

Annex 3

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

WHO Medical device technical series

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1. Introduction	183
2. Purpose and scope	184
3. Terminology	186
4. Definition, classification, essential principles and conformity assessment of medical devices	194
4.1 Definition of medical device and in vitro diagnostic medical device	194
4.2 Medical devices classification and classification rules	196
4.3 Principles of safety and performance	200
4.4 Specific considerations for regulation of IVDs	205
5. Enabling conditions for effective regulation of medical devices including IVDs	208
5.1 Legal requirements	208
5.2 Gap analysis of existing controls	210
5.3 Implementation plan	213
5.4 Monitoring implementation	214
5.5 National regulatory authority	214
5.6 Funding the regulatory system	215
5.7 Conflict of interest and impartiality	215
5.8 Regulatory competencies and resources	216
5.9 Reliance and recognition	218
6. Establishing a stepwise approach to regulating medical devices	222
6.1 Stepwise approach	222
6.2 Basic-level regulatory controls and their enforcement	223
6.3 Expanded-level regulatory controls and their enforcement	235
6.4 Stepwise approach – harmonization, reliance and recognition	259
7. Regulatory pathways	261
7.1 Regulatory pathways for pre-market conformity assessment of medical devices according to risk class	261
7.2 Regulatory pathways for pre-market conformity assessment of medical devices based on reliance	263

7.3	Regulatory pathway for emergency use authorization or derogation	265
7.4	Regulatory pathway for borderline products	268
7.5	Regulatory pathway for combination products	272
7.6	Regulatory pathway for donated medical devices	275
8	Additional topics	277
8.1	Disposal	277
8.2	Reprocessing of single-use medical devices	279
8.3	Refurbishing medical devices	281
8.4	New medical device technologies – software as a medical device (SaMD) and software in a medical device (SiMD)	282
8.5	Substandard and falsified medical devices	288
8.6	Companion diagnostics	289
8.7	WHO prequalification of IVDs and male circumcision devices	291
8.8	Collaborative registration procedure	292
8.9	Emergency use listing procedure	294
9.	Implementation	295
9.1	Implementation – involving stakeholders in the regulatory process	295
9.2	Implementation – developing a road map	299
9.3	Implementation – regulatory capacity-building	304
	Authors and acknowledgments	309
	References	310
Appendix 1	Hierarchy of regulation	323
Appendix 2	Further reading	325

Guidance documents published by the World Health Organization (WHO) are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs).

Abbreviations

AI	artificial intelligence
AMDF	Africa Medical Devices Forum
APEC RHSC	Asia Pacific Economic Cooperation Regulatory Harmonization Steering Committee
ASEAN	Association of Southeast Asian Nations
CAB	conformity assessment body
CDx	companion diagnostic in vitro medical device
CRP	collaborative registration procedure
CLSI	Clinical and Laboratory Standards Institute
EMDN	European Medical Device Nomenclature
EU	European Union
EUL	WHO emergency use listing (procedure)
FSCA	field safety corrective action(s)
FSN	field safety notice
GBT	WHO global benchmarking tool
GDP	good distribution practice
GHTF	Global Harmonization Task Force
GHWP	Global Harmonization Working Party (formerly Asian Harmonization Working Party – AHWP)
GMDN	Global Medical Device Nomenclature
GMRF	WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices
GRP	good regulatory practice(s)
HIBCC	Health Industry Business Communications Council
IEC	International Electrotechnical Commission
IEEE	Institute for Electrical and Electronics Engineers
IFU	instructions for use
IMDRF	International Medical Device Regulators Forum
ISO	International Organization for Standardization

IT	information technology (also ICT = information and communications technology)
IVD	in vitro diagnostic medical device
LMIC	low- and middle-income countries
ML	machine learning
MLMD	machine learning-enabled medical device
NRA	national regulatory authority
PI	product identifier
PPE	personal protective equipment
PQ	prequalification of medical products (also WHO PQ)
QMS	quality management system
SaMD	software as a medical device
SDO	standards development organization
SF	substandard and falsified (medical products)
SiMD	software in a medical device
STED	summary technical documentation
SUMD	single-use medical device
UDI	unique device identification
UDI-DI	UDI device identifier
UDI-PI	UDI production identifier
UDID	UDI database
UMDNS	Universal Medical Device Nomenclature System
USFDA	United States Food and Drug Administration

1. Introduction

The regulation of medical devices including in vitro diagnostics is critical in assuring their quality, safety and performance. In May 2014, the World Health Assembly adopted resolution WHA67.20 on regulatory system strengthening for medical products (1). This underscored the importance of effective regulatory systems as an essential component of health system strengthening and contributor to public health. WHO decided to develop guidance to support countries that had yet to develop and implement, or that were revising, their national regulatory controls for medical devices.

The previous WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices (GMRF) was published in 2017 in English and was then translated into French and Russian. Since then, the GMRF has served as a background document in WHO workshops on medical devices. It was also considered a standard during the integration of medical devices indicators into the development of the WHO global benchmarking tool (GBT), version VI (2, 3). Underpinning the GMRF are the WHO Good regulatory practices in the regulation of medical products (4) and WHO Good reliance practices in the regulation of medical products: high level principles and considerations (5), both published in 2021.

The field of medical devices is rapidly changing. Technologies are advancing with regard to their nature and complexity, and are increasingly being used in less traditional settings such as the home or remote care. In addition, new suppliers are entering the field, often without relevant experience or qualifications, and often with little local regulatory oversight. Jurisdictions are adapting their laws and regulations to ensure the improved and more timely regulation of medical devices in order to protect and promote public health. They have also had to quickly develop the increased regulatory capacities needed to implement those regulations. The COVID-19 pandemic clearly demonstrated the importance and urgency of ensuring equitable and timely access to safe, reliable and appropriate quality medical devices, including in vitro diagnostic medical devices (IVDs). It also highlighted the importance of integrity in domestic and international supply chains for medical devices and related personal protective equipment (PPE). As important as they are, vaccines are not effective if they cannot be safely delivered, while infections cannot be diagnosed and conditions treated without medical devices including IVDs.

The regulation of medical devices involves many stakeholders. The national regulatory authority (NRA) has the authority under laws adopted by legislators to establish and enforce regulatory requirements. Technology developers, manufacturers, and their authorized representatives, importers, distributors and outlets, are all part of supply chains in which the integrity and quality of medical devices must be ensured. Health care professionals,

laboratory staff, and patients or users, should be able to rely on the safety, quality and performance of medical devices, from the simplest to the most advanced, when used as intended. Users and health systems also have a stake in continuing innovation in medical technologies to diagnose and treat conditions for which there are unmet clinical needs.

The GMRF focuses on the responsibilities of the legislator and the NRA in establishing, implementing and enforcing the legal and regulatory framework. It also indirectly outlines the compliance obligations of industry stakeholders. The GMRF recognizes the importance of the health care system in providing feedback on the safety and performance of medical devices.

Many countries have neither the financial resources nor the technical expertise to move from a minimally regulated market directly to one with a comprehensive medical devices law and regulatory controls. The GMRF recommends instead a stepwise approach to regulating the quality, safety and performance of medical devices. This staged development starts from basic-level regulatory controls – such as the publication of the law, import controls, and resourcing the regulatory authority to take enforcement actions – then progresses to expanded-level regulatory controls – such as inspection of registered establishments and oversight of clinical investigations.

The resources available in any country for the regulatory control of medical devices (that is, people, funds, technology and facilities) are – and probably always will be – limited. Mechanisms for benefitting from the regulatory work of other jurisdictions can be established through reliance and recognition – practices well known both to countries with less developed regulatory systems and to mature jurisdictions.

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

2. Purpose and scope

This revised GMRF recommends guiding principles and harmonized definitions, and specifies the attributes of effective and efficient regulations to be embodied within binding and enforceable national laws. Its main elements are derived from international regulatory harmonization guidance documents developed by the Global Harmonization Task Force (GHTF) and its successor, the International Medical Device Regulators Forum (IMDRF), along with regional harmonization initiatives. Those guidance documents rely in turn upon a large body of recognized international consensus standards covering specific technical elements in the GMRF. As medical device technology continues to advance, as more experience is gained by regulators and industry, and as medical device regulation spreads

to more countries, this body of guidance will continue to evolve and support broader regulatory convergence.

The GMRF is written for the legislative and executive branches of government as they develop and establish national systems of medical devices regulation. This current version describes the roles and responsibilities of a country's regulatory authority in implementing and enforcing such regulations. The range of topics has been expanded to include regulatory pathways for the use of reliance and recognition, emergency use authorization, borderline products and donated medical devices, along with policies on medical devices testing and local production. It also addresses new topics such as software as a medical device (SaMD) and combination products, and provides implementation guidance on stakeholder involvement, developing a road map and regulatory capacity-building.

Despite the expanded range of topics covered in this revised GMRF, a number of medical device subjects have not been addressed, including orphan medical devices, off-label use of medical devices, in-house developed medical devices, 3D printing of medical devices and medical device registries. Updates in these areas will be provided in future revisions as more information becomes available.

Section 4 of this document recommends definitions of the terms “medical device” and “in vitro diagnostic medical device”. It describes how devices 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 have a quality management system (QMS) and demonstrate to an NRA that its medical device has been designed and manufactured to be safe and to perform as intended during its life-cycle.

Section 5 presents the principles of good regulatory practices (GRP) and enabling conditions for the effective regulation of medical devices. It then introduces essential tools for regulation, explaining the functions of the regulatory authority and the resources required. Increasingly, and as medical device regulation spreads to low- and middle-income countries (LMIC), the need for collaboration, information exchange and regional harmonization initiatives will grow. Few countries, even those with mature regulatory systems, will have the ability to perform all regulatory functions with their own resources. Reliance and recognition have become more important as ways to protect public health. As countries implement or revise regulatory systems, they should consider which elements must be done at national level and which may be done by relying upon and recognizing the work done by others.

Section 6 presents a stepwise approach to implementing and enforcing regulatory controls for medical devices, as the regulations progress from a basic

to an expanded level. It describes elements from which a country may choose according to its national priorities and challenges.

Section 7 describes the regulatory pathways for different risk classes of medical devices. It provides a clear overview of steps to be taken by the regulatory authority before a medical device may be placed on the market.

Section 8 covers 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 that they are appropriately addressed.

Section 9 presents topics that are relevant for the implementation of regulatory controls in an effective manner.

The current document outlines a general approach to the regulation of medical devices including IVDs but, as different countries will have different legal frameworks and policy priorities, it cannot provide country-specific guidance on implementation. While it does not offer detailed guidance on regulatory topics, it does provide references to numerous relevant documents where further information may be found. The GMRF is therefore not intended to be a detailed compendium of all relevant information but rather a “pointer” to guide readers to sources, while aiding understanding of such guidance in the context of a comprehensive regulatory framework. Nor does it directly detail the responsibilities of other stakeholders such as manufacturers, distributors, procurement agencies and health care professionals – all of whom have a role to play in assuring the quality, safety and performance of medical devices.

3. Terminology

The definitions given below apply to the terms as used in this WHO guidance document. These terms may have different meanings in other contexts.

