical device in some countries, will 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.

⁴¹ This is not an exhaustive list of borderline products, but a number of examples

To be predictable and transparent, the 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 device” based on interpretation of the NRA's rules and regulations for medical product classification, technology, primary mode of action, medical claims made by the manufacturer, intended use and indications for use of the product, e.g. cosmetic contact lenses, wound-healing gel, etc.

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 intended purpose of the product including the claims (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 mode of action through pharmacological, immunological or metabolic means, but which may be assisted by such means.

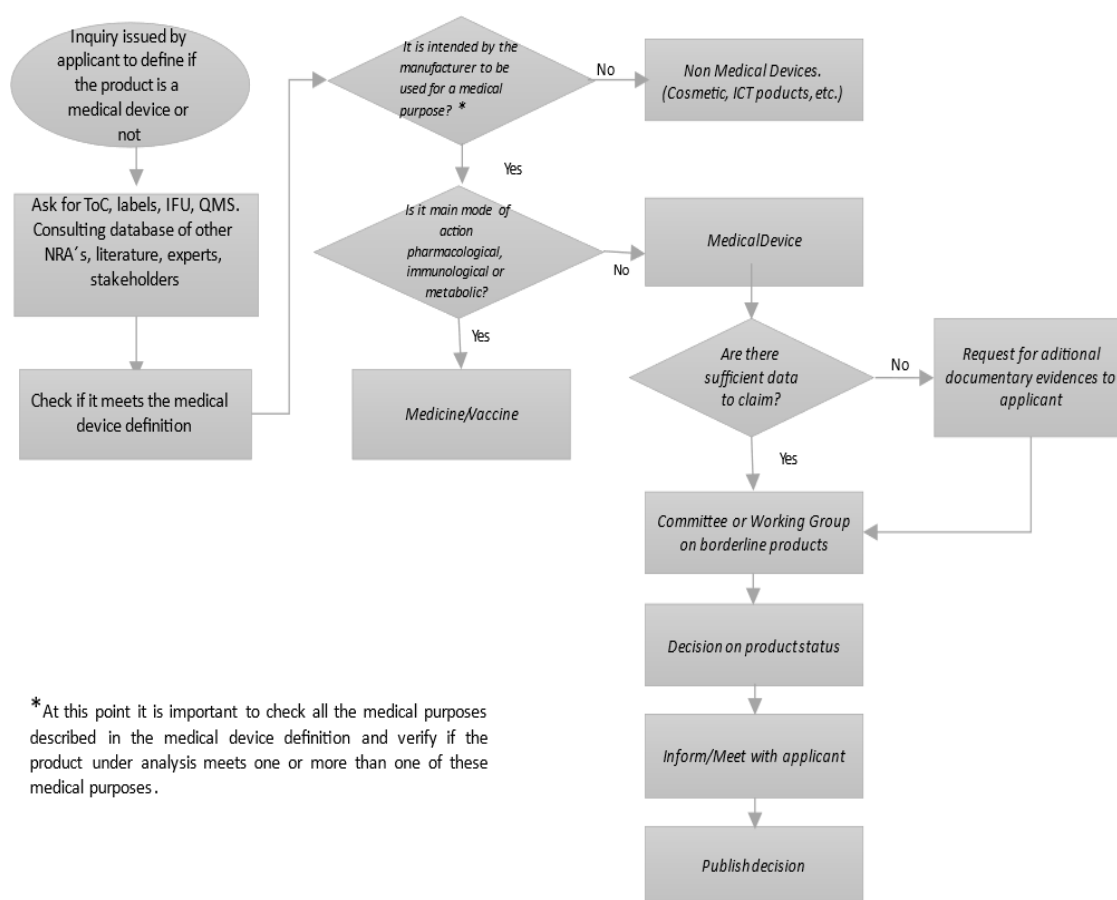
Whether there are any similar products on the local market and how they are being regulated.

This can be through consulting databases of regulatory authorities of other product categories

in the jurisdiction. If available, the applicant may submit product classification and evidence of marketing authorization from another regulatory authority.

It is important to note that not all equipment used in healthcare settings or used by a healthcare professional meet the definition of a medical device.

Fig. 5.7 Process for borderline products



5.5 Regulatory pathway for combination products

There is no internationally harmonized definition of a combination product.⁴² As such, the definition may vary in scope across regulatory jurisdictions, especially as the field continues to

⁴² 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), such that the distinctive nature of the drug component and device component is integrated in a singular product.

2608 evolve. A combination product is defined by many jurisdictions as a product comprised of two
2609 or more different types of medical products (i.e., a combination of a medicine, device, and/or
2610 biological product with one another). The medicine, devices, and biological products included
2611 in combination products are referred to as constituent parts of the combination product.⁴³
2612 Depending on the applicable regulations, the medicine constituent of a combination product
2613 may be a pharmaceutical, radiopharmaceutical, natural health product, biologic, cell, tissue,
2614 organ, gene therapy, or human blood and its components.

2615 Some jurisdictions have distinct definitions for a medicine and a biologic. As such, they also
2616 include in the definition of a combination product a medicine-device and a biologic-device.

2617 The evolution of medicines and medical technologies worldwide has created a broad spectrum
2618 of medicine-device combination products that range from relatively simple in nature to highly
2619 complex. These products have the potential to provide enhanced health benefits to patients, and
2620 it is in the public interest for regulatory authorities to ensure their safety, quality, and
2621 performance through appropriate regulatory controls.

2622 The regulatory requirements for combination products arise from the statutory and regulatory
2623 requirements applicable to medicine, devices, and biological products, which may have
2624 modified regulatory requirements when they are constituent parts of a combination product. At
2625 the same time, combination products comprise a distinct category of medical products that can
2626 be subject to specialized regulatory requirements, where appropriate. Specialized regulatory
2627 requirements for combination products generally are designed to address the risk-based
2628 considerations raised by the combined use on constituent parts which may include the overlaps
2629 and distinctions between the statutory and regulatory requirements applicable to the drug,
2630 device, and biological product constituent parts that comprise them. [77] [78] Globally,
2631 examples of medicinal product-device combination products include drug-eluting stents, pre-
2632 filled syringes, transdermal medicine patches, metered dose inhalers, heparin coated vascular
2633 catheters, or orthopaedic bone cement containing antibiotics.

2634 Considerations for regulating combination products.

2635 In the interest of consistency, transparency and predictability, the national regulatory authority
2636 should adopt and publish guidance on how to:

⁴³ 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>

- 1) determine what qualifies as a combination product;
- 2) determine an appropriate regulatory pathway; and
- 3) establish suitable pre- and post-authorization requirements.⁴⁴

It is recommended that the designation of a product that combines a medicine, a biological product or 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 streamlined 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 constituent and protecting the health and safety of the public. A streamlined regulatory pathway also helps avoid overlapping administrative requirements imposed by the NRA. Where a streamlined regulatory pathway is not possible, a clean distinction is required on the expectation for technical review of combination products by medicines and medical devices authorities.

This pathway determines both the type of application and the type of marketing authorization for the combination product: the criteria for review is different depending on whether the product is predominantly drug or device. The designation may be based on the primary mode of action [35] 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

⁴⁴ GMP requirements may be developed specifically for combination products e.g. <https://www.fda.gov/media/90425/download> or should follow the regulatory requirements of the constituent parts of the combination product.

2665 should be primarily subject to medical device regulations.⁴⁵ In some situations, elements of
2666 both medicine and device regulations may be applicable. [79] [80]

2667 In addition to designating the combination product into the appropriate regulatory pathway, the
2668 regulatory authority would also need to decide on the extent of requirements to apply to the
2669 ancillary constituents of a combination product. For example, the safety and performance of the
2670 medical device that contains a medicinal substance should be verified as a whole, as well as the
2671 identity, safety, quality and efficacy of the medicinal substance in its intended function in the
2672 specific combination product. [81]

2673 Regulators may also describe considerations and a process by which an applicant may obtain a
2674 designation decision from the regulatory authority. Where necessary, the process may allow for
2675 consultation with subject matter experts as well as with regulators from other product sectors
2676 and with the manufacturers or authorized representatives concerned. Regulators may also take
2677 into account determinations made by regulatory authorities of other jurisdictions. National
2678 authorities may take decisions on a case-by-case basis, taking account of all the characteristics
2679 of the product. A decision by the regulatory authority on the regulatory status of a product
2680 should always have the option of appeal in case the applicant does not agree with the decision.

2681 Reliance and recognition of medicine-device combination product may be a challenge due to
2682 the diversity and complexity of drug-device combination products, however it is not impossible.
2683 General reliance principles (*see Section 3.9*) should be applied. As there are currently no
2684 international harmonization guidance on combination products, therefor national regulatory
2685 authorities using reliance or recognition may consider which requirements in other benchmark
2686 jurisdictions would best serve their country's needs. Given the challenges with convergence
2687 and harmonization of combination products, medical devices stakeholders should continue in
2688 ongoing convergence and harmonization efforts.

2689 **5.6 Regulatory pathway for donated medical devices**

2690 Donations of medical devices and IVDs can be very helpful, may improve the efficiency of
2691 health facilities, may save costs of purchasing new medical devices and may make some
2692 diagnoses or therapies accessible to patients, especially in resource-limited settings. Donations

⁴⁵ 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/ghrf/final/sg1/technical-docs/ghrf-sg1-n15-2006-guidance-classification-060627.pdf>, accessed 17 April 2022

may be beneficial, but they can also pose health risks if the donated medical devices' safety and performance are not verified and if they do not correspond to the clinical needs, and skills of end-users and local technical staff. Another potential challenge is a lack of clear documentation, label and labelling of the donated medical device, as well as data regarding its state, its origin and technical history and the responsibilities of donors. [82]

Quality problems associated with donated medical devices have been reported in many countries [83] [84]. They include short or outdated expiry dates, defective medical devices⁴⁶ 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 of the donated medical devices. It may also create the impression that the medical devices are “substandard” or even waste that donors “dumped”⁴⁷ receiving countries [83] [85] [84] 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 an expressed request from the end-users, corresponding to a real clinical need;
- be authorized by regulatory authorities of the receiving country and/or meet current international safety standards;
- have all its parts and accessories;
- be accompanied by documentation in a language understood in the receiving setting;
- be adapted to the local context such as electrical power;
- match the operating and maintenance human resource, skills and capacities, and or be accompanied by training;
- be imported with a plan for its disposal in the receiving country after prior investigation and (if possible) identification of a disposal solution to be implemented once the medical device has reached end-of-life and can no longer be used.⁴⁸

⁴⁶ 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.

⁴⁷ ‘Dumping’ of obsolete equipment by high-income countries (HICs) has been described as ‘morally reprehensible’ (1)

⁴⁸ Upon arrival the medical devices specifically IVDs, the remaining shelf life should be reasonable and should allow the use of the entire donated lot according to the specifications set between donor and recipient. [17150-Manual for procurement of diagnostics.pdf \(who.int\)](#)

2720 Authorities from countries from which donations originate are urged to develop policies,
2721 regulations and guidelines on exportation of donated medical devices to other countries,
2722 particularly to prevent the export of waste or hazardous medical devices to LMICs.

2723 A national policy for donations in the receiving country is key to guide all parties involved so
2724 that they can develop their own institution-level operational donation guidelines and standard
2725 operating procedures by drawing inspiration from this document. Policy on donations should
2726 address three phases. The key features include:

- 2727 • Pre-donation phase: Assessment and identification potential recipient, familiarization
2728 of requirements, donation proposals, agreement between donor and recipient,
2729 application to obtain authorization to export/import donated medical devices,
2730 specifications and application to import/export;
- 2731 • Donation phase: Importation, document verification, physical inspection, sample
2732 collection (where applicable) and verification studies (where applicable);
- 2733 • Post-donation: Installation and commissioning, verification of functioning status and,
2734 post market surveillance⁴⁹. This implies feedback to the donor on performance and post
2735 market surveillance data.

2736

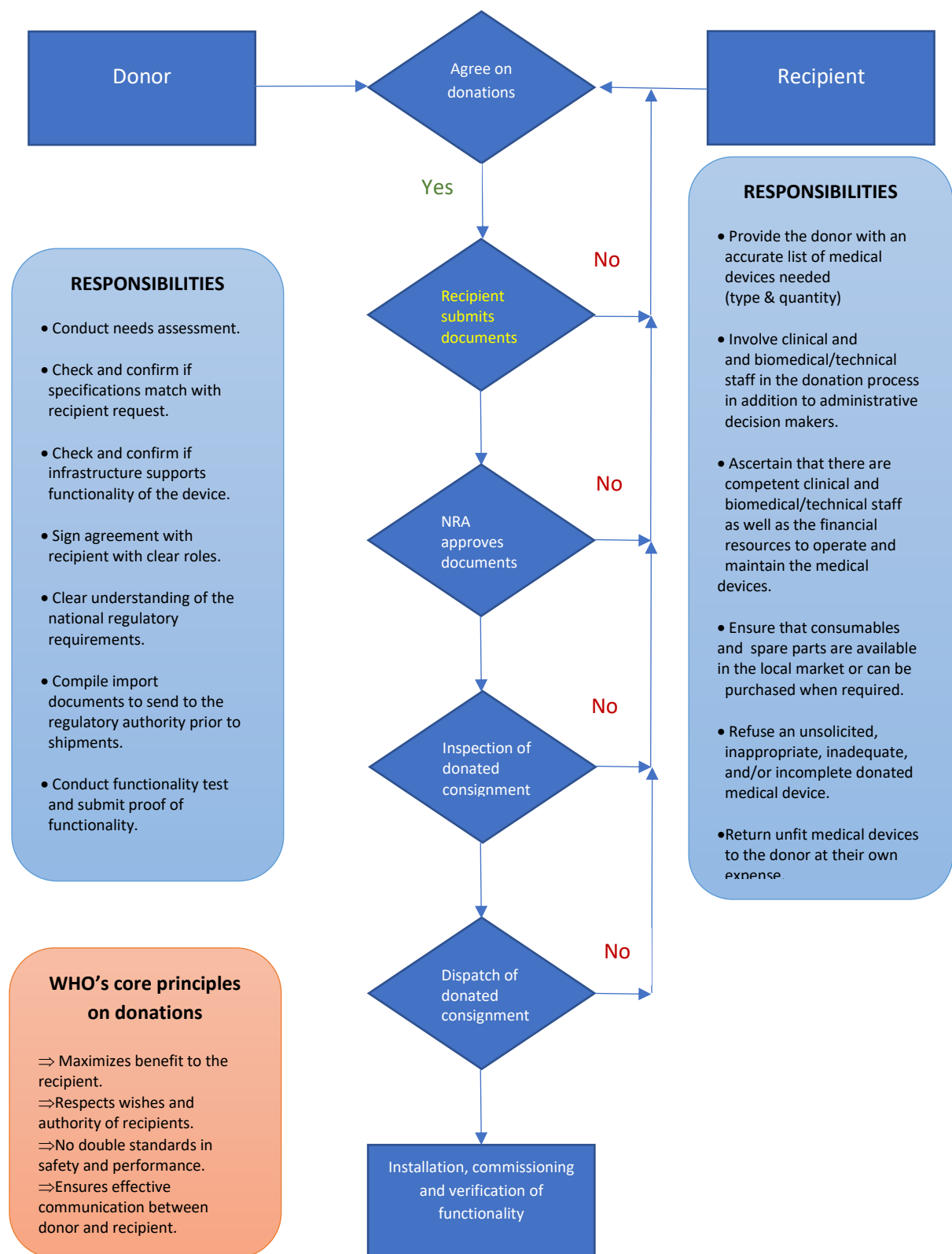
2737 To safeguard public health, medical devices imported as donations should comply with all
2738 regulatory requirements on safety, quality and performance and should not differ from those
2739 that are imported through a regular supply chain. It is the responsibility of the donor, a
2740 (charity) organization, a private person or a (medical devices) company in consultation with
2741 the recipient and vice versa, to ensure that medical devices intended to be donated are in
2742 compliance with the regulatory requirements of the receiving country. This also applies to
2743 donation *within* a jurisdiction. During emergency situations (natural disasters, pandemic etc.)
2744 public safety prevails and the recipient should take action according to guidance on donations.
2745 Regulatory authorities should therefore establish a mechanism to verify and authorize the
2746 importation of donated medical devices. Institutions that intend to donate devices should
2747 communicate (and even more closely during emergency situations) with the recipient to
2748 determine their needs, make relevant donations proposals and obtain their approval before the
2749 products are shipped. To avoid delay and additional expense, importation documents as well

⁴⁹ 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 preventive and corrective maintenance and lack of spare parts

2750 as supporting documents for the device's technical requirements must be submitted to the
2751 regulatory authority of the recipient's country for assessment and authorization decision by
2752 the authority before shipment of the consignment. These documents will typically include but
2753 are not limited to: a list of products to be donated, each product's (package) label, name and
2754 address of manufacturer(s) of the products, evidence that the products are
2755 approved/authorized in the donor's country or the manufacturer's QMS certificate (for high
2756 risk medical devices), expiry dates (if applicable), and a commitment letter that confirms the
2757 safety and performance of the devices to be donated along with all documents of proof of
2758 proper functioning. [85] All donors are required to familiarize themselves with the donation
2759 requirements in force in the receiving country before they decide to donate medical devices.
2760 Donations that do not comply with the requirements should be rejected and sent back to the
2761 donor at the donor's expense. Annex X shows typical regulatory pathway for donated medical
2762 devices.

2763

Fig. 5.8 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 lifecycle must be disposed of safely according to the manufacturer's 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 or e-label should include information on proper decontamination and disposal at the end of device life, if 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)⁵⁰. 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 standards⁵¹. The responsible regulatory authority, in coordination with other concerned governmental bodies,

⁵⁰ 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](https://trade.tanzania.go.tz/media/THE%20TANZANIA%20FOOD,%20DRUGS%20AND%20COSMETICS(%20medical%20device)%20regulation.pdf)

⁵¹ E.g. WEEE https://ec.europa.eu/environment/topics/waste-and-recycling/waste-electrical-and-electronic-equipment-weee_en

should establish criteria for replacement and decommissioning based on the manufacturer's recommendations. Consultation between the user and manufacturer is critical especially for high-technology and complicated products in order to decide the best way to dispose of them. 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 single use medical devices (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, only in extremely rare and dire situations (*see below*). 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. 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. [40] [86] [87] [88] 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,⁵² 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 [40] [87] [89] 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

⁵² <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)

traceability [90] [89]The original manufacturer should be identified in the technical dossier submitted to the regulatory authority. The label of the reprocessed SUMD does not necessarily 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. [91]

Reprocessing SUMDs: health care facilities

Regulatory requirements for reprocessing may equally apply to a healthcare facility fully reprocessing SUMDs for reuse within its own facility. 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.⁵³ If a healthcare facility is not able to meet these conditions, it shall refrain from reprocessing SUMDs. [92]

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 medical devices

Some medical devices on durable electromedical devices or mechanical medical devices, are meant to be reused many times over a long design life. In some cases, they may be subject to

⁵³ EU MDR 2017/745 <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN>

refurbishing by an organization or entity other than the original manufacturer to extend their service life, often for economic reasons.