Accessory to an IVD: an article intended specifically by its manufacturer to be used together with a particular IVD to enable or assist that device to be used in accordance with its intended use (6).

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 (6).

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 (7).

Adverse event and incident: in this document, the terms “adverse event” and “incident” are both used. The term adverse event denotes an event that impacts the patient while incident denotes events primarily attributed to the medical device. However, it should be noted that, depending on jurisdiction, the

terms adverse event (in the context of post-market surveillance) and incident can be used interchangeably. Further information on the precise meaning of these terms in the context of medical devices including in vitro medical devices can be found in the highly detailed terminological and related guidance provided by IMDRF (8–10) and WHO (11).

Analytical performance: the ability of an IVD to detect or measure a particular analyte (12).

Analytical validation: measures the ability of software as a medical device (SaMD) to accurately, reliably and precisely generate the intended technical output from the input data (13).

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 (14).

Audit: a 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 (7).

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 its behalf for specified tasks, with regard to the latter's obligations under that country or jurisdiction's legislation (15).

Certification: the term applied to third party attestation related to products, processes, systems or persons (7).

Clinical evaluation: 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 (16).

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 (see section 4.3 below). It should be cross-referenced to other relevant parts of the technical documentation that impact on its interpretation (17).

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 (18).

Clinical performance: the ability of an IVD to yield results that are correlated with a particular clinical condition/physiological state in accordance with target population and intended user. Clinical performance data can be derived from multiple sources such as clinical performance studies, literature or experience gained by routine diagnostic testing (12).

Clinical validation of SaMD: measures the ability of 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 (13).

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 (19).

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 (20).

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 (20).

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, 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 (4).

Corrective action: action to eliminate the cause of a detected non-conformity or other undesirable situation (21).

Declaration of conformity: a mandatory document that a manufacturer or authorized representative signs to declare that products comply with the regulatory requirements – amended from EU declaration of conformity (22).

Device identifier (DI): 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 **UDI database (UDID)** (23).

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 (15).

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 (24).

Falsified: denoting medical products that deliberately/fraudulently misrepresent their identity, composition or source (25).

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 (FSN)** (26).

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 (FSCA)** (27).

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 (28).

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 (29).

Harmonization (regulatory): a process whereby the technical guidelines of participating authorities in several countries are made uniform (4).

Hazard: a potential source of **harm** (29).

Health technologies: 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 (30).

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 (15).

Inspection: examination of an object of conformity assessment and determination of its conformity with detailed requirements or, on the basis of professional judgment, with general requirements (7).

Instructions for use (IFU): information provided by the manufacturer to inform the device user of the medical device's intended purpose and proper use, and any precautions to be taken (31).

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 other information provided by the manufacturer (32).

In vitro diagnostic medical device (IVD): 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 (6).

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 (31).

Labelling: the label, IFU and any other information that is related to identification, technical description, intended purpose and proper use of the medical device, but excluding shipping documents (31).

Laboratory: body that performs one or more of the following activities: testing, calibration and/or sampling associated with subsequent testing or

calibration. In the current document “laboratory activities” refer to these three activities (33).

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 (31).

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 (34).

Machine learning-enabled medical device (MLMD): a medical device that uses machine learning (ML), in part or in whole, to achieve its intended medical purpose (35).

Manufacturer: any natural or legal person with responsibility for the 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 themselves or on their 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 device(s) 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 (15).

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. *Note:* “relevant legislation” has been used here in place of “Union harmonisation legislation” in the EU source document (36).

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 physiological process;
- supporting or sustaining life;
- control of conception;
- cleaning, disinfection or sterilization 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 (37).

Medical product: any product including, but not limited to, finished pharmaceutical products, medical devices including in vitro diagnostic medical devices, and vaccines (38).

Performance evaluation of an IVD: assessment and analysis of data to establish or verify the scientific validity and analytical and, where applicable clinical, performance of an IVD (37).

Personal protective equipment (PPE): 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 laboratories (39).

Placing on the market: all controls applied by the NRA 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 NRA 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 for proactively collecting and reviewing experience gained from the use of 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 (36).

Pre-market controls: all controls applied by the NRA to the manufacturer and/or 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) (40).

Production identifier (PI): a numeric or alphanumeric code that identifies the unit of device production. The different types of PI include serial number, lot/batch number, SaMD version and manufacturing and/or expiration date (23).

Quality management system (QMS): 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 (41).

Recall: any measure aimed at achieving the return of a device that has already been made available to the end-user (36).

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 (5).

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 a regulatory authority to inform its own regulatory decisions (5).

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 (42).

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 (34).

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 (20).

Reliance: the act whereby a 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 (5).

Reprocessing: a process carried out on a used device in order to allow its safe re-use, including cleaning, disinfection, sterilization and related procedures,

as well as testing and restoring the technical and functional safety of the used device (43).

Risk: the combination of the probability of occurrence of harm and the severity of that harm (29).

Sameness: sameness of product means that two products have identical essential characteristics (that is, the product being submitted to the relying authority and the product approved by the reference regulatory authority should be essentially the same) (5).

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 health care situation and condition identified in the SaMD definition statement (13).

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.

Self-testing IVD: an IVD intended for use by a lay user who is responsible for collecting the data or specimen by themselves, relying solely on the instructions provided by the manufacturer. This use can also include performing the test and interpreting the results by themselves and on themselves (44).

Serious public health threat: any event type which results in imminent risk of death, serious injury or serious illness that requires prompt medical action. A serious injury is either:

- a life-threatening illness or injury;
- a permanent impairment of a body function or permanent damage to a body structure;
- a condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure (26).

Single-use medical device (SUMD) – also referred to in other documents as disposable devices or single-use devices (SUDs): 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 (31).

Software as a medical device (SaMD): software intended to be used for one or more medical purposes and that performs these purposes without being part of a hardware medical device (45).

Standard: a document established by consensus and approved by a recognized body that provides, for common and repeated use, rules, guidelines

or characteristics for activities or their results, aimed at the achievement of the optimum degree of order in a given context (46).

Substandard (also called “out of specification”): authorized medical products that fail to meet either their quality standards or specifications, or both (25).

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 QMS, that demonstrates that the medical device complies with the relevant principles of safety, performance and labelling specified through legislation (20).

Unique device identification (UDI): a series of numeric or alphanumeric characters that is created through a globally accepted device identification and coding standard. The UDI allows for the unambiguous identification of a specific medical device on the market and comprises the UDI device identifier (UDI-DI) and UDI production identifier (UDI-PI) (23).

UDI database (UDID): the UDID contains identifying information and other elements associated with the specific medical device (23).

User: the person, either professional or lay, who uses a medical device. The patient may be the user (31).

Withdrawal: any measure aimed at preventing a device in the supply chain from being further made available on the market (36).

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

4.1 Definition of medical device and in vitro diagnostic medical device³⁸

The GHTF developed definitions of the terms “medical device” and “in vitro diagnostic medical device”. Major jurisdictions have accepted the principles of these definitions. In the interest of international regulatory convergence and harmonization, it is recommended to promote their widespread use.

Medical device:³⁹ any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or

³⁸ “In vitro diagnostic medical device” is a synonym of “in vitro diagnostic” and is abbreviated as “IVD” in the current document.

³⁹ Notes from IMDRF definition (37): *Note 1:* For clarification purposes, in certain regulatory jurisdictions, devices for cosmetic/aesthetic purposes are also considered medical devices. *Note 2:* For clarification purposes, in certain regulatory jurisdictions, the commerce of devices incorporating human tissues is not allowed.

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 physiological process;
- supporting or sustaining life;
- control of conception;
- cleaning, disinfection or sterilization 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 (37).

In vitro diagnostic medical device (IVD):^{40, 41} 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 (6).

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 public health protection, these may be regulated as if they were medical devices. Examples include: PPE to avoid cross-infection;⁴² lead aprons to protect

⁴⁰ Notes from GHTF definition (6): *Note 1*: 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 IVD medical devices may be covered by other regulations.

⁴¹ See also the definition of an IVD in the ASEAN Medical Device Directive (<https://asean.org/wp-content/uploads/2016/06/22-September-2015-ASEAN-Medical-Device-Directive.pdf>, accessed 21 January 2023).

⁴² Whether a product is classified as PPE or not depends on the intended purpose of the product. If the product is intended exclusively for the protection of the user (the person wearing it) against one or more health and safety hazards, then it is considered to be PPE. Products intended to protect patients or users are considered to be medical devices. If a product is intended for both purposes, it is both a medical device and PPE (<https://www.johner-institute.com/articles/regulatory-affairs/and-more/marketing-personal-protective-equipment-ppe/>, accessed 23 January 2023), and may be subject to both regulatory regimes.

against radiation; some medical gases;⁴³ and implantable or other invasive products for cosmetic rather than medical purposes, such as dermal fillers (see section 7.4 below).

4.2 Medical devices classification and classification rules⁴⁴

The universe of medical devices is diverse with wide variations in potential severity of harm to the patient or user. This GMRF recommends that the NRA allocates its resources and imposes controls proportionate to the potential for harm associated with medical devices (32, 44).

Regulations should specify the way in which a manufacturer shall demonstrate conformity with safety, performance and quality requirements. Regulatory oversight should increase in line with the potential of a medical device to cause harm to a patient or user, and with the severity of that harm (that is, the risk it presents). The risk class of a medical device is determined by factors such as the level of invasiveness and duration of use in the body, and whether it incorporates medicines or human/animal tissues/cells. The risk class of an IVD is determined primarily by the impact of an incorrect result, either on the health of the individual or on public health. A classification system for medical devices and IVDs will guide the regulatory controls to be implemented for each device class.

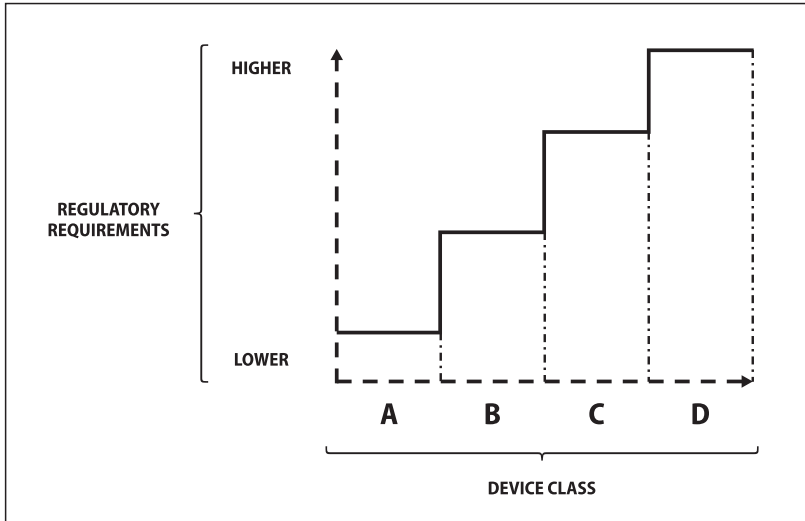
It is widely accepted that medical devices can be separated into groups or classes – typically the four classes A, B, C and D⁴⁵ – by applying a set of risk-based classification rules (32) and specifying separately the different conformity assessment procedures that should apply to each group of devices (Fig. 4.1). A medical device can generally be classified to one risk class. If, however, more than one risk class could apply, the higher class shall be applied.