Refurbishing can be described as a restoration of a device to a condition of safety and performance that is comparable to its condition when new. [39] 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 be 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. The NRA also states the role of the original equipment manufacturer to provide information to facilitate refurbishing. [93]

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 of such technologies include stand-alone software for medical purposes, networked systems, computational modelling and simulation, 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” [41]

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. [94] 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. A **Machine Learning-enabled Medical Device (MLMD) is a medical device that uses machine learning, in part or in whole, to achieve its intended medical purpose.** Unlike traditional medical devices where manufacturers generally modify devices by planning future changes and collecting data before performing a planned change request, the continuous learning MLMDs have the potential to be continuously exposed to new data such that their performance may change as they learn and adapt over time. [32] [95] [96]

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.⁵⁴ [97]

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:

⁵⁴ Certain jurisdictions apply the concept of software functions in their regulatory approaches with the option of multiple function products and “device functions” versus “other functions” when developing new regulatory strategy for these devices.

• 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 manufacture. [98] [95] 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. [99]

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". [50] [100]

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
Serious	III	II	I
Non-serious	II	I	I

2984

2985 While applicable to device software functions broadly, the IMDRF notes that, “A SaMD
 2986 manufacturer is expected to implement on-going lifecycle processes to thoroughly evaluate the
 2987 product’s performance in its intended market”. [8]

2988 It is important that all devices software functions demonstrate:

2989 • Scientific validity – refers to the extent to which the SaMD’s output (concept,
 2990 conclusion, measurements) is clinically accepted or well founded (existence of an established
 2991 scientific framework or body of evidence) that corresponds accurately in the real world to the
 2992 healthcare situation and condition identified in the SaMD definition statement;

2993 • Analytical validity – measures the ability of a SaMD to accurately and reliably
 2994 generate the intended technical output from the input data;

2995 • Clinical performance – the ability of a device to yield results that are correlated
 2996 with a particular clinical condition/physiological state in accordance with the target population
 2997 and intended user. [8]

2998

2999 The manufacturing of SaMD, which is a software-only product, is primarily based on
 3000 the development lifecycle activities often supported by the use of automated software
 3001 development tools. However, the principles in a QMS that provide structure and support to the
 3002 lifecycle processes and activities are still applicable and important to control the quality of
 3003 SaMD. [101] [102]

3004 Increasingly, medical devices that employ SaMD and SiMD including MLMD are being made
 3005 available in regions with more limited regulatory systems and capacity, often those with little
 3006 domestic manufacturing, that are primarily dependent on imported products. Data quality
 3007 assurance and data management should be taken into consideration as part of the manufacturer's
 3008 QMS. Requirements for evaluating dataset quality should be established. Training and test-data
 3009 sets are maintained independent of each other. Monitoring of the MLMD post-deployment
 3010 ensures continued safety and performance as potential variation of data in the real world may
 3011 challenge algorithm robustness and generalizability. [101]

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 including MLMDs 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. [63] [103] 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. [26]

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. 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 severity, and com-morbidities), 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 the MLMD is designed with appropriate human interaction and oversight of the intended use.

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 IEEE⁵⁵) 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 products⁵⁶. Falsified diagnostic tests, facemasks and COVID test kits and other products for the management of COVID. have been reported.^{57 58} The trade in SF medical devices is driven and motivated by

⁵⁵ <https://www.ieee.org>

⁵⁶ <https://www.who.int/teams/regulation-prequalification/incidents-and-SF/full-list-of-who-medical-product-alerts>, accessed 3 August 2021

⁵⁷ <https://www.cbp.gov/newsroom/local-media-release/cbp-baltimore-field-office-seizes-nearly-59000-counterfeit-covid-19>, accessed 3 August 2021.

⁵⁸ <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.

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 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 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 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:

(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.⁵⁹ [49]

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. [28] [29] However, countries may opt to classify CDx according to their classification rules for IVDs, and should develop regulatory requirements that reflect lessons learned to date and are appropriate for their own regulatory system.

Depending on how an NRA classifies CDx, a more complex scope of regulatory controls may apply to CDx. Regulation of CDx should enable clear pathways for authorization of clinical studies involving both products, as well as coordinated review and approval and may include guidance regarding roles and responsibilities of parties bringing a CDx and medicinal product to market. To ensure compliance with regulatory requirements, the following scope of regulatory controls should be implemented for CDx: authorization of clinical 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.⁶⁰

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.

⁵⁹ 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.

⁶⁰ 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>

In such cases there is no requirement for simultaneous filing or synchronized approval for the CDx and the medicinal products. The regulatory controls (premarket authorization and authorization of clinical performance studies) of the medicinal product and the device may 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, reliance may be used as an appropriate approach to ensure these controls are performed.

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.⁶¹ 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.⁶²

⁶¹ WHO is extending the prequalification of medical devices to other categories soon.

⁶² The criteria for IVDs eligible for prequalification are listed on the page through the link <https://extranet.who.int/pqweb/vitro-diagnostics/eligibility>

The WHO Prequalification of IVDs and male circumcision devices undertakes an assessment of individual IVDs and male circumcision devices through a standardized procedure aimed at determining whether the product meets WHO prequalification requirements. The process includes three components:

- review of the technical documentation (product dossier) ;
- 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 authorities⁶³ 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.⁶⁴

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)⁶⁵ was introduced to accelerate registration of medical products i.e. in member states through information sharing between WHO and national

⁶³ <https://www.who.int/initiatives/who-listed-authority-reg-authorities>

⁶⁴ <https://extranet.who.int/pqweb/vitro-diagnostics/vitro-diagnostics-lists>

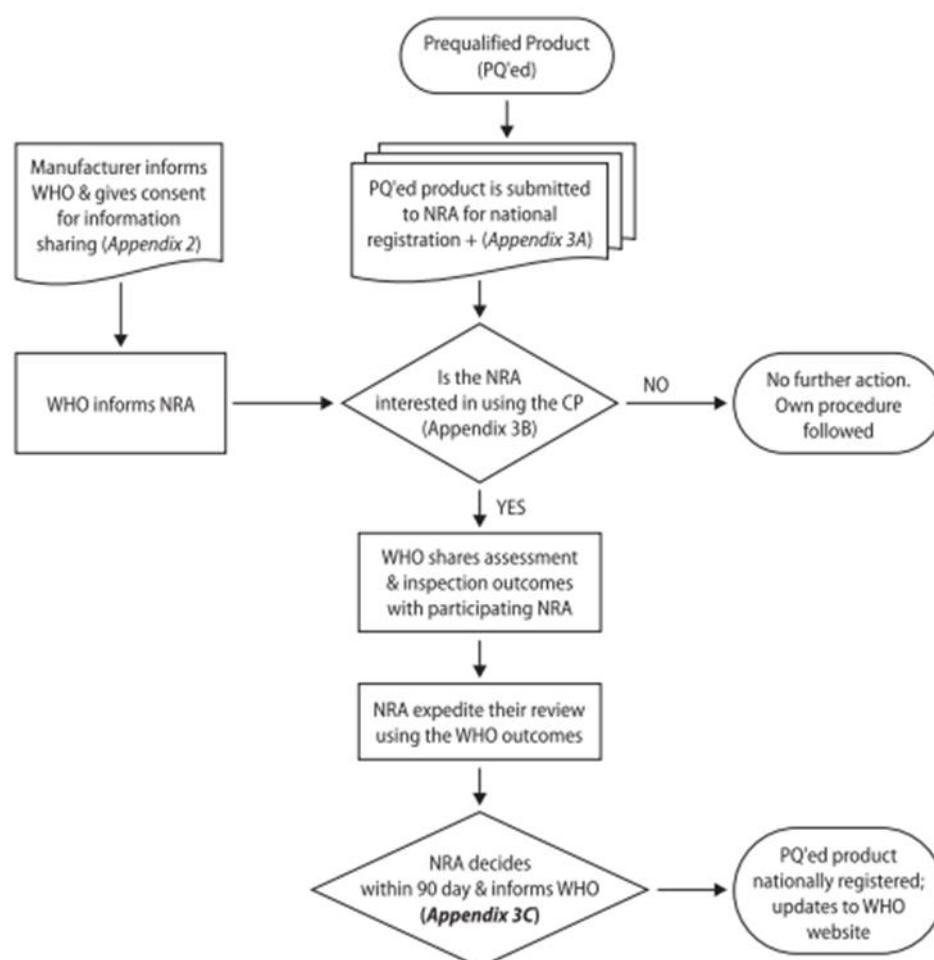
⁶⁵ Reference <https://apps.who.int/iris/handle/10665/341239>

regulatory authorities upon the consent of a manufacturer of the respective prequalified medical product. Collaborative Procedure for IVDs was successfully piloted in 2019 and was rolled out in May 2020 after approval of the guidelines on the Collaborative procedure between the WHO and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified IVDs by the Expert Committee on Biological Standardization, published through the WHO technical report series 1030.⁶⁶ The collaborative procedure for IVDs 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. IVDs 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.

⁶⁶ <https://apps.who.int/iris/handle/10665/341239>

Fig. 6.1 Steps in joining 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 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. [104]

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 stakeholders⁶⁷ 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. [105]

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 multidisciplinary team with experience in each of the stages of the life cycle of the medical device, by posing questions such as:

⁶⁷ 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/>

- 3269 1. How and who can be impacted by the regulatory controls, the implementation
3270 process, policy, etc.?
- 3271 2. Who has or may have influence over the regulatory controls, the implementation,
3272 process, policy, etc.?
- 3273 3. Who has or may have an interest in the regulatory controls the implementation,
3274 process, policy, etc., either being successful or unsuccessful? [106]

3275 Subsequently, a list should be made of the stakeholders according to the stage of the life cycle:
3276 the pre-market, placing on market and post-market stages.

3277 According to Schmeer [107] the multidisciplinary team must define the characteristics that each
3278 stakeholder must have, considering the following:

- 3279 • *Position and organization.*
- 3280 • *Internal/external: internal stakeholders work within the organization promoting or*
3281 *implementing the policy; all other stakeholders are external.*
- 3282 • *Knowledge of the policy: the exact level of knowledge that the actor has about the policy*
3283 *under analysis, and how each actor defines the policy in question.*
- 3284 • *Position: whether the stakeholder supports, opposes or is neutral with respect to the*
3285 *policy, which is key to establishing whether it will block the implementation of the*
3286 *policy.*
- 3287 • *Interest: the stakeholder's interest in the policy, or the advantages and disadvantages*
3288 *that implementing the policy may bring to the stakeholder or their organization.*
3289 *Determining stakeholders' vested interests helps policymakers and managers better*
3290 *understand their position and address their concerns.*
- 3291 • *Alliances: organizations that collaborate to support or oppose policy. Alliances can*
3292 *strengthen a weak stakeholder or provide a way to influence several stakeholders by*
3293 *dealing with a key stakeholder.*
- 3294 • *Resources: the number of resources (human, financial, technological, political and*
3295 *others) available to the actor and its capacity to mobilize them. This is an important*
3296 *characteristic that is summarized in a power indicator and will determine the level of*
3297 *strength with which the actor can support or oppose the policy.*
- 3298 • *Power: the stakeholder's ability to affect the implementation of health reform policy.*
- 3299 • *Leadership: the willingness to initiate, convene or lead an action for or against pro-*
3300 *health reform policy.*

Fig. 7.1 Diagram with proposed 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 [16] 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

3317 considered to be an integral part of regulatory quality. The stakeholders should be involved
3318 when deciding, developing, reviewing, amending or getting feedback on the following
3319 regulatory factors.

- 3320 • Legislation
- 3321 • Regulatory Strategy, Roadmap and policy
- 3322 • Status of the NRA
- 3323 • Regulations and Guidelines
- 3324 • Requirements for registration, licencing, and post market surveillance
- 3325 • Transition period for implementing specific regulatory processes
- 3326 • Regulatory fees and timelines
- 3327 • and other factors as may be determined.

3328 The importance of involving or informing the stakeholders on the above factors will lead into
3329 among other things;

- 3330 • Transparency and access to information: Stakeholder consultation can increase the
3331 transparency of the rule-making process because stakeholders have access to the
3332 process itself. Additionally, consultation enables policy makers to make use of the
3333 stakeholder's precious experience and knowledge. Stakeholder engagement in rule
3334 making can raise support for mentioned regulatory factors, as they feel connected to
3335 the policy-making process which therefore enhances alienation and connectivity.
- 3336 • Increased compliance and regulatory literacy: Engaging the stakeholders and striving
3337 for consensus can help to increase the social acceptance of mentioned regulatory
3338 factors. It can contribute to greater compliance and, therefore, reduce enforcement
3339 costs. Stakeholder engagements promotes stakeholder education on rule making, and
3340 provides stakeholders with a chance to increase their regulatory literacy.
- 3341 • Managing conflict and Legitimacy: Stakeholder consultation provides a mechanism to
3342 manage conflicts at an early stage. Greater stakeholder engagement has the potential to
3343 create a source of legitimacy and proof of successful governance.
- 3344 • Credibility, confidence and social cohesion: Stakeholder consultation can help to re-
3345 establish stakeholder trust and government credibility by means of creating new and
3346 better ways to communicate with stakeholders. Stakeholder consultation can promote
3347 stakeholder confidence which in turn contributes to greater social cohesion and buy-in
3348 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 a 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. [108]

As part of GRP 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 [104] [16] [37] [2] and international harmonization consensus guidance documents. [61] 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 risks⁶⁸ are mapped to the probability of a risk occurring [109] makes it possible to prioritize the identified objectives and the necessary actions to comply with the regulatory processes of the regulatory authority.

⁶⁸ ISO 31000: risk is the “effect of uncertainty on objectives”

Fig. 7.2 An example of the “probability – impact” matrix for risk ranking. [109]

	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

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. [55]

The road map must be updated on a regular basis.

3429

3430 *Table 7.3 Example of a high level road map*

Objective	Responsible	Outcome/ Indicator	Information source	Interested stakeholder	Communication	Timeline
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.	Meetings, workshops, internet	
Placing on the market						
Oversight: Registration of establishments	NRA	Number of establishment registrations	NRA	Importers, distributors.	Meetings, mailings, internet	
Oversight: Listing of medical devices	NRA	Number of medical devices	NRA	Importers, distributors, authorized persons	Meetings, mailings, internet	
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	Meetings, mailings, internet	
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	Internet, mailings, media	

3431

7.3 Implementation: regulatory capacity building

The 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. [56, 16, 56] 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 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 7.4 Core competencies for regulators [110]

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
Management of non-compliance	• Ability to select proportionate responses to non-compliance and potential non-compliance • Ability to communicate effectively with businesses that have failed to comply • 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

3484

3485 Exploring training opportunities.

3486

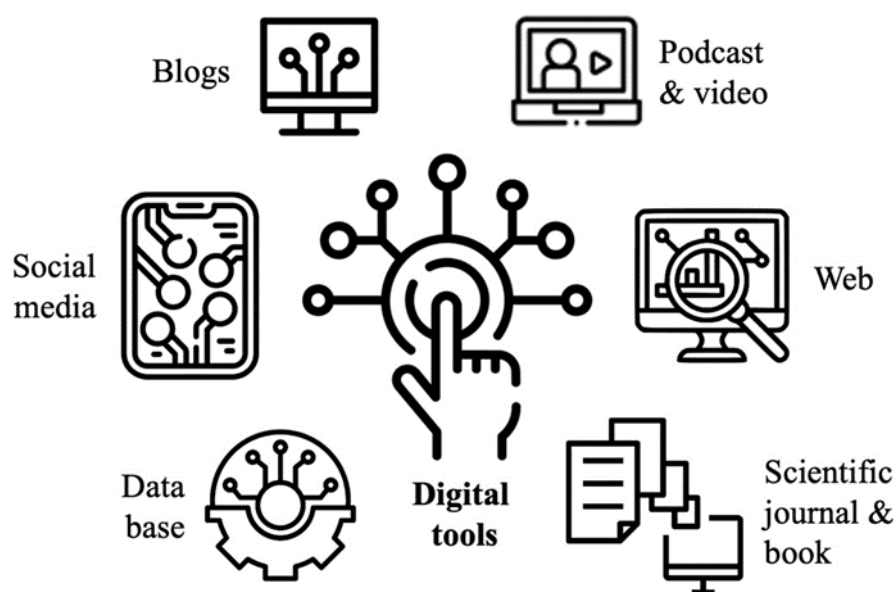
3487 Options for training are workshops, courses, webinars, worktables, and discussion, as well as
 3488 evaluations of regulatory processes that shows improvements to be made in a specific area.

3489 E- learning and digital information resources will facilitate access to updated training options.

3490 Examples of digital sources of information are shown in the diagram below

3491 *Fig. 7.5 Digital sources to strengthen regulatory capacities.*

3492



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, APEC RHSC;
- WHO-listed Authorities;

- 3513 • Internal portfolio of national and international experts;
- 3514 • Academic Institutions.

3515

3516 The creation of these instruments allows the entry of non-binding opinions from external
 3517 experts that can guide the actions of regulators within the NRA and serve as support to achieve
 3518 a greater understanding regarding medical devices including IVD, innovative or therapeutic
 3519 devices of recent creation.

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3521 Bibliography

3522

[“Regulatory system strengthening for medical products,” World Health Organization, 2014.

1 [Online]. Available: [https://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R20-](https://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R20-en.pdf?msckid=ec1ea049c16211ec8d2c08f65afcf2bb)

] en.pdf?msckid=ec1ea049c16211ec8d2c08f65afcf2bb. [Accessed April 2022].

[“Global Benchmarking Tool Revision VI GBT,” World Health Organization, 2021. [Online].

2 Available: <https://www.who.int/publications/i/item/9789240020245>. [Accessed April 2022].

]

[“Global Benchmarking Tool Revision VI + medical devices GBT+,” World Health Organization,

3 2022. [Online]. Available: [https://www.who.int/tools/global-benchmarking-tools/evaluation-of-](https://www.who.int/tools/global-benchmarking-tools/evaluation-of-national-regulatory-systems-of-medical-devices-in-vitro-diagnostics)

] national-regulatory-systems-of-medical-devices-in-vitro-diagnostics. [Accessed June 2022].

[“Definition of the terms “medical device” and “in vitro diagnostic (IVD) medical device”.,”

4 International Medical Device Regulators Forum, 2012. [Online]. Available:

] [http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n071-2012-definition-of-](http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n071-2012-definition-of-terms-120516.pdf)
 terms-120516.pdf. [Accessed August 2021].

[“Conformity assessment – vocabulary and general principles,” International Organization for

5 Standardization, 2020. [Online]. Available: <https://www.iso.org/standard/29316.html>. [Accessed

] April 2022].

[“Reportable events during pre-market clinical investigation,” International Medical Device

6 Regulators Forum, 2012. [Online]. Available: [http://www.imdrf.org/docs/ghtf/final/sg5/technical-](http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n5-2012-reportable-events-120810.pdf)

] docs/ghtf-sg5-n5-2012-reportable-events-120810.pdf. [Accessed September 2021].

[“Clinical Evidence for IVD medical devices – Key Definitions and Concepts,” International Medical

7 Device Regulators Forum, 2012. [Online]. Available:

]

<https://www.imdrf.org/sites/default/files/docs/gh tf/final/sg5/technical-docs/gh tf-sg5-n6-2012-clinical-evidence-ivd-medical-devices-121102.pdf>. [Accessed April 2022].