⁴³ Gases intended for administration to a patient are regulated as medicinal products, whereas the associated administration equipment is regulated as a medical device(s). Some gases used for medical purposes may also be classified as medical device gases where they do not have a specific intended therapeutic outcome for the patient. Medical gases that are considered medical devices have a mechanical or physical action (that is, they do not act by immunological, metabolic or pharmacological means). Examples include gases for insufflation of the abdominal wall during surgery and liquid nitrogen for the removal of warts (<https://bcga.co.uk/topics/medical-gases/>, accessed 23 January 2023).

⁴⁴ The terms “medical devices classification” and “medical devices risk classification” are interchangeable.

⁴⁵ Some jurisdictions indicate the risk classes of medical devices differently such as: (a) Class I, II, III (for example, USFDA, <https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device>, accessed 23 January 2023); (b) Class I, IIa, IIb, III (for example, European Union, <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN>, Article 51, accessed 23 January 2023); and (c) Class I, II, III and IV (for example, Health Canada, <https://laws-lois.justice.gc.ca/eng/regulations/sor-98-282/fulltext.html>, Schedule 1 (section 6), accessed 23 January 2023, and NMPA, http://subsites.chinadaily.com.cn/nmpa/2019-10/11/c_415411.htm, accessed 23 January 2023).

Fig. 4.1

Impact of device classification on regulatory scrutiny

Note: as the regulatory requirements increase, so does the scrutiny by the NRA.

Source: reproduced from *Principles of medical devices classification* (32).

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

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

The 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 lay persons places specific requirements on the manufacturer to provide necessary ergonomic features to ensure a high likelihood of correct use and to provide information and instruction on 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 health care 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; and
- the impact of the result (true or false) on the individual and/or public health (44).

Classification may differ between jurisdictions. For example, rapid diagnostic tests may be classified as Class B in one jurisdiction but as Class C in a country where a disease is endemic.⁴⁶ In general, however, adherence to the internationally harmonized classification rules is encouraged.

Reclassification of medical devices may be appropriate as experience and knowledge about a device increase. The original classification of a device may be changed through reclassification to a higher risk class when available scientific evidence shows that existing controls are not sufficient to assure the safety and performance of the device. Reclassification to a lower risk class may be acceptable if the available scientific evidence shows that less rigorous controls would provide reasonable assurance of the safety and performance of the device.⁴⁷ General reclassification may be accomplished through revision of the classification rules if they are found to be deficient, thereby affecting a category of similar devices. Alternatively, an individual device may be reclassified by an evidence-based regulatory decision, without changing the general classification rules.

The NRA may develop explanatory guidance to help manufacturers apply the classification rules (47, 48).⁴⁸ While the manufacturer has the primary obligation to classify its medical device, its decision may be reviewed and challenged by the NRA. Table 4.1 shows illustrative examples of medical devices and their risk classes.

For IVDs, a four-class alphabetical system is recommended to identify the risk-based classes as shown in Table 4.2 (see section 4.4.1 below).

⁴⁶ Examples of such different classifications are available at: <https://extranet.who.int/pqweb/vitro-diagnostics/risk-based-classification-ivds>, accessed 23 January 2023.

⁴⁷ For example, see: <https://www.fda.gov/about-fda/cdrh-transparency/reclassification>, accessed 23 January 2023.

⁴⁸ For example, see: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN>, Annex VIII, accessed 23 January 2023.

Table 4.1
Examples of medical devices by risk class⁴⁹

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 (in which case, Class D); infusion pumps; neonatal incubators; therapeutic and diagnostic X-ray; lung ventilators; haemodialyzers; anaesthesia equipment.
D	High	Implantable cardioverter defibrillators; pacemakers; breast implants; cardiovascular stents; spinal needle.

Table 4.2
Examples of IVDs by risk class⁵⁰ (44)

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/AIDS diagnosis.

⁴⁹ The actual classification of each device will depend 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 Table 4.1. 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 into account its particular design and intended use.

⁵⁰ The actual classification of each IVD 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 IVDs that should conform to the rule have been provided in Table 4.2. However, it must be emphasized that a manufacturer of such an IVD should not rely on it appearing as an example but should instead make an independent decision on classification taking into account its particular design and intended use.

4.3 Principles of safety and performance

Regulations should specify that a medical device shall be safe and perform as intended by the manufacturer when placed on the market. IMDRF has established a list of essential principles of safety and performance for medical devices including IVDs (37, 49).⁵¹ These requirements have been widely adopted. The manufacturer shall demonstrate to the NRA that its product complies with these essential principles and has been designed and manufactured to be safe and perform as intended throughout a product's life-cycle when used in accordance with 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 (for example, implants, electrically powered devices or IVDs).

The general essential principles of safety and performance for medical devices that apply to all devices include the following:

- The design and production processes should ensure that a medical device when used according to its intended purpose and by its intended user (lay person or professional) 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 including IVDs 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 to eliminate 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 transport, packaging and storage are followed.

⁵¹ In the EU Regulations, 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, accessed 23 January 2023).

Beyond these general essential principles, further essential principles apply to some categories of medical devices, including principles related to the biocompatibility of materials, sterilization, electrical and mechanical safety, and software controls.

Ensuring and documenting that a medical device of any class conforms to all relevant essential principles (37) before placing it on the market is the responsibility of the manufacturer. The GMRF recommends that the NRA encourages manufacturers to apply recognized international consensus standards to demonstrate conformity 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 NRA, either before or after market introduction (see Table 4.3). The medical device regulations shall specify the extent of the NRA's pre-market evaluation of different classes of devices (20, 32, 44). While retaining responsibility for the decisions it makes, the NRA may appoint one or more conformity assessment bodies (CABs)⁵² to assist it in this task (see section 5.9 below).

The manufacturer is also responsible for ensuring that any changes to the intended purpose, design, specifications, labelling and/or manufacture of a device after its initial placing on the market also conform to the essential principles. Depending on the device classification, a further pre-market evaluation by the NRA of such changes may also be necessary.

4.3.1 Clinical evidence for non-IVD medical devices

Clinical evidence (17) 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". Manufacturers should provide information on both the inherent risks and the benefits associated with using the device, and on the uncertainty associated with how accurately they can define the risks and benefits. Clinical evidence is important for demonstrating compliance with these requirements. In deciding whether to authorize a medical

⁵² 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 pre-market 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 NRA may make its final decision on compliance. The CAB performs its evaluation under the oversight of the NRA and may be subject to periodic assessments by that authority.

device, the NRA 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 and in accordance with the characteristics of the population within the authority's jurisdiction.

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, (manufacturer's) reports of clinical experience, reports of post-market experience (if applicable) 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 data under the control of its QMS. The clinical evaluation report will become 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 (18).

4.3.2 Assessing conformity to the essential principles

To a large extent the quality, safety and performance of a medical device, regardless of its classification, 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 a QMS, coupled with comprehensive technical documentation showing that the device conforms to the essential principles. The degree of assessment of the QMS by the NRA or CAB depends on the medical device risk class (Table 4.3). Depending on the class of the medical device, the evidence of conformity may be subject to regulatory assessment by the NRA or CAB (7, 20).

Table 4.3

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 NRA should have confidence that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to market authorization.	The NRA should have confidence that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to market authorization.	The NRA should have confidence that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to market authorization.
Technical documentation ⁵³	Pre-market submission normally not requested.	Not normally reviewed pre-market. The NRA may request and conduct a pre-market or post-market review sufficient to determine conformity with essential principles.	The NRA will undertake a review sufficient to determine conformity with essential principles prior to the device being placed on the market.	The NRA 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 NRA.	Review and verify compliance with requirements by the NRA.	Review and verify compliance with requirements by the NRA.

⁵³ There are many terms used to describe a product's technical documentation. These 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 NRA by listing (34) before being placed on the market. They are generally not subject to pre-market on-site QMS audits or routinely audited by the NRA after being placed on the market. Although Class A medical devices do not require pre-market submission of technical documentation, the manufacturer is required to retain technical documentation, along with a declaration of conformity, demonstrating conformity with the essential principles. The NRA may, at its discretion, require submission of a summary of the technical documentation and/or other evidence of conformity with the regulatory requirements.

For medical devices in all classes, the NRA or CAB shall have access to 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 C and D devices, 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 Class B and C devices, the NRA can generally rely upon assessments and audits conducted by a reference regulatory authority or CAB, when such audits have been conducted. For Class D devices, the NRA or CAB may supplement such reliance with its own QMS inspections or audits. The depth of the QMS audit is at the discretion of the NRA or CAB. In all cases, the NRA should retain the power and discretion to conduct its own QMS audits.

For Class C and D medical devices, the pre-market 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) (50) on design and manufacturing, clinical evidence, product validation and verification, post-market surveillance plan and labelling. The NRA should specify whether summarized or detailed information should be submitted – for Class D devices, detailed information would typically be needed, while Class C devices may require only a summary of the technical information. For Class D devices, a QMS audit prior to market authorization is usually performed. The NRA could rely upon or recognize the work of a reference regulatory authority but the final responsibility lies with the NRA. For all classes of devices, the manufacturer should prepare, hold and be prepared to submit as required a declaration of conformity that the device complies fully with all regulatory requirements (20).

A regulatory pathway for medical devices according to risk class is described in section 7.1 below.

4.4 Specific considerations for regulation of IVDs

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

4.4.1 Classification of IVDs

As with other medical devices, risk-based classification provides a basis for allocating and prioritizing resources for the assessment of 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 proportionate 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 incorrect diagnosis, disease staging, monitoring or surveillance for both the patient being examined and the population in general. For example, an undiagnosed patient with a serious infectious disease could put a whole community at risk.

The classification of an IVD 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 health care 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) on the individual and/or public health.

An IMDRF classification scheme for IVDs has been published that includes classification rules based on risk to the individual and to public health (44). Software as a medical device (SaMD) that processes output from an IVD should be classified based on the SaMD's intended diagnostic purpose (51).

The IMDRF 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, with a higher risk class assigned where the IVD is the sole determinant in making a diagnosis.

4.4.2 Essential principles of safety and performance for IVDs

The IMDRF has developed additional essential principles that apply to IVDs (37). 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.

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;
- include requirements for performance evaluation of the IVD (whereas clinical evaluation is appropriate for non-IVD medical devices); and
- include the requirement that values assigned to calibrators and controls of IVDs should be traceable to available reference measurement procedures and/or available reference materials of a higher order.⁵⁴

⁵⁴ ISO 17511:2020: In vitro diagnostic medical devices – Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples. International Organization for Standardization. 2020 (available at: <https://www.iso.org/standard/69984.html>, accessed 24 January 2023).

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 (37).

4.4.3 Clinical evidence for IVDs

As with medical devices in general, the clinical performance for an IVD is all the information that supports the scientific validity and performance for its use as intended by the manufacturer (12, 17). 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 file (risk management plan, risk assessment, and risk management report) (50) and manufacturing information is needed to allow a manufacturer to demonstrate conformity with the essential principles (37, 52, 53). Clinical evidence includes analytical performance, clinical performance and clinical validity data.

A considerable amount of information on IVD performance is gained from analytical and clinical performance studies carried out on specimens obtained from human sources. 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 (18) is therefore not suited to IVDs. A standard specific to IVDs has been developed, namely ISO 20916: 2019: In vitro diagnostic medical devices – Clinical performance studies using specimens from human subjects – Good study practice (54).

4.4.4 Lot verification testing of IVDs

Countries may implement a system of risk-based lot verification of high-risk IVDs (Class D), either before distribution to users, post distribution or 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 pre-market 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 NRA may designate a national reference laboratory or other competent laboratory⁵⁵ that is assigned

⁵⁵ 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 – see ISO 15189:2022 (84) for medical laboratories or ISO 17025:2017 (33) for other testing laboratories.

the overall responsibility for coordinating and conducting lot verification testing on its behalf.

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

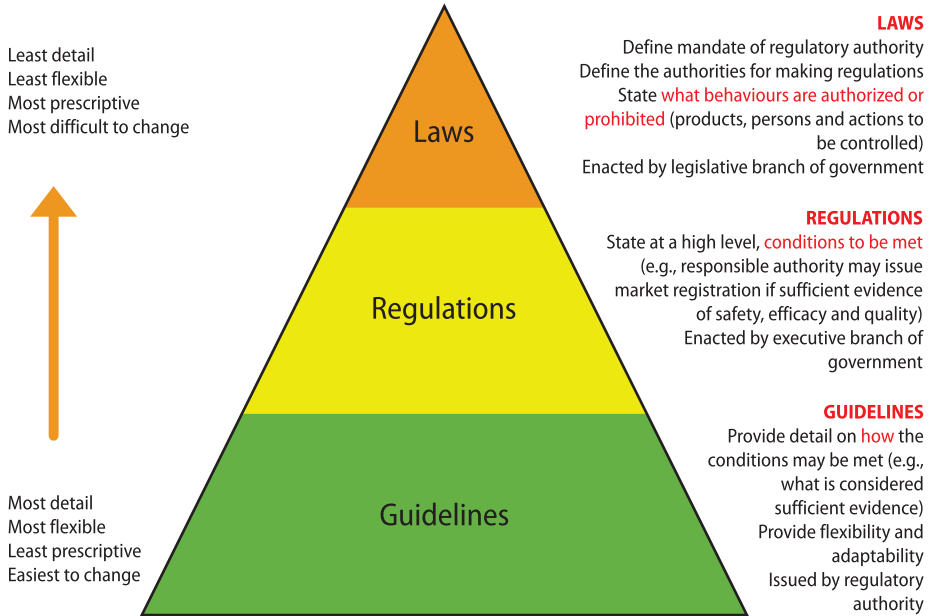
Public confidence in medical devices including IVDs requires effective and efficient regulation built upon a sound legal and policy foundation, as well as GRP. The general principles provided in WHO Good regulatory practices in the regulation of medical products (4) should be applied when establishing a new – or revising an existing – system for regulating medical devices including IVDs. These principles include:

- legality
- consistency
- independence
- impartiality
- proportionality
- flexibility
- clarity
- efficiency
- transparency
- science based.

5.1 Legal requirements

Medical device regulations must have a sound basis in law. There is no single approach to the legal foundation of a regulatory framework as this will depend upon the national constitution and existing general national legal and administrative systems within the country. A generalized architecture of such a framework is shown in Fig. 5.1.

Fig. 5.1

Architecture of a regulatory framework (4)

In all cases, 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 NRA and establish its enforcement powers to include restricting the circulation of, or withdrawing products from, the market, as well as imposing penalties. It should establish mechanisms for ensuring the accountability of the executive, judicial and legislative branches of government (see also Appendix 1 below). 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 regulatory authority is delegated to an independent administrative agency there should be clear lines of political oversight and accountability – for example through the Ministry of Health. It should be clear to stakeholders which authority is responsible for what. The legal framework

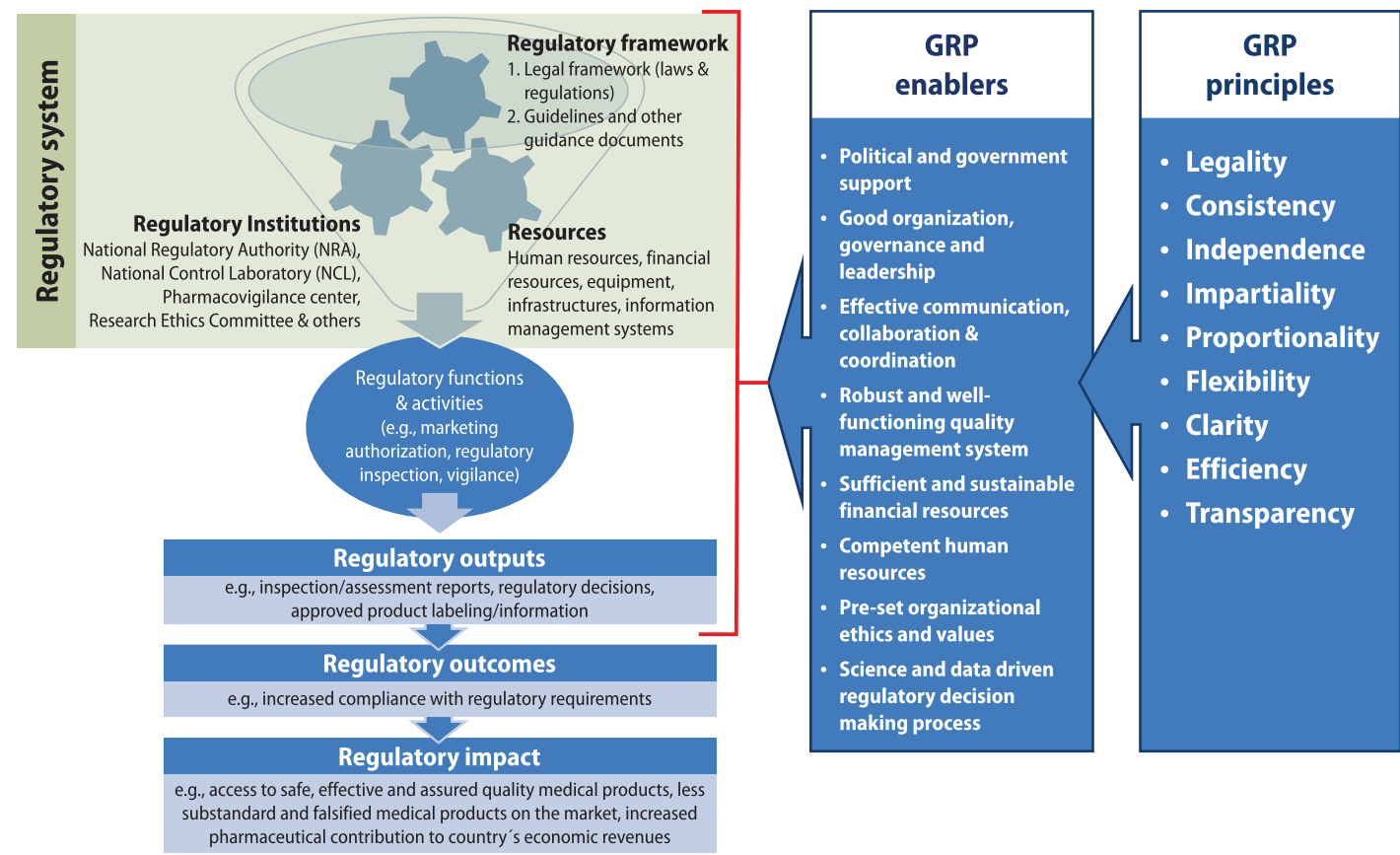
should also provide scope for administrative and enforcement discretion and authorize the NRA to implement the principles of reliance and recognition within a set timeline (see section 5.9 below). This provision will ensure that the NRA implements an effective reliance and recognition pathway and leverages decisions, including but not limited to assessments and regulatory decisions made by authorities in other jurisdictions, CABs and trusted institutions such as WHO. The law should allow the NRA to establish approval pathways for specific circumstances and categories of devices – for example, donated medical devices, investigational use only and research-only products (that is, not intended for diagnostic use), emergency use authorization and personal use medical devices including IVDs. It should also allow the NRA to respond to public health emergencies in an appropriate and timely manner. The law should accommodate a transition period when new regulatory requirements are established and when moving from basic-level to expanded-level regulatory controls as resources allow and as experience is gained.

The NRA should adhere to GRP such as creating opportunities to obtain and review public comments on proposals, assessing regulatory impacts, allowing reasonable transition periods for stakeholders, and adopting requirements that are proportionate and offer the least burdensome ways of achieving policy goals. Regular interactions with stakeholders, including patient organizations, consumer groups and academic professional associations are key in obtaining support and commitment. Stakeholders should be consulted on the development of new laws and regulations in order to receive feedback and guidance on the proposed laws and regulations (see section 9.1 below). The provisions of laws, regulations and guidelines should be as transparent, predictable and internally consistent as possible. Measures should also be non-discriminatory, so that all similarly situated parties are treated in the same way and decisions taken without regard to the national or international origin of a medical device or to the source of financing or the sector of the health care system in which it is used – for example, whether primary, secondary, tertiary or emergency health care, or whether delivered through a public, private or military facility. The principles and enablers of GRP and components of a regulatory system are shown in Fig. 5.2.

5.2 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 policy-makers 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 (4).

Fig. 5.2
Principles and enablers of GRP and components of a regulatory system (4)



The NRA should conduct a gap analysis and seek the views of interested parties, including patient, health care sector and industry representatives. The results of the analysis 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 such diseases. Box 5.1 lists the elements to be considered in a gap analysis (55).

Box 5.1

Non-exhaustive list of elements to be considered in a gap analysis of 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 the regulation of medical devices including IVDs?

Does the NRA observe GRP when drafting regulations?

Has a regulatory impact analysis been performed?

Is there a clear definition of the term “medical device” and does it match the definition recommended by this GMRF?⁵⁶

What are the public health risks that exist in the country, and can those risks be mitigated by the use of medical devices including IVDs?

Is there a system of market authorization?

Does the NRA use international standards and harmonization or benchmarks in its regulatory process?

Does the NRA use reliance or recognition mechanisms in its regulatory process?

Is there an NRA with clear powers and oversight for health products?

Does the regulator have the proper competencies required for effective implementation and enforcement?

Where there is a legal framework, is it enforced, and does the NRA have sufficient resources, expertise and funding to perform its duties?

Does the NRA adopt codes of conduct to be observed by all its staff 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?

⁵⁶ The definition used in this GMRF is taken from the GHTF (6) and from the IMDRF (37).

Box 5.1 *continued*

Are all relevant stakeholders adequately represented in consultations?

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 SF medical devices including IVDs?

Do existing laws and regulations comply with international good practices and treaty obligations?