[“Software as a Medical Device (SaMD): Clinical Evaluation,” International Medical Device

8 Regulators Forum, 2017. [Online]. Available:

] https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-170921-samd-n41-clinical-evaluation_1.pdf. [Accessed June 2022].

[“Competence and Training Requirements for Regulatory Authority Assessors of Conformity

9 Assessment Bodies Conducting Medical Device Regulatory Reviews,” International Medical Device

] Regulators Forum, 2020. [Online]. Available: <http://imdrf.org/docs/imdrf/final/technical/imdrf-tech-wgn63.pdf>. [Accessed May 2022].

[“Definitions of the terms manufacturer, authorised representative, distributor and importer,”

1 International Medical Device Regulators Forum, 2009. [Online]. Available:

0 [http://www.imdrf.org/docs/gh tf/final/sg1/technical-docs/gh tf-sg1-n055-definition-terms-](http://www.imdrf.org/docs/gh tf/final/sg1/technical-docs/gh tf-sg1-n055-definition-terms-090326.pdf)

] 090326.pdf. [Accessed April 2020].

[“Clinical evaluation. IMDRF MDCE WG/N56FINAL:2019 (formerly GH TF/SG5/N2R8:2007),”

1 International Medical Device Regulators Forum, 2019. [Online]. Available:

1 [https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-191010-mdce-](https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-191010-mdce-n56.pdf)

] n56.pdf. [Accessed April 2022].

[“Clinical evidence, key definitions and concepts.IMDRF MDCE WG/N55 FINAL:2019 (formerly

1 GH TF/SG5/N1R8:2007),” International Medical Device Regulators Forum, 2019. [Online].

2 Available: <http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-191010-mdce-n55.pdf>.

] [Accessed August 2021].

[“Clinical investigation of medical devices for human subjects-Good clinical practice,” International

1 Organization for Standardization, 2020. [Online]. Available:

3 <https://www.iso.org/standard/71690.html>. [Accessed April 2022].

]

[“Managing conflict of Interest in the Public Sector,” Organisation for economic co-operation and

1 development , 2005. [Online]. Available: <https://www.oecd.org/gov/ethics/49107986.pdf#>.

4 [Accessed April 2022].

]

[“Principles of conformity assessment for medical devices. GH TF/SG1/N78:2012,” International

1 Medical Device Regulators Forum, 2012. [Online]. Available:

5 [http://www.imdrf.org/docs/gh tf/final/sg1/technical-docs/gh tf-sg1-n78-2012-conformity-](http://www.imdrf.org/docs/gh tf/final/sg1/technical-docs/gh tf-sg1-n78-2012-conformity-assessment-medical-devices-121102.pdf)

] assessment-medical-devices-121102.pdf. [Accessed July 2021].

[“Good regulatory practice. WHO Expert Committee on Specifications for Pharmaceutical

1 Preparations Fifty-fifth report, Annex 11, p 269-304,” World Health Organization, 2021. [Online].

6 Available: <https://apps.who.int/iris/bitstream/handle/10665/340323/9789240020900-eng.pdf>.
] [Accessed June 2022].

[“Quality management system – Medical Devices – Guidance on corrective action and preventive
1 action and related QMS processes,” International Medical Device Regulators Forum, 2010.
7 [Online]. Available: [http://www.imdrf.org/docs/ghrf/final/sg3/technical-docs/ghrf-sg3-n18-2010-](http://www.imdrf.org/docs/ghrf/final/sg3/technical-docs/ghrf-sg3-n18-2010-qms-guidance-on-corrective-preventative-action-101104.pdf)
] [qms-guidance-on-corrective-preventative-action-101104.pdf](http://www.imdrf.org/docs/ghrf/final/sg3/technical-docs/ghrf-sg3-n18-2010-qms-guidance-on-corrective-preventative-action-101104.pdf). [Accessed April 2022].

[“UDI guidance – unique device identification (UDI) of medical devices,” International Medical
1 Device Regulators Forum, 2013. [Online]. Available:
8 <http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-131209-udi-guidance-140901.pdf>.
] [Accessed September 2021].

[“Code of Federal Regulations Title 21,” US Food and Drug Administration, [Online]. Available:
1 <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=26.1>. [Accessed April
9 2022].
]

[“Substandard and falsified medical products,” World Health Organization, [Online]. Available:
2 <https://www.who.int/news-room/fact-sheets/detail/substandard-and-falsified-medical-products>.
0 [Accessed August 2021].
]

[“Medical devices: post-market surveillance: national competent authority report exchange
2 criteria and report form,” International Medical Device Regulators Forum, 2017. [Online].
1 Available: [https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-](https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-170921-pms-ncar-n14-r2.pdf)
] [170921-pms-ncar-n14-r2.pdf](https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-170921-pms-ncar-n14-r2.pdf). [Accessed 2022].

[“Medical Devices Post Market Surveillance: Content of Field Safety Notices,” International
2 Medical Device Regulators Forum, 2006. [Online]. Available:
2 [http://www.imdrf.org/docs/ghrf/final/sg2/technical-docs/ghrf-sg2-n57r8-2006-guidance-field-](http://www.imdrf.org/docs/ghrf/final/sg2/technical-docs/ghrf-sg2-n57r8-2006-guidance-field-safety-060627.pdf#search=%22FSN%22)
] [safety-060627.pdf#search=%22FSN%22](http://www.imdrf.org/docs/ghrf/final/sg2/technical-docs/ghrf-sg2-n57r8-2006-guidance-field-safety-060627.pdf#search=%22FSN%22). [Accessed 2022].

[“Good governance for medicines: model framework, updated,” World Health Organization, 2014.
2 [Online]. Available:
3 <https://apps.who.int/iris/handle/10665/129495?msclid=6345652ac15411ecbd54ac7b848ff7c5>.
] [Accessed April 2022].

[“Guide to the development and inclusion of aspects of safety in International Standards for
2 medical devices ISO/IEC Guide 63,” International Organization for Standardization, 2019. [Online].
4 Available:
] [https://isotc.iso.org/livelink/livelink/fetch/2000/2122/4230450/8389141/ISO_IEC_Guide_63_201](https://isotc.iso.org/livelink/livelink/fetch/2000/2122/4230450/8389141/ISO_IEC_Guide_63_2019%28E%29_-%20_Guide_to_the_development_and_inclusion_of_all_aspects_of_safety_in_International_Standards_for_medical_devices.pdf?nodeid=8387464&vernum=3)
9%28E%29_-%20_Guide_to_the_development_and_inclusion_of_all_aspects_of_safety_in_Inter
national_Standards_for_medical_devices.pdf?nodeid=8387464&vernum=3. [Accessed June
2022].

- [“Health technologies,” World Health Organization, 2007. [Online]. Available:
2 [https://www.who.int/publications/i/item/WHA60.29?msclkid=4329a3a3c15911ec943a015a72c1](https://www.who.int/publications/i/item/WHA60.29?msclkid=4329a3a3c15911ec943a015a72c157f47)
5 7f47. [Accessed June 2022].
]
- [“Guidance for post-market surveillance and market surveillance of medical devices, including in
2 vitro diagnostics,” World Health Organization, 2021. [Online]. Available:
6 <https://www.who.int/publications/i/item/9789240015319>. [Accessed August 2021].
]
- [“Principles of Labelling for Medical Devices and IVD Medical Devices,” International Medical
2 Device Regulators Forum, 2019. [Online]. Available:
7 <http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-190321-pl-md-ivd.pdf>,. [Accessed
] August 2021].
- [“Principles of medical devices classification. GHTF/SG1/N77:2012,” International Medical Device
2 Regulators Forum, 2012. [Online]. Available: [http://www.imdrf.org/docs/ghtf/final/sg1/technical-](http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n77-2012-principles-medical-devices-classification-121102.pdf)
8 [docs/ghtf-sg1-n77-2012-principles-medical-devices-classification-121102.pdf](http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n77-2012-principles-medical-devices-classification-121102.pdf). [Accessed October
] 2021].
- [“Principles of In Vitro Diagnostic (IVD) Medical Devices Classification,” International Medical
2 Device Regulators Forum, 2021. [Online]. Available:
9 <http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-wng64.pdf>. [Accessed July 2021].
]
- [“General requirements for the competence of testing and calibration laboratories,” International
3 Organization for Standardization, 2017. [Online]. Available:
0 <https://www.iso.org/standard/66912.html>. [Accessed April 2022].
]
- [“Registration of manufacturers and other parties and listing of medical devices,” International
3 Medical Device Regulators Forum, 2010. [Online]. Available:
1 [http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n065-listing-of-medical-](http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n065-listing-of-medical-devices-100827.pdf)
] [devices-100827.pdf](http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n065-listing-of-medical-devices-100827.pdf). [Accessed August 2021].
- [“Machine Learning-enabled Medical Devices—A subset of Artificial Intelligence-enabled Medical
3 Devices: Key Terms and Definitions,” International Medical Device Regulators Forum, 2021.
2 [Online]. Available: [https://www.imdrf.org/sites/default/files/2021-10/Machine%20Learning-](https://www.imdrf.org/sites/default/files/2021-10/Machine%20Learning-enabled%20Medical%20Devices%20-%20A%20subset%20of%20Artificial%20Intelligence-enabled%20Medical%20Devices%20-%20Key%20Terms%20and%20Definitions.pdf)
] [enabled%20Medical%20Devices%20-%20A%20subset%20of%20Artificial%20Intelligence-](https://www.imdrf.org/sites/default/files/2021-10/Machine%20Learning-enabled%20Medical%20Devices%20-%20A%20subset%20of%20Artificial%20Intelligence-enabled%20Medical%20Devices%20-%20Key%20Terms%20and%20Definitions.pdf)
enabled%20Medical%20Devices%20-%20Key%20Terms%20and%20Definitions.pdf. [Accessed
May 2022].