5.3 Implementation plan

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

The elements subject to risk management for medical devices including IVDs can be derived from the WHO global benchmarking tool plus medical devices (GBT + medical devices) for evaluation of national regulatory systems of medical devices including in-vitro diagnostics – Revision VI (3) – namely, the national regulatory system, registration and market authorization, adverse event and incident reporting, market surveillance and control (including import controls), registration of establishments, regulatory inspections, laboratory testing and 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 on the market, in the distribution chain or in use will be handled – for example, through the allowing of well-defined exemptions and transition provisions. The NRA should hold meetings and publish guidance documents to ensure that medical device manufacturers, importers, distributors and purchasers are aware of their responsibilities, thereby avoiding disruption to the supply of medical devices including IVDs during the transition period.

A road map of actions, timelines and deliverables may be a useful tool during the implementation of the plan (see section 9.2 below) (56).

5.4 Monitoring implementation

At the time of development of the implementation plan, goals, regulatory processes, and performance-based indicators should be established to allow the progress of implementation to be assessed against a baseline of the current status of the legal framework for medical devices including IVDs. The WHO GBT + medical devices resource (3) provides the functions and indicators which enable regulatory authorities to establish their baseline in a systematic manner and to develop their institutional development plan. Progress should be reported to the legislature, parliament and the public, bearing in mind that the strategy, implementation plan and enforcement aims should be aligned with available resources. Such reports will help towards ensuring transparency and political accountability. They may also be used to evaluate the adequacy and use of resources. The progress made may also 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 (4). If expanded-level regulatory controls are established, it may be appropriate to include performance measures such as timely response by the NRA in monitoring manufacturer responses to quality defects and/or serious injury associated with the use of their medical devices including IVDs. Other, more general, performance measures may include the holding of 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 NRA and its use of resources is justified.

5.5 National regulatory authority

Implementation of the medical device law will require the appointment of an NRA with the power to exercise independent decision-making within the legal framework. The NRA may be established either within an existing government department (such as the Ministry of Health) or as an independent administrative agency accountable to a ministry. The governance structure and mechanisms of the NRA should be defined, and appropriate checks and balances established, along with 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 powers to the NRA to issue regulations (also known as statutory instruments or implementing acts), while specifying the substantive requirements and procedural regulations for implementing them. It should also provide the NRA with the necessary enforcement powers (see also Appendix 1 below).

While retaining in full the responsibilities placed upon it by the law, the NRA may designate CABs to assist it in carrying out some of its duties. In this

situation, the regulations will include the requirements for appointing a CAB, setting the scope of its responsibilities and monitoring its performance. Although the CAB may perform some evaluation functions under the supervision of the NRA, the final decisions and enforcement powers remain with the NRA.

5.6 Funding the regulatory system

Implementation of the regulatory system will require well-trained staff, infrastructure, facilities and information technology (IT). The resources allocated should be consistent with the responsibilities and activities mandated in the law, with a legal provision that allows for such resources to be increased as the regulatory system moves from basic-level to expanded-level regulatory 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 (that is, 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. Permission for the NRA to impose fees for selected activities should be established through the medical devices law. One way for the NRA to increase efficiency and thereby reduce costs is to take into account the outputs (for example, reports and decisions) of regulatory authorities in other jurisdictions in reaching its own decisions (that is, reliance or recognition) as appropriate.

The costs of doing business – both direct costs (for example, user fees) and indirect costs (for example, 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 to the potential of a given market, or if regulatory requirements are not harmonized with those of other countries, manufacturers and importers may be discouraged from offering their products, which may in turn impede the achieving of national public health goals.

5.7 Conflict of interest and impartiality

Public confidence in the integrity of the NRA and its actions is essential. The authority and its staff, advisory committees and CABs should be seen to act consistently, impartially and transparently. Any actual or perceived lack of impartiality with regard to regulatory decisions could lead to unfair and unjust competitive advantages for parties in the medical device sector, as well as a lack of confidence in the medical devices including IVDs supplied to the market. This can be prevented by the adoption of, 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 NRA.

Staff must avoid situations where there may be a conflict, real or perceived, between their private interests and the public good. The NRA should establish a conflict-of-interest policy, avoid improper bias, be transparent in funding and base its decision-making on scientific criteria. Leaders within the organization must set the tone through the good example of their own conduct (4).

5.8 Regulatory competencies and resources

Regulating medical devices including IVDs effectively and efficiently and according to GRP requires appropriate individual expertise, reinforced by the institutional capacity of the NRA. General competencies for regulatory professionals include an understanding of public health principles, analytical and communication skills, information handling, and effective intervention and crisis management skills. These competencies are needed even where the NRA relies on or recognizes the regulatory decisions of reference regulatory authorities. Additional specific competencies include essential knowledge of the regulatory system for medical devices including IVDs, and awareness and understanding of the responsibilities of the NRA, the concepts of international standards and harmonization, and the importance of QMS, along with an understanding of a range of different device technologies and their applications.

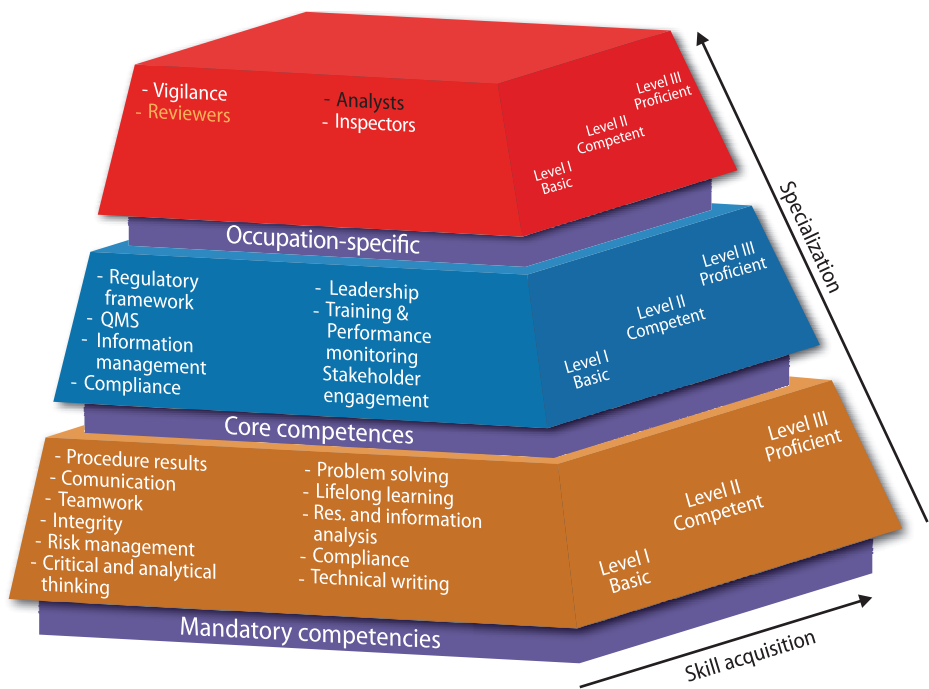
For each stage of implementing the regulatory system, a sufficient transition period should be established. A transition period allows the NRA to ensure that it has sufficient qualified and trained staff, appropriate resources and adequate information systems for its increased responsibilities and functions. Any transition period should aim to avoid disruption to the supply of medical devices needed to treat or diagnose patients. The NRA will also require legal support to interpret its responsibilities under the law, particularly with respect to its monitoring, enforcement and safeguarding activities. In addition, IT and administrative resources will be required.

Basic-level regulatory controls will require general technical expertise on medical devices including IVDs – whereas expanded-level regulatory controls will require some regulatory staff to have more specific technical expertise in particular fields (57). As the regulatory system and its implementation become more comprehensive, additional resources will be required (58, 59). All regulatory staff within the NRA should have mandatory and core competencies appropriate for their level. As shown in Fig. 5.3, the WHO global competency framework (60) is modelled as follows: (a) mandatory competencies; (b) core competencies; and (c) occupation-specific competencies.

In view of the importance of the manufacturer's QMS, the NRA 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 NRA to provide appropriate oversight

and control throughout the life-cycle of the medical device (58). When elements of the regulatory framework are delegated to CABs (see section 6.3.1.2 below), authorities should have competent regulatory staff to assess compliance by the CAB with the relevant requirements (14, 61).

Fig. 5.3
The WHO global competency framework (60)



Given the diverse nature of medical devices including IVDs, the NRA should over time, and according to the priorities in regulating specific medical devices including IVDs, recruit technical staff with a variety of appropriate expertise (58, 59). Ensuring a career path, professional development and recognition of the value of regulating medical devices including IVDs as a profession, may all be important in recruiting and retaining staff.

Even for advanced or well-resourced regulatory authorities it is impractical to have all the required expertise in-house. Instead, an advisory committee(s) can be created consisting of independent experts in a variety of fields to advise in specific technical areas. The process of nominating advisers and creating advisory committees should be transparent and be made public. Particular attention must be paid to ensuring the impartiality of members,

avoidance of potential or actual conflicts of interest, and establishing procedures for the exchange of confidential information. The NRA remains responsible for the decision even when based on the advice of advisers. Performing an assessment of the NRA's current regulatory competencies and capacities will provide insights into any gaps in technical knowledge, the regulatory system and related functions.

Further information can be obtained from the WHO global benchmarking tool (2) and from published IMDRF guidance on good regulatory review practices (59).

Based on the findings of the gap analysis, both the initial and ongoing training of regulators for medical devices including IVDs should be implemented according to a training plan (see section 9.3 below).

5.9 Reliance and recognition

Reliance, recognition and abridged assessment through WHO prequalification⁵⁷ are facilitated by international regulatory convergence – a process of gradual alignment of regulatory requirements in different countries, regions or globally (5).

The law should establish to what extent the NRA may reasonably use the assessment outcomes of a reference regulatory authority, a CAB or trusted institution such as WHO when assessing whether a device conforms to national requirements. When regulations do not make explicit provision for the application of reliance, it may be adopted through interpretation of existing regulations – for example, during emergency situations. Reliance can be implemented through policy change, as long as it is broadly consistent with national legislation. If the application of reliance is prohibited, revision of the legislation to enable reliance 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 other authoritative information available from other authorities and institutions. For example, where a reference regulatory authority authorizes a medical device to be placed on its own market, the relying NRA may use this information, possibly supplemented with information from the manufacturer, to reach its own decision. When relying on a reference regulatory authority, a relying NRA should only request additional information from the manufacturer 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 adverse event and incident reports, and for other post-authorization activities

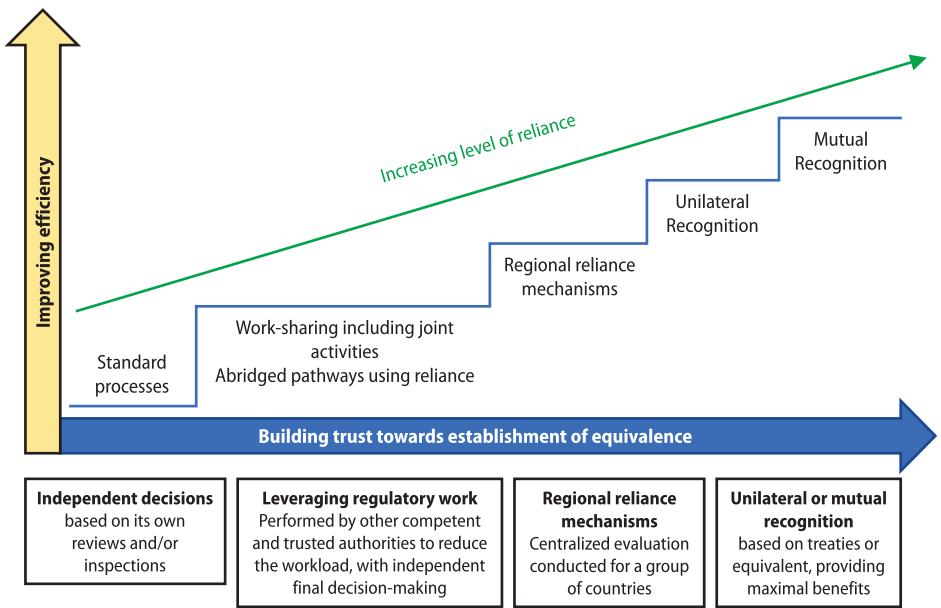
⁵⁷ <https://extranet.who.int/pqweb/vitro-diagnostics/eligibility-abridged-assessment>, accessed 4 February 2023.

(for example, post-approval changes and inspections) given the substantial regulatory resources required to evaluate safety and post-approval changes during a product’s life-cycle. If an NRA has relied on a reference regulatory authority, CAB or trusted institution such as WHO for its initial approval, the use of similar reliance measures for post-approval changes and adverse event and incident reports is beneficial provided that the sameness of the product initially authorized is maintained.

Recognition may be seen as a special and more complete form of reliance whereby one NRA relies on the regulatory decisions of another reference regulatory authority, system or institution, thus reducing the need for additional regulatory assessment in reaching its own decision.

As shown in Fig. 5.4, the usual phases of reliance and recognition evolve from confidence-building (during which work-sharing and joint activities are undertaken) through to reliance on regulatory information from the reference regulatory authority, to unilateral or mutual recognition of a regulatory decision.

Fig. 5.4
Key concepts of reliance (5)



In considering whether to use either the reliance or recognition option in its own decision-making, the NRA must have a clear understanding of the regulatory system and requirements of the reference regulatory authority as applied to the device under review. The reference regulatory system upon which

an NRA relies – or which it recognizes – should be equivalent or superior to the NRA’s own regulatory system. That decision should be based on defined criteria such as those used to determine maturity level in the WHO global benchmarking tool (3) and specifically those related to medical devices. It should also take into consideration that reliance will refer to a specific element of the regulatory process while recognition is the overall acceptance of the regulatory decision of the reference regulatory authority.⁵⁸ For example, medical device regulations in some jurisdictions permit a manufacturer to specify some medical devices as “export only” and allow such medical devices to be subjected to only minimal controls rather than full evaluation of their conformity to national regulatory requirements.⁵⁹ This places responsibility on the NRA of the importing country and may make reliance and recognition inappropriate. Reliance and recognition are also not appropriate for the assessment of specific requirements, such as language of labelling and electrical supply, that do not apply in the exporting country.

Medical devices may also have different configurations (regulatory versions) for different markets. These may vary in aspects such as 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 that the regulatory version is the same⁶⁰ as the product being proposed for placing on the market. Specifically, for IVDs, the use of reliance or recognition as mechanisms for market authorization is complex. This is because of the variation in classification of IVDs in existing regulatory systems (which determines the level of regulatory scrutiny) or because of newly accepted regulations in some jurisdictions. For example, the current European regulation on IVDs – Regulation (EU) 2017/746 (62) – replaced the IVD directive EU IVD Directive 98/79/EC. The new Regulation came into force in May 2017 with a transition period until 2025.⁶¹ As a result, IVDs on the market during the transition period (and for some years after that) may be subject to two substantially different regulatory frameworks. This example clearly illustrates why knowledge of the regulatory system upon which reliance or recognition is based is crucial.

⁵⁸ In addition to the description provided in the **Terminology** section of this document, in the context of medical devices a “reference regulatory authority” is a trusted authority or institution that is competent and efficient in its performance with regard to medical device and IVD regulation and oversight.

⁵⁹ Such double standards, whereby some jurisdictions set lower requirements for use in other jurisdictions, are considered to be unacceptable.

⁶⁰ Sameness of product means that two products have identical essential characteristics (that is, the product being submitted to the relying authority and the product approved by the reference regulatory authority should be essentially the same) (5).

⁶¹ See: https://ec.europa.eu/health/sites/default/files/md_newregulations/docs/timeline_ivdr_en.pdf (accessed 4 February 2023).

All regulations are subject to occasional revision that could affect the applicability of the reliance or recognition procedure. Importing countries must therefore be alert to any such plans in the exporting jurisdiction and take them into account when relying upon or recognizing a regulatory decision of that jurisdiction. In general, where an NRA 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.⁶² The same considerations apply to the outsourcing of any activities, for example to CABs (63) or experts (locally or internationally based). An example of a specific pathway in reliance is the collaborative registration procedure (CRP) abridged assessment⁶³ (see section 8.8 below). In this case, the relying NRA takes into account the output of work performed by reference regulatory authorities,⁶⁴ while performing only a limited assessment of the technical dossier – for example, with regard to labelling, stability or other country-specific requirements. This may also extend to the assessment of post-market changes to the medical device. The rationale is that prior stringent assessment provides assurance of quality, safety and performance. This approach therefore relies on the assessment of documentary evidence produced by a reference regulatory authority or WHO.

5.9.1 National responsibilities

There are certain regulatory activities that, due to their nature, fall only within the responsibility of the NRA. Examples include: (a) import controls; (b) the registration of domestic manufacturers, importers, distributors and authorized representatives; (c) handling reports of adverse events and incidents occurring in or affecting the domestic market; (d) market surveillance activities; (e) communication and monitoring of field safety corrective actions (FSCA); and (f) market withdrawals. Information sharing on adverse events and incidents and on any FSCA, as well as on market surveillance, is important. Although these regulatory activities should principally be performed by the responsible NRA, international collaboration and reliance approaches (for example, work-sharing) can also be beneficial in facilitating these activities.

⁶² An example of reliance between mature jurisdictions is provided in the case of Australia and the EU: <https://www.tga.gov.au/medical-devices-reforms-mutual-recognition-agreements-mra>, accessed 4 February 2023).

⁶³ Abridged regulatory pathways are regulatory procedures facilitated by reliance, whereby a regulatory decision is solely or partially based on application of reliance (5).

⁶⁴ 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 NRAs (5).

5.9.2 International collaboration

Where resources permit, the NRA should participate in formal and informal information-sharing networks with other regulatory authorities. This will also facilitate confidence-building, with the possibility of work-sharing and reliance upon other regulatory authorities. International collaboration facilitates the exchange of information on regulating medical devices, and expedites prompt contact in the case of a serious public health threat.

6. Establishing a stepwise approach to regulating medical devices

6.1 Stepwise approach

This GMRF recommends establishing a regulatory system for medical devices taking a stepwise approach – from basic-level to expanded-level regulatory controls. The basic-level regulatory controls will form the foundation of the expanded-level regulatory controls. In addition, building a risk-based regulatory system requires a solid legal foundation (see section 5.1 above). The regulatory framework must also be sustainable and expandable, and able to accommodate advances in clinical practices, public health needs and evolving technologies. In order to promote international regulatory convergence and harmonization, this GMRF encourages countries to adopt the principles and elements recommended in internationally harmonized technical guidance into their legislation (64, 65).

Basic-level and expanded-level 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 NRA to respond to national public health priorities and to progressively develop the capacities, knowledge and experience required. This approach will also help the NRA determine the resources needed for further implementation. Without effective implementation of the basic-level regulatory controls as a foundation, the elements of expanded-level regulatory controls will be of limited value and difficult to manage effectively.

Initially, the NRA may reduce the demands on its own resources and staff by either relying upon or recognizing the work or decisions made by other regulatory authorities or trusted institutions such as WHO. Resources may then be directed to post-market controls, which are the responsibility of the NRA. Furthermore, the NRA will indirectly gain knowledge of the regulatory status in other jurisdictions of devices placed on its own national market. The

implementation of expanded-level pre-market regulatory controls does not mean that a regulator should discontinue existing regulatory reliance practices. As an NRA subsequently implements such expanded controls, emphasis will shift to pre-market controls such as authorizing devices to be placed on the market, while continuing to rely upon or recognize the work of other NRAs or trusted institutions, where appropriate.

6.2 Basic-level regulatory controls and their enforcement

This GMRF recommends that the basic-level regulatory controls shown in Table 6.1 are incorporated into a medical devices law that determines the scope of regulation, stipulates the responsibilities of the NRA, describes the conditions under which a medical device may be placed on the market, requires parties that place medical devices on the market to register their establishments, establishes import controls, and requires the listing of medical devices placed on the market. Typically, the market surveillance activities of the NRA would include establishing a system for reporting adverse events and incidents to the NRA and ensuring that manufacturers have in place systems for taking appropriate action in response to reports of quality, safety or performance problems associated with the use of a medical device.

6.2.1 Publish law including definitions and regulations with transition period

The national law for medical devices will set out principles and broad requirements and delegate authority to the NRA (see section 5.1 above). In particular it will include provisions that:

- define the products and parties within its scope, in particular the terms “medical device” and “IVD”, using harmonized definitions (6, 37);
- ensure the regulatory framework is capable of adapting to new technologies and treatment modalities;
- designate the NRA, its enforcement powers, market oversight responsibilities, powers to issue implementing regulations, responsibility for publishing guidance documents to aid understanding of legal requirements, and the requirement to take action where the health of patients or users is compromised;
- provide the NRA with administrative discretion for reliance upon and recognition of the work or decisions of reference regulatory authorities in other jurisdictions (see section 5.9 above);
- require that only safe medical devices of good quality that perform as the manufacturer intends may be placed on the market;
- specify the market entry requirements for medical devices;

- establish record-keeping and reporting requirements for all parties within the scope of the law;
- create the option to appeal regulatory decisions;
- specify a transition period sufficient to allow parties affected by the law to comply with its requirements, and to ensure minimal disruption to the continuing supply of medical devices to health facilities and other users;
- specify that after the transition period, manufacturers shall comply with the regulatory requirements; and
- specify regulatory approaches during special situations such as public health emergencies.

To allow for progressive adoption and implementation of the stepwise approach recommended in this GMRF, the law should foresee and include provisions covering the expanded level of regulatory control and enforcement, even though those provisions would not likely be implemented in the early stages.

Experience in many jurisdictions with established regulatory systems suggests that stakeholders must be allowed time (that is, a transition period) to adapt to the law. 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. The length of the transition period will reflect the number of stakeholders potentially affected 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 NRA during the transition period will be the development and dissemination of voluntary guidance documents to stakeholders.

6.2.1.1 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 (32, 44). It should also include provisions for the NRA to issue implementing acts and guidance on the classification of medical devices including IVDs. The manufacturer would then determine the risk class of a medical device based on the classification rules established by the NRA. Its decision may be challenged by the NRA during review and evaluation of the application for market approval, or at any time for Class A devices that do not require pre-market authorization. It is recommended that the NRA establishes a voluntary consultation process whereby manufacturers can ask for regulatory review of the proposed classification of a device (see sections 4.2 and 4.4 above).