- [“Regulation of the European Parliament and the Council on medical devices,” European
3 Commission, 2017. [Online]. Available: [https://eur-lex.europa.eu/legal-](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745)
3 content/EN/TXT/PDF/?uri=CELEX:32017R0745. [Accessed October 2021].
]
- [“Personal Protective Equipment for Infection Control,” U.S. Food and Drug Administration, 2020.
3 [Online]. Available: [https://www.fda.gov/medical-devices/general-hospital-devices-and-](https://www.fda.gov/medical-devices/general-hospital-devices-and-supplies/personal-protective-equipment-infection-control#:~:text=Personal%20protective%20equipment%20%28PPE%29%20refers%20to%20protective%20clothing%2C,such%20as%20hospitals%2C%20doctor%27s%20)
4 supplies/personal-protective-equipment-infection-
] control#:~:text=Personal%20protective%20equipment%20%28PPE%29%20refers%20to%20protective%20clothing%2C,such%20as%20hospitals%2C%20doctor%27s%. [Accessed April 2022].
- [“Definition of Primary Mode of Action of a Combination Products,” US FDA, 2005. [Online].
3 Available: [https://www.federalregister.gov/documents/2005/08/25/05-16527/definition-of-](https://www.federalregister.gov/documents/2005/08/25/05-16527/definition-of-primary-mode-of-action-of-a-combination-product)
5 primary-mode-of-action-of-a-combination-product. [Accessed July 2022].
]
- [“Medical devices, quality management systems, requirements for regulatory purposes,”
3 International Organization for Standardization, 2016. [Online]. Available:
6 <https://www.iso.org/obp/ui/#iso:std:iso:13485:ed-3:v1:en>. [Accessed August 2021].
]
- [“Good reliance practice. WHO Expert Committee on Specifications for Pharmaceutical
3 Preparations Fifty-fifth report, Annex 11, p 237-267,” World Health Organization, 2021. [Online].
7 Available: <https://apps.who.int/iris/bitstream/handle/10665/340323/9789240020900-eng.pdf>.
] [Accessed June 2022].
- [“Medical laboratories — Requirements for quality and competence,” International Organization
3 for Standardization, 2012. [Online]. Available: <https://www.iso.org/standard/56115.html>.
8 [Accessed April 2022].
]
- [“Decommissioning medical devices,” World Health Organization, 2019. [Online]. Available:
3 <https://www.who.int/publications/i/item/9789241517041>. [Accessed May 2022].
9
]
- [“Reprocessing of medical devices,” European Commission, [Online]. Available:
4 [https://health.ec.europa.eu/medical-devices-topics-interest/reprocessing-medical-](https://health.ec.europa.eu/medical-devices-topics-interest/reprocessing-medical-devices_en#more-on-reprocessing-of-medical-devices)
0 devices_en#more-on-reprocessing-of-medical-devices. [Accessed August 2021].
]
- [IMDRF, “Software as a Medical Device (SaMD): Key Definitions,” International Medical Device
4 regulators forum, 2013. [Online]. Available:
1 [https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-131209-samd-](https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf)
] key-definitions-140901.pdf. [Accessed June 2022].

- [“Role of standards in the assessment of medical devices. Global Harmonization Task Force,”
4 International Medical Device Regulators Forum, 2008. [Online]. Available:
2 <http://www.imdrf.org/docs/ghrf/final/sg1/procedural-docs/ghrf-sg1-n044-2008-standards-in->
] [assessment-of-medical-devices-080305.pdf#search=%22role%20of%20standards%22](http://www.imdrf.org/docs/ghrf/final/sg1/procedural-docs/ghrf-sg1-n044-2008-standards-in-assessment-of-medical-devices-080305.pdf#search=%22role%20of%20standards%22).. [Accessed
July 2021].
- [“World Health Assembly,” World Health Organization, [Online]. Available:
4 <https://www.who.int/about/governance/world-health-assembly>. [Accessed June 2022].
3
]
- [“Medical devices: guidance document – classification of medical devices,” European Commission
4 DG Health and Consumer., 2010. [Online]. Available: MEDDEV 2.4/1 Rev. 9;
4 http://www.meddev.info/_documents/2_4_1_rev_9_classification_en.pdf. [Accessed August
] 2021].
- [“Guidance on the Risk-based Classification System for Non-In Vitro Diagnostic Devices (non-
4 IVDDs),” Health Canada, 2015. [Online]. Available: [https://www.canada.ca/en/health-](https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/guidance-document-guidance-risk-based-classification-system-non-vitro-diagnostic.html)
5 [canada/services/drugs-health-products/medical-devices/application-information/guidance-](https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/guidance-document-guidance-risk-based-classification-system-non-vitro-diagnostic.html)
] [documents/guidance-document-guidance-risk-based-classification-system-non-vitro-](https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/guidance-document-guidance-risk-based-classification-system-non-vitro-diagnostic.html)
diagnostic.html. [Accessed June 2022].
- [“Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices.,”
4 International Medical Device Regulators Forum, 2018. [Online]. Available:
6 [http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-181031-grrp-essential-principles-](http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-181031-grrp-essential-principles-n47.pdf)
] [n47.pdf](http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-181031-grrp-essential-principles-n47.pdf). [Accessed July 2021].
- [“Recognized essential principles of safety and performance.,” International Organization for
4 Standardization, 2016. [Online]. Available: <https://www.iso.org/standard/63939.html>. [Accessed
7 October 2021].
]
- [“Non-In Vitro Diagnostic Device Market Authorization Table of Contents (nIVDMAToC),”
4 International Medical Device Regulators Forum, 2019. [Online]. Available:
8 <http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-190321-nivd-dma-toc-n9.pdf>.
] [Accessed August 2021].
- [“Regulation of the European Parliament and the Council on in vitro diagnostic medical devices.,”
4 European Commission, 2017. [Online]. Available: [https://eur-lex.europa.eu/legal-](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0746&from=EN)
9 [content/EN/TXT/PDF/?uri=CELEX:32017R0746&from=EN](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0746&from=EN). [Accessed October 2021].
]
- [“SaMD Possible Framework for Risk Categorization and Corresponding Considerations.,”
5 International Medical Device Regulators Forum, 2014. [Online]. Available:

0 [https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-140918-samd-](https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-140918-samd-framework-risk-categorization-141013.pdf)
] [framework-risk-categorization-141013.pdf](https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-140918-samd-framework-risk-categorization-141013.pdf). [Accessed January 2022].

[“Clinical evidence for IVD medical devices-Scientific Validity Determination and Performance
5 Evaluation,” International Medical Device Regulators Forum, 2012. [Online]. Available:
1 [https://www.imdrf.org/sites/default/files/docs/ghrf/final/sg5/technical-docs/ghrf-sg5-n7-2012-](https://www.imdrf.org/sites/default/files/docs/ghrf/final/sg5/technical-docs/ghrf-sg5-n7-2012-scientific-validity-determination-evaluation-121102.pdf)
] [scientific-validity-determination-evaluation-121102.pdf](https://www.imdrf.org/sites/default/files/docs/ghrf/final/sg5/technical-docs/ghrf-sg5-n7-2012-scientific-validity-determination-evaluation-121102.pdf). [Accessed July 2022].

[“Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices,” International
5 Medical Device Regulators Forum, 2008. [Online]. Available:
2 [https://www.imdrf.org/sites/default/files/docs/ghrf/final/sg1/procedural-docs/ghrf-sg1-n046-](https://www.imdrf.org/sites/default/files/docs/ghrf/final/sg1/procedural-docs/ghrf-sg1-n046-2008-principles-of-ca-for-ivd-medical-devices-080731.pdf)
] [2008-principles-of-ca-for-ivd-medical-devices-080731.pdf](https://www.imdrf.org/sites/default/files/docs/ghrf/final/sg1/procedural-docs/ghrf-sg1-n046-2008-principles-of-ca-for-ivd-medical-devices-080731.pdf). [Accessed April 2022].

[“A risk based approach for the assessment of in vitro diagnostics (IVDs). Prequalification of
5 Diagnostics,” WHO, 2014. [Online]. Available:
3 [https://extranet.who.int/pqweb/sites/default/files/documents/140513_risk_based_assessment_](https://extranet.who.int/pqweb/sites/default/files/documents/140513_risk_based_assessment_approach_buffet.pdf)
] [approach_buffet.pdf](https://extranet.who.int/pqweb/sites/default/files/documents/140513_risk_based_assessment_approach_buffet.pdf). [Accessed October 2021].

[“In vitro diagnostic medical devices — Clinical performance studies using specimens from human
5 subjects— Good study practice,” ISO, 2019. [Online]. Available:
4 <https://www.iso.org/standard/69455.html>. [Accessed April 2022].
]

[“Road Map for Implementing and Monitoring Policy and Advocacy Interventions,” Health Policy
5 Project, [Online]. Available:
5 [http://www.healthpolicyproject.com/pubs/322_RoadMapforImplementingandMonitoringPPILED.](http://www.healthpolicyproject.com/pubs/322_RoadMapforImplementingandMonitoringPPILED.pdf)
] [pdf](http://www.healthpolicyproject.com/pubs/322_RoadMapforImplementingandMonitoringPPILED.pdf). [Accessed July 2022].

[[Online].
5
6
]

[“Towards a global competency framework for regulators of medical products,” World Health
5 Organization, 2019. [Online]. Available:
7 [https://apps.who.int/iris/bitstream/handle/10665/330894/DI331-6-9-](https://apps.who.int/iris/bitstream/handle/10665/330894/DI331-6-9-eng.pdf?sequence=1&isAllowed=y)
] [eng.pdf?sequence=1&isAllowed=y](https://apps.who.int/iris/bitstream/handle/10665/330894/DI331-6-9-eng.pdf?sequence=1&isAllowed=y). [Accessed July 2022].