Table 6.1
Basic-level regulatory controls and enforcement for medical devices within the legal framework⁶⁵

EXPANDED

Basic level controls and enforcement		
Pre-market	Placing on the market	Post-market
Publish law including definitions and regulations with transition period	Registration of establishments	Establish a system for reporting adverse events and incidents
	Listing of medical devices	
Establish medical device classification for regulatory purposes	Import controls	Require mandatory notification by the manufacturer of field safety corrective actions
Establish Essential Principles of safety and performance		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 requirements for manufacturers for Quality Management System		
Establish requirements for labels and labelling		
Prohibit deceptive, misleading and false advertising		
Establish provisions for exceptional pre-market situations		

⁶⁵ Expanded-level regulatory controls are discussed in section 6.3 below.

6.2.1.2 Establish essential principles of safety and performance

The law should also establish the fundamental requirement that all medical devices are shown to be safe, perform as intended and are of good quality before they are placed on the market. This would require the manufacturer, or its authorized representative or importer, to declare, and be prepared to provide timely evidence showing, that their device is in compliance with the essential principles (see sections 4.3 and 4.4 above) (37). Failure to make such a declaration of conformity (see section 6.2.2.2 below) (20), or making a false declaration, would be grounds for enforcement action by the NRA.

The preferred way in 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 NRA to formally recognize such standards⁶⁶ for that purpose (see section 6.3.1.3 below).

6.2.2 Basic-level regulatory controls and enforcement – pre-market

Basic-level regulatory controls are intended to provide assurance that only medical devices that are safe, perform as intended and are of good quality are placed on the national market and put into service. Measures including the identification of manufacturers, authorized representatives, importers and distributors, as well as the listing of the medical devices they handle, are intended to provide tools that the NRA may use in enforcing regulatory requirements.

6.2.2.1 Establish a basis for reliance and recognition

The medical devices law should allow reliance and recognition practices to be used by the NRA in evaluating and determining whether a medical device complies with the regulatory requirements for placement on the domestic market. Nonetheless, the NRA is ultimately responsible for determining whether a medical device may be supplied in its jurisdiction (5).

6.2.2.2 Establish requirements for declaration of conformity

The medical devices law should require a manufacturer or any other natural or legal person seeking to place a medical device on the market to draw up, hold and, as required, submit or make available a written declaration of conformity attesting that the device complies fully with the law and all regulatory requirements.

At a minimum, this declaration should contain the following:

⁶⁶ Standards indicated in this document were current at the time of publication. Users should refer directly to the standards body to verify the currently used standards.

- The name and address of the natural or legal person with responsibility for the design and/or manufacture of a medical device with the intention of making the medical device available for use under its name.
- The regulation(s) under which the declaration is being made.
- A description of the device and its classification according to the regulation(s).
- A declaration that the medical device is of good quality, is safe and will perform as intended during its life-cycle when used for its intended purpose as stated in the instructions for use (IFU).
- Sufficient information to identify the device(s) to which the declaration of conformity applies.
- The list of standards used to demonstrate compliance with the relevant essential principles.
- The name, position and signature of the responsible person who has completed the declaration on the manufacturer's behalf.
- The date on which the declaration is made.

The NRA should have the power to verify the declaration of conformity at any time, pre- or post-market, including at the point of importation – either as part of routine market surveillance or “for cause” in the case of suspected non-conformity. That verification process may include examination of supporting evidence from the manufacturer's technical documentation.

6.2.2.3 Establish requirement for manufacturers to have a QMS

To ensure that devices are designed and manufactured to meet safety, performance and quality requirements during their life-cycle, the law should require manufacturers of all classes of medical devices to establish and maintain a QMS and associated records. The QMS should be appropriate to the specific characteristics of the manufacturer's processes and products. This GMRF recommends that the QMS requirements should be aligned with the specifications in ISO 13485:2016: Medical devices – Quality management systems – Requirements for regulatory purposes (41) and ISO 14971:2019: Medical devices – Application of risk management to medical devices (50).⁶⁷

The QMS is important not only for systematically 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 preparing the declaration of conformity (see section 6.2.2.2 above).

⁶⁷ In all cases, the latest version of an ISO standard should be applied.

6.2.2.4 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, on how to install, maintain and dispose of them. Information on intended purpose and proper use, contraindications, precautions and warnings should be provided. Labels, IFU and other labelling (for example, displays, service manuals and information for patients provided through web applications) serve that purpose and help to reduce the 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 should set language(s) requirements.⁶⁸ 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 NRA should also consider whether the IFU may be provided in addition to or instead of the printed instructions in alternative media, for example, via the internet or connected devices. However, printed IFU shall be provided if requested by the user and be provided for medical devices for use at home.

Labels should allow the identification of medical devices, for example by batch or lot number, or serial number. This will allow traceability by users to facilitate FSCA and help in the reporting and investigating of adverse events and incidents. One recent development has been the addition of internationally harmonized unique device identification (UDI) data on the label to identify the medical device both in human- and machine-readable form (see section 6.3.1.5 below).

Guidance may be provided by the NRA indicating whether specific information, for example authorized representative, establishment registration, specific markings and/or environmental information, could be made available via electronic media (e-labelling) (31).

A label (or labels) showing the identity and location of the manufacturer and, where applicable, distributor, authorized representative and/or importer should be provided on medical devices or on their outer packaging. This must be consistent with the information shown in the establishment registration. More detailed and specific information may be made available through e-labelling. Country-specific requirements for the label format or labelling information should be kept to the least-burdensome minimum. Where possible, the NRA should allow such information to be made available through electronic means.

⁶⁸ ISO 15223-1:2021: Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements. International Organization for Standardization; 2021 (<https://www.iso.org/standard/77326.html>, accessed 5 February 2023).

6.2.2.5 Prohibit deceptive, misleading and false advertising

In addition to the requirements for labelling of medical devices, consideration should be given to provisions and prohibitions regarding the advertising and promotion of medical devices, including explicit enforcement measures. The NRA should issue clear and detailed guidance, including on the use of recognized international labelling standards and symbols. The NRA 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 placing on the market;
- is consistent with intended use and other information in the product labelling; and
- does not make false or misleading claims.

As a basic-level regulatory control, the NRA should investigate any suspected violations brought to its attention. If the NRA discovers that a requirement has been breached, it shall take appropriate enforcement actions, which could include correcting advertising materials or preventing the medical device from being placed on the market.

6.2.2.6 Establish provisions for exceptional pre-market situations

In situations such as public health emergencies, or for individual patients in exceptional circumstances, exemptions from some regulatory requirements may be appropriate. Such exemptions should, however, be applied in such a way as to allow the NRA to evaluate the risks and benefits of the specific situation and to authorize the proposed deviation. Such exemptions should be clearly stipulated and communicated to the stakeholder(s).

The law should establish defined exemptions from, and provide enforcement discretion for, compliance with certain requirements – for example, with regard to medical devices for humanitarian use, public health emergencies, clinical investigations and exhibition use, or medical devices donated to the country by charities or the manufacturer. Regulators should issue clear guidance on such exemptions (see section 5.1 above and section 7.3 below).

6.2.3 Basic-level regulatory 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 (15, 66).

6.2.3.1 Registration of establishments

A key element of basic-level regulatory control is effective oversight of medical devices placed on the domestic market and of the parties responsible for bringing such 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 NRA. Significant changes in a registered establishment (for example, changes in ownership, location, name of the responsible person or scope of activities) should be notified to the authorities in a timely manner to ensure that registration information is up to date and correct. Establishment registration is also useful in facilitating regulatory actions such as compliance inspections (for example, of warehouses or manufacturing plants), and notifying and monitoring of FSCA, as well as law enforcement actions. Making information on the registration of establishments and the listing of medical devices publicly accessible allows device purchasers or users to identify products available to them and to determine the identity and location of manufacturers and/or distributors, exporters and/or importers. It is the responsibility of the NRA to periodically check the validity of the registration information and to determine the interval for these checks (34).

6.2.3.1.1 Authorized representatives

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

- submitting a listing (34) of medical devices placed on the domestic market and keep the list updated by notifying the NRA of any renewals or withdrawals;
- providing the NRA with the information it requires when the manufacturer seeks authorization to market its device(s);
- informing the manufacturer of all user feedback on adverse events, incidents and complaints related to safety and performance – in certain jurisdictions, the authorized representative may also be responsible for reporting adverse events and incidents to the NRA

within the local market, and ensuring that users (for example, health care facilities and pharmacies) act on any FSCA initiated by the manufacturer;

- reporting, in certain jurisdictions, an FSCA to the regulator on behalf of the manufacturer;
- cooperating with the manufacturer's importers and distributors;
- ensuring training is provided to users by the distributor, manufacturer or third party, according to the manufacturer's requirements; and
- cooperating with the NRA and providing it with any information it requires during market surveillance activities (11).

6.2.3.1.2 *Importers and distributors*

The minimum requirement for any person/entity to engage in the importation or distribution of medical devices should be that they are registered with the NRA. Beyond this, the regulation may require the importer or distributor to attest that it will at a 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 (for example, IFU and labels);
- ensure that all information, user feedback on adverse events and incidents, and any complaints related to safety and performance received from its clients or customers, is brought to the attention of 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 (34, 66).

6.2.3.2 *Listing of medical devices*

The NRA should establish an information system and a requirement for manufacturers, authorized representatives, and importers and distributors to submit a listing of medical devices when placed on the national market, and

to periodically ensure that the listing information is up to date (34). Among other elements, the listing should provide the standardized generic descriptive names of the medical devices, where possible using an internationally recognized nomenclature (see section 6.3.1.4 below). Listing of medical devices will allow the NRA to determine which products are placed on the market and by whom. The NRA should specify the information set to be submitted for listing purposes. The information shall be consistent with that shown in the technical documentation of the medical device. In the event of a suspected problem with a medical device, listing also allows the NRA to contact the parties responsible for that product. The NRA should also have a means (such as an internet portal) of providing information to other parties, upon request, on medical devices legally placed on the market. Listing is not of itself equivalent to, or evidence of, a market authorization.

6.2.3.3 Import controls

In addition to the basic-level regulatory controls of registering establishments and listing marketed medical devices, import controls and documents such as QMS certificates, proof of market authorization in the exporting country, declaration of conformity and test reports may be appropriate. These controls and documents may include approval of importation documents by the NRA 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 for a review of evidence of compliance with regulatory requirements. The NRA determines which categories or risk classes of medical devices would require additional import controls. Collection of samples may be required in the case of suspected SF medical devices including IVDs. Inspection and/or panel testing, based on product risk, may also be required (for example, lot verification testing for IVDs – see section 4.4.4 above). Once the systems for the registration of establishments and listing of devices become mature, the imposition of these additional import controls may no longer be necessary.

There should be mechanisms put in place for cooperation between the NRA and other government bodies so that customs service and other relevant government officials can receive appropriate training in applying medical-device-specific rules (for example, on labelling). Medical devices should not be released by customs officials from the port of entry unless there is proof that the NRA has authorized them to be placed on the market. The NRA shall be equipped with enforcement powers to prevent medical devices that do not comply with regulatory requirements from entering the country. It may be helpful to designate official ports of entry for medical devices so that the NRA may better focus its resources and enforcement activities.