[IMDRF, “Requirements for Medical Device Auditing Organizations for Regulatory Authority
5 Recognition: IMDRF/MDSAP WG/N3 FINAL:2016,” [Online].
8
]

[“Competence, training and conduct requirements for regulatory reviewers,” International
5 Medical Device Regulators Forum, [Online]. Available:

9 [https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-170316-](https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-170316-competence-conduct-reviewers.pdf)
] [competence-conduct-reviewers.pdf](https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-170316-competence-conduct-reviewers.pdf). [Accessed April 2022].

[“Conformity assessment — Requirements for the operation of various types of bodies performing
 6 inspection,” International Organization for Standardization, 2020. [Online]. Available:
 0 <https://www.iso.org/obp/ui/#iso:std:iso-iec:17020:ed-2:v1:en>. [Accessed May 2022].
]

[“IMDRF,” International Medical Device Regulators Forum, [Online]. Available:
 6 <https://www.imdrf.org/>.
 1
]

[“GHWP,” [Online]. Available: <http://www.ahwp.info/>.
 6
 2
]

[“ISO 14971:2019 Medical devices: application of risk management to medical devices,”
 6 International Organization for Standardization, 2019. [Online]. Available:
 3 <https://www.iso.org/standard/72704.html>. [Accessed July 2022].
]

[“Quality Management System-Medical Devices. Requirements for Distributors, Importers and
 6 Authorized Representatives.,” Asian Harmonization Working Party, 2016. [Online]. Available:
 4 [http://www.ahwp.info/sites/default/files/2017-
 \] 07/AHWP%20WG7%20F001%202014%20rev%20ISO%2013485%202016%20%20final%20\(1\)_R2.p
 df#:~:text=In%20some%20AHWP%20jurisdictions%2C%20distributors%20are%20required%20to,
 performs%20activities%20which%20are%20part%20of%20](http://www.ahwp.info/sites/default/files/2017-07/AHWP%20WG7%20F001%202014%20rev%20ISO%2013485%202016%20%20final%20(1)_R2.pdf#:~:text=In%20some%20AHWP%20jurisdictions%2C%20distributors%20are%20required%20to,performs%20activities%20which%20are%20part%20of%20). [Accessed April 2022].

[“99. MDCG 2019-6 Rev3. Questions and answers: Requirements relating to notified bodies.
 6 Revision 3 - October 2021 EU Requirements Notified Body (including testing facilities),” [Online].
 5 Available:
] [https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_qa_requirements_no
 tified_bodies_en.pdf](https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_qa_requirements_notified_bodies_en.pdf) . [Accessed 24 April 2022].

[“Nomenclature of medical devices,” World Health Organization, [Online]. Available:
 6 [https://www.who.int/teams/health-product-policy-and-standards/assistive-and-medical-
 6 technology/medical-devices/nomenclature](https://www.who.int/teams/health-product-policy-and-standards/assistive-and-medical-technology/medical-devices/nomenclature). [Accessed April 2022].
]

[“Webinar: WHO Nomenclature Mapping Feasibility Study,” [Online]. Available:
 6 [https://www.who.int/news-room/events/detail/2021/12/13/default-calendar/webinar-medical-
 devices-nomenclature-mapping](https://www.who.int/news-room/events/detail/2021/12/13/default-calendar/webinar-medical-devices-nomenclature-mapping). [Accessed April 20 2022].

7

]

[“Standardization of medical devices nomenclature International classification, coding and
6 nomenclature of medical devices. EB150/14 Add.1,” World Health Organization, 2021. [Online].
8 Available: https://apps.who.int/gb/ebwha/pdf_files/EB150/B150_14-en.pdf. [Accessed
] April 2022].

[“Standardization of medical devices nomenclature. EB148/13,” World Health Organization , 2021.
6 [Online]. Available: https://apps.who.int/gb/ebwha/pdf_files/EB148/B148_13-en.pdf. [Accessed
9 July 2022].

]

[“Unique Device Identification system (UDI system) Application Guide.,” International Medical
7 Device Regulators Forum, 2019. [Online]. Available: [https://www.imdrf.org/documents/unique-](https://www.imdrf.org/documents/unique-device-identification-system-udi-system-application-guide)
0 device-identification-system-udi-system-application-guide. [Accessed January 2022].

]

[“In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC),”
7 International Medical Device Regulators Forum, 2019. [Online]. Available:
1 <http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-190321-ivd-mdma-toc-n13.pdf>.
] [Accessed August 2021].

[“Medical Device Guidance. Guidance on Preparation of a Product Registration,” ASEAN, 2010.
7 [Online]. Available: [https://www.asean.org/wp-](https://www.asean.org/wp-content/uploads/images/archive/SnC/Guidance%20to%20ASEAN%20CSDT_Final_21%20Oct%202010.pdf#:~:text=The%20ASEAN%20CSDT%20document%20contains%20elements%20of%20the,medical%20device%20regulatory%20authorities%20of%20ASEAN%20member%20c)
2 content/uploads/images/archive/SnC/Guidance%20to%20ASEAN%20CSDT_Final_21%20Oct%2020
] 010.pdf#:~:text=The%20ASEAN%20CSDT%20document%20contains%20elements%20of%20the,
medical%20device%20regulatory%20authorities%20of%20ASEAN%20member%20c. [Accessed
July 2022].

[“Medical devices post-market surveillance: global guidance for adverse event reporting for
7 medical devices.,” International Medical Device Regulators Forum, 2006. [Online]. Available:
3 [https://www.imdrf.org/sites/default/files/docs/ghrf/final/sg2/technical-docs/ghrf-sg2-n54r8-](https://www.imdrf.org/sites/default/files/docs/ghrf/final/sg2/technical-docs/ghrf-sg2-n54r8-guidance-adverse-events-061130.pdf)
] guidance-adverse-events-061130.pdf. [Accessed April 2022].

[“Strengthening local production of medicines and other health technologies to improve access.,”
7 World Health Organization, 2021. [Online]. Available: [https://cdn.who.int/media/docs/default-](https://cdn.who.int/media/docs/default-source/medicines/local-production/a74_r6-resolution_published.pdf?sfvrsn=bffd3814_1&download=true)
4 source/medicines/local-production/a74_r6-
] resolution_published.pdf?sfvrsn=bffd3814_1&download=true. [Accessed July 2022].

[“Towards improving access to medical devices through local production. Report of a case study in
7 four sub-Saharan countries. Phase II,” World Health Organization, 2016. [Online]. Available:
5 <https://apps.who.int/iris/handle/10665/206545>. [Accessed April 2022].

]

- [WHO, “Local Production and Technology Transfer to Increase Access to Medical Devices. Addressing the barriers and challenges in low- and middle-income countries,” World Health Organization, 2012. [Online]. Available: <https://www.who.int/publications/i/item/9789241504546>. [Accessed April 2022].
- [“Principles of premarket pathways for combination products. Guidance for Industry and FDA Staff,” USFDA, 2022. [Online]. Available: <https://www.fda.gov/media/119958/download>. [Accessed April 3 2022].
- [“Combination products guidance documents,” USFDA, [Online]. Available: <https://www.fda.gov/combination-products/guidance-regulatory-information>. [Accessed June 8 2022].
- [“Interface between medicinal product and medical devices development - Update on EMA implementation of the new medical devices legislation,” European Commission, 2018. [Online]. Available: https://www.ema.europa.eu/en/documents/presentation/presentation-interface-between-medicinal-product-medical-devices-development-update-ema_en.pdf. [Accessed April 2022].
- [“Guidance on application of UDI rules to device-part of products referred to in Article 1(8), 1(9) and 1(10) of Regulation 745/2017 MDCG 2019-2,” European Commission, 2019. [Online]. Available: https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2019_2_gui_udi_dev_en.pdf. [Accessed April 2022].
- [“Early Development Considerations for Innovative Combination Products,” US FDA, 2006. [Online]. Available: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/early-development-considerations-innovative-combination-products#clinical>. [Accessed July 2022].
- [e. Bruce Compton, “Access to Medical Devices in Low-Income Countries: Addressing Sustainability Challenges in Medical Device Donations,” *National Academy of Medicine*, 2018.
- [H. T. B. E. F. Isobel H Marks, “Medical equipment donation in low- resource settings: a review of the literature and guidelines for surgery and anaesthesia in low-income and middle-income countries,” *BMJ Global Health*, 2019.
- [R. DzwonczykI, C. Rihall and R, “Medical equipment donations in Haiti: flaws in the donation process,” *Rev Panam Salud Publica*, pp. 345-8, 2012 Apr; 31 (4) .

4

]

[“WHO Medical device donations,” World Health Organization, 2011. [Online]. Available:

8 <https://www.who.int/publications/i/item/9789241501408>. [Accessed April 2022].

5

]

[Canadian Agency for Drugs and Technologies in Health (CADTH), “Reprocessing of Single-Use

8 Medical Devices: A 2015 Update,” 16 April 2016. [Online]. Available:

6 <https://www.cadth.ca/reprocessing-single-use-medical-devices-2015-update>. [Accessed August 2

] 2021].

[H. Canada, “Notice to Stakeholders - Health Canada's Regulatory Approach to Commercial

8 Reprocessing of Medical Devices Originally Labelled for Single Use, Health Canada, Ottawa,,,”

7 [Online].

]

[TGA, “Australian regulatory guidelines for medical devices (ARGMD), single use devices (SUMDs)

8 and the reuse of SUMDs. Woden ACT,” 2011. [Online]. Available:

8 <https://www.tga.gov.au/sites/default/files/devices-argmd-01.pdf>; [Accessed October 1 2021].

]

[“Reprocessing of Single Use Devices, Compliance Policy Guide,” U.S. Food and Drug

8 Administration, 2018. [Online]. Available: CPG Sec. 300.500 *Reprocessing of Single Use* Devices

9 | FDA. [Accessed 2022].

]

[USFDA, “Medical Device User Fee and Modernization Act of 2002, Validation Data in Premarket

9 Notification Submissions (510(k)s) for Reprocessed Single-Use Medical Devices,” 2004. [Online].

0 Available: [https://www.fda.gov/regulatory-information/search-fda-guidance-](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-device-user-fee-and-modernization-act-2002-validation-data-premarket-notification)

] [documents/medical-device-user-fee-and-modernization-act-2002-validation-data-premarket-](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-device-user-fee-and-modernization-act-2002-validation-data-premarket-notification)
notification. [Accessed April 2022].

[USFDA, “Labeling Recommendations for Single-Use Devices Reprocessed by Third Parties and

9 Hospitals,” 2001. [Online]. Available: [https://www.fda.gov/regulatory-information/search-fda-](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/labeling-recommendations-single-use-devices-reprocessed-third-parties-and-hospitals)

1 [guidance-documents/labeling-recommendations-single-use-devices-reprocessed-third-parties-](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/labeling-recommendations-single-use-devices-reprocessed-third-parties-and-hospitals)

] [and-hospitals](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/labeling-recommendations-single-use-devices-reprocessed-third-parties-and-hospitals). [Accessed April 3 2022].

[USFDA, “Frequently-Asked-Questions about the Reprocessing and Reuse of Single-Use Devices by

9 Third-Party and Hospital Reprocessors - Three Additional Questions,” 2003. [Online]. Available:

2 ([https://www.fda.gov/regulatory-information/search-fda-guidance-documents/frequently-asked-](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/frequently-asked-questions-about-reprocessing-and-reuse-single-use-devices-third-party-and-hospital-0)

] [questions-about-reprocessing-and-reuse-single-use-devices-third-party-and-hospital-0](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/frequently-asked-questions-about-reprocessing-and-reuse-single-use-devices-third-party-and-hospital-0). [Accessed
aPRIL 3 2022].

[“Remanufacturing and Servicing Medical Devices. Draft Guidance for Industry and Food and Drug Administration Staff,” U.S. Food and Drug Administration, 2021. [Online]. Available:
 9 <https://www.fda.gov/media/150141/download>. [Accessed July 2022].
 3
]

[WHO, “Generating evidence for artificial intelligence-based medical devices: a framework for
 9 training, validation and evaluation. World Health Organization,” [Online]. Available:
 4 <https://www.who.int/publications/i/item/9789240038462>. [Accessed July 2022].
]

[“Good Machine Learning Practice for Medical Device Development: Guiding Principles,” US FDA,
 9 2019. [Online]. Available: <https://www.fda.gov/media/153486/download>. [Accessed January
 5 2022].
]

[“Machine Learning-enabled Medical Devices: Key Terms and Definitions,” International Medical
 9 Device Regulators Forum, 2022. [Online]. Available:
 6 [https://www.imdrf.org/sites/default/files/2022-
 \] 05/IMDRF%20AIMD%20WG%20Final%20Document%20N67.pdf](https://www.imdrf.org/sites/default/files/2022-05/IMDRF%20AIMD%20WG%20Final%20Document%20N67.pdf). [Accessed July 2022].

[TGA, “Examples of regulated and unregulated software (excluded) software based medical
 9 devices,” 2020. [Online]. Available: [https://www.tga.gov.au/sites/default/files/examples-
 7 regulated-and-unregulated-software-excluded-software-based-medical-devices.pdf](https://www.tga.gov.au/sites/default/files/examples-regulated-and-unregulated-software-excluded-software-based-medical-devices.pdf). [Accessed
] July 2022].

[“IEC 82304-1:2016 Health Software – Part 1: General requirements for product safety,”
 9 International Electrotechnical Commission, 2016. [Online]. Available:
 8 <https://www.iso.org/standard/59543.html>. [Accessed July 2022].
]

[“Principles and Practices for Medical Device Cybersecurity,” International Medical Device
 9 Regulators Forum, 2020. [Online]. Available:
 9 [https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-200318-pp-mdc-
 \] n60.pdf](https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-200318-pp-mdc-n60.pdf). [Accessed June 2022].

[“Guidance document on Risk Categorisation of Software as a Medical Device,” Asian
 1 Harmonization Working Party, 2016. [Online]. Available:
 0 [http://www.ahwp.info/sites/default/files/2017-07/FINAL_AHWP-WG3-SaMD-
 0 002_Risk%20Categorisation%20of%20SaMD%20Final%20\(2\)%20SR.pdf?msclkid=aa15579bc3a711
 \] ec9f57f3368b54b07f](http://www.ahwp.info/sites/default/files/2017-07/FINAL_AHWP-WG3-SaMD-002_Risk%20Categorisation%20of%20SaMD%20Final%20(2)%20SR.pdf?msclkid=aa15579bc3a711ec9f57f3368b54b07f). [Accessed May 2022].

[IMDRF, “Software as a Medical Device (SaMD): Application of Quality a Quality Management
 1 System,” International Medical Device Regulators Forum, 2015. [Online]. Available:
 0

1 <https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-151002-samd->
] qms.pdf. [Accessed January 2022].

[“Notice concerning the Publication of Guidance Materials concerning Application for Marketing
1 Approval of Medical Device Software,” PMDA, 2016. [Online]. Available:

0 <https://www.pmda.go.jp/files/000231038.pdf>. [Accessed February 2022].

2

]

[“IEC 62304:2006/Amdt 1:2015 Medical device software—Software lifecycle processes,”

1 International Electrotechnical Commission, 2015. [Online]. Available:

0 <https://www.iso.org/standard/64686.html>. [Accessed July 2022].

3

]

[WHO, “Regulation of medical devices. A step-by-step guide,” 2016. [Online]. Available:

1 <https://applications.emro.who.int/dsaf/emropub>.

0

4

]

[“Universidad de Missouri. Stakeholder Analyses // Institutional Research & Quality

1 Improvement,” [Online]. Available: <https://irqi.missouri.edu/planning-and-improvement/tools->

0 and-techniques/stakeholder-analysis/. [Accessed March 14 2022].

5

]

[OECD, “Regulatory Policy in Colombia: Going beyond Administrative Simplification,” 2014.

1

0

6

]

[S. K., “Stakeholder Analysis Guidelines,” 1999. [Online]. Available:

1 <http://www.fx1234.com/workforcealliance/knowledge/toolkit/33.pdf> .

0

7

]

[“Guía metodológica para la implementación de la evaluación Ex Post de la regulación,” [Online].

1 Available:

0 https://colaboracion.dnp.gov.co/CDT/ModernizacionEstado/ERel/Guia_Metodol%C3%B3gica_Ev

8 aluaci%C3%B3n_ExPost.pdf. [Accessed July 2022].

]

[“Risk Management in Regulatory Frameworks: Towards a Better Management of Risks, United Nations Economic Commission for Europe, Geneva 2012.” United Nations, 2012. [Online]. Available: https://unece.org/DAM/trade/Publications/WP6_ECE_TRADE_390.pdf. [Accessed 9 March 2022].]

[“Core competencies for regulators,” 2016. [Online]. Available: <https://www.gov.uk/guidance/core-competencies-for-regulators>. [Accessed April 2022].]

[[Online].]

3523

3524

3525

3526

3527

3528

3529

3530

3531

3532

3533

3534

3535

3536

Further reading

- The GHTF Regulatory Model. Global Harmonization Task Force; 2011 (GHTF/AHWG-GRM/N1R13: 2011; <http://www.imdrf.org/docs/ghtf/final/steering-committee/technical-docs/ghtf-sc-n1r13-2011-ad-hoc-regulatory-model-110413.pdf>) accessed 20 April 2022.
- Playbook for implementation of medical device regulatory frameworks. Asian Harmonization Working Party; AHWPTC/OB/R001:2014. <http://www.ahwp.info/sites/default/files/AHWP%20Playbook%20for%20Implementation%20of%20MD%20Reg%20Framework.pdf>, accessed July 2022
- Regulation of medical devices. A step-by-step guide. WHO Regional Publications, Eastern Mediterranean Series 38. World Health Organization. https://applications.emro.who.int/dsaf/emropub_2016_EN_18962.pdf?ua=1&ua=1&ua=1, accessed July 2022
- International Medical Device Regulators Forum (IMDRF) [website] (<http://www.imdrf.org/>, accessed 20 April 2022).
- Medical devices. WHO/medical devices [website]. Geneva: World Health Organization (https://www.who.int/health-topics/medical-devices?msclkid=a197181cc09611ec9afe3d483743fdf3#tab=tab_1, accessed 20 April 2022.
- Medical devices, managing the mismatch. Geneva: World Health Organization; 2010 (http://apps.who.int/iris/bitstream/10665/44407/1/9789241564045_eng.pdf, accessed 20 April 2022).
- A model regulatory program for medical devices: an international guide. Washington (DC): Pan American Health Organization; 2001 (http://new.paho.org/hq/dmdocuments/2009/AmodelRegulatoryProgramforMedicalDevices_AnInternalGuide.pdf?ua=1, accessed 20 April 2022).
- National drug regulatory legislation: guiding principles for small drug regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-fifth report. Geneva: World Health Organization; 1999 (WHO Technical Report Series, No. 885: Annex 8; https://www.who.int/publications/i/item/WHO_TRS_885?msclkid=04150679c09711ec86b2bcfe6d6ed91d, accessed 20 April 2022

- Wong J, Tong RKY, editors. Handbook of medical devices regulatory affairs in Asia. Singapore: Pan Stanford; 2013.