6.2.4 Basic-level regulatory 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.

6.2.4.1 Establish a system for adverse event and incident reporting including serious public health threats

At the basic level, the NRA should establish a system whereby users, patients and the manufacturer of medical devices (either directly or through their authorized representative) can report adverse events and incidents, and submit user feedback (including complaints) regarding medical devices. Manufacturers should be obliged to report to the NRA if any of the following events associated with the use of their medical device occur within their jurisdiction:

- discovery of a serious public health threat;
- death, serious deterioration in the state of health of a patient, user or other person; or
- no death or serious deterioration in health of a user, patient/client or other person but the failure, malfunction, improper or inadequate design, manufacture, labelling or user error of the medical device that could lead to death or serious deterioration in the health of a user, patient/client or other person (11).

For IVDs, the risk of harm is usually indirect as the device itself is not used on the body. However, in view of the potential hazard to public health, any false-negative test result for Class D IVDs is reportable. To expedite the review of reportable events, it is recommended that the user or health care provider report such incidents directly to the manufacturer or, in the case of a non-domestic company, to the authorized representative. Reports of adverse events received by the NRA from health care professionals, patients or end-users, or obtained during regulatory inspections, must be passed on to the device manufacturer or the authorized representative for investigation and trend analysis. The manufacturer or its authorized representative should inform the NRA of the outcome of its investigation. If necessary, it should take steps such as an FSCA or the issuing of a field safety notice (FSN). The NRA may also conduct its own risk assessment. NRAs should exchange information with other NRAs if they find any indication that the use of a medical device may have led (or is highly likely to lead) to a serious public health threat or that may affect other jurisdictions (26).

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 an FSCA.

6.2.4.2 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 NRA in a timely manner any FSCA it is undertaking in the country. If an NRA learns, either through its own market surveillance or through information exchange with other NRAs or manufacturers, of any newly identified potential hazard associated with a device, it should have an established procedure for issuing information notices to users, along with a publicly accessible repository (such as a website) for these notices. Such a system should also, in addition to the FSN sent by the manufacturer, allow for the targeting of specific parties, usually in consultation with health care professionals, so that they may act appropriately to protect public health and prevent unnecessary concern or confusion among medical device users or patients who are not affected. Communications should be appropriate with regard to both the intended recipients and the urgency of the action. The NRA should have in place means by which the effectiveness of corrective or remedial actions by the manufacturer or its authorized representative shall be monitored. The NRA should also be prepared to respond to questions from the public, clinicians, media and the government, and to exchange information with authorities in other jurisdictions.

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

NRAs have an obligation to enforce laws and regulations on medical devices to ensure that the public is protected from non-compliant, unsafe or SF products. Regulators are required to monitor compliance with requirements by registered manufacturers, importers, authorized representatives and distributors, and to take appropriate action when the NRA believes that public health has been put at risk, while also informing the public of this action through appropriate means.

Various approaches to enforcing regulations may be used – for example: (a) suspension or withdrawal of registration of local manufacturers, authorized representatives, importers or distributors; (b) withdrawal from the list of marketed medical devices; and (c) 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 unforeseen harm and the labelling shown to be inadequate. Enforcement may also include the 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 with the manufacturer (and possibly with external advisers; see section 5.8 above) before issuing a public alert, the regulator can more thoroughly investigate the issue and provide important context in the alert. While the NRA's primary responsibility is for the health of its own citizens, where it believes that an imported medical device is

unsafe or of poor quality, it should consider sharing its opinion with the NRA or CAB responsible for auditing the device manufacturer's QMS, for the purpose of preventing identical devices being exported to other markets.

For SF devices, the enforcement of medical device regulations will often depend not only on the resources of the NRA itself, but also on effective collaboration with other bodies and groups. These may include regulatory authorities from other jurisdictions, customs officials, law enforcement and the judiciary, manufacturers, and user and patient groups.

6.2.4.4 **Establish a procedure for issuing safety alerts to users**

Although the manufacturer, directly or through its authorized representative, would typically have primary responsibility for notifying users of problems with a medical device, this GMRF recommends that the NRA establish a procedure for directly notifying health care facilities and other users of the affected medical device through the issuing of safety alerts. Where possible, the text of any such alerts should be discussed with the manufacturer or its authorized representative, but the final decision lies with the NRA.

6.2.4.5 **Undertake market surveillance (see section 6.3.3.2 below)**

Market surveillance is the NRA activity related to the oversight of medical devices on the domestic market. Market surveillance activities should be prioritized using a risk-based approach. The NRA may undertake targeted activities based on a risk assessment of the distribution chain, evaluation of user feedback (on the safety, quality and performance of devices) and/or information received from the post-market surveillance systems of medical device manufacturers and their authorized representatives.

6.3 **Expanded-level regulatory controls and their enforcement**

Once the basic-level regulatory controls have been implemented effectively and efficiently, the regulatory authority may consider implementing more advanced controls. To do so: (a) the law should provide the legal basis for such expanded-level regulatory controls; (b) the regulatory authority must have effectively enforced the basic-level regulatory controls; and (c) additional resources (including financing and technical expertise) must be available for this purpose. Building on the basic-level regulatory controls, the expanded-level regulatory controls are intended to be more comprehensive. In adopting such expanded controls, the regulatory authority may choose to implement one or more of the controls described below, according to the priorities of the country. As with basic-level regulatory controls, a stepwise approach should be taken when implementing the individual elements of expanded controls

(Table 6.2) and this will be dependent upon the available technical expertise and other resources. Implementation should always be consistent with available resources – enacting and enforcing a limited set of requirements is preferable to attempting to implement a larger range of regulatory controls in the absence of proper enforcement (4).

Table 6.2
Expanded-level regulatory controls and enforcement for medical devices within the legal framework^a

Expanded level controls and enforcement		
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 adverse events and incidents by manufacturers
Adopt standards		Inspection of registered establishments
Adopt medical device nomenclature system		Provide for testing laboratories
Control advertising and promotion		

Table 6.2 *continued*

Basic level controls and enforcement		
Pre-market	Placing on the market	Post-market
Publish law including definitions and regulations with transition period	Registration of establishments	Establish a system for reporting adverse events and incidents
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		

^a The empty boxes shown in Table 6.2 indicate the option for an NRA to tailor its activities based on national priorities.

6.3.1 Expanded-level regulatory controls – pre-market

6.3.1.1 Create oversight of clinical investigations

The general essential principles established for basic-level regulatory controls (see section 4.3 above) includes the requirement that a device must be shown to be safe and perform as intended before being placed on the market. To fulfil this requirement, the manufacturer must maintain and be able to present evidence (including clinical evidence along with a clinical evaluation) of clinical safety and performance in the summary technical documentation (16–18). Such clinical evidence may (but does not necessarily) include the results of clinical investigations of that specific device. Where required as a part of the assessment of the technical documentation, the NRA or CAB will evaluate the adequacy of that clinical evidence and its evaluation (17, 67). In-country clinical

investigations may not be appropriate or necessary, especially if the jurisdiction has implemented good reliance practices (GRelP) (5). However, there may be situations in which a country may require a local clinical investigation – for example, where a domestically manufactured device has not previously been evaluated by a reference regulatory authority or CAB, where the domestic population has specific genetic characteristics or an ethnic composition not sufficiently represented in clinical investigations conducted elsewhere, or where a medical device intended for a particular disease or condition specific to the population requires evaluation with a specific companion diagnostic test (see section 8.6 below). In addition, a previously authorized medical device may require a new clinical investigation if the manufacturer seeks to add a previously unevaluated claim to the device's intended purpose.

The national regulatory framework should grant to the NRA the power to regulate and oversee the conducting of clinical investigations. Manufacturers may choose to undertake a clinical investigation in a particular country, primarily to collect and provide clinical evidence to an NRA that a device for which it is seeking approval is safe and performs as intended in the population of interest. Factors to be taken into account when establishing a requirement for the clinical investigation of a medical device include risk class, technologies used, level of invasiveness, and the adequacy of existing clinical evidence and its applicability to the local population. Where there is no compelling scientifically sound justification for a new clinical investigation, ethical considerations generally do not favour such a requirement.

The regulatory framework should clearly distinguish between pre-market clinical investigations of unauthorized devices and market-acceptability studies where a device is being tested for factors such as its ergonomics. Such market-acceptability studies are not considered clinical investigations and should not be subject to regulatory controls.

There should be a requirement that any sponsor⁶⁹ wishing to conduct a new clinical investigation seeks prior authorization from the NRA. To ensure that adequate consideration is given to the study design and to protecting the interests of participating subjects (including through the use of informed consent), investigations should also be conducted under the oversight of a local ethics committee or institutional review board.⁷⁰ A widely used international standard for the design and conducting of a clinical investigation

⁶⁹ The individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation (18).

⁷⁰ The international standard for testing in humans is the WMA 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/>, accessed 6 February 2023).

is ISO 14155:2020: Clinical investigation of medical devices for human subjects – good clinical practice (18).

The NRA should also establish a mechanism for publishing periodic progress reports and for the reporting of serious incidents that occur during clinical investigations. The NRA should also have provisions in place to suspend or terminate a clinical investigation in the case of identified harm to patients and/or public health (68).

In-country clinical investigations (that is, systematic clinical investigation in the country in which market authorization is being sought) should not generally be a requirement. When adequate clinical evidence from another country, along with a clinical evaluation, have been provided to the NRA as part of a market authorization application, then a new in-country clinical investigation should not generally be required unless there is a compelling and sound scientific reason.

6.3.1.2 Appoint and have oversight of CABs

The performance of certain technical evaluation or auditing elements of the regulatory framework may be delegated to recognized CABs. The NRA should establish criteria for CAB recognition (see section 4.3 above). These bodies may perform initial certification and surveillance audits of device manufacturer QMS and/or pre-market reviews of the conformity of a device to the essential principles. A CAB may be recognized by the NRA to undertake conformity assessments of specific categories of medical devices where it is judged to have the necessary skills (for example, active implantable and/or IVDs and/or electromedical devices) (61, 63). Satisfactory compliance with requirements is typically documented with a CAB certificate and subject to periodic review and renewal. The NRA may consider adopting mechanisms to rely upon, or recognize, certificates issued by a CAB, even those outside its jurisdiction or direct oversight (69). Based on the CAB evaluation, the NRA then makes its final decisions on compliance and market authorization. The CAB performs its evaluation under the oversight of the NRA.

6.3.1.3 Recognition of standards⁷¹

Conformity with recognized international consensus standards is a means by which the manufacturer may demonstrate that a medical device conforms to one or more of the essential principles of safety and performance consistently throughout its life-cycle.

⁷¹ Standards indicated in this document were current at the time of publication. Users should refer directly to the standards body to verify the currently used standards.

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 – these include QMS (41), risk management systems (50) and clinical investigation (18).
- Group standards (also known as semi-horizontal standards) which cover aspects applicable to families of similar products or processes with reference to basic standards – such as those on sterility, electrical safety or biocompatibility.
- Product standards (also known as vertical standards) which cover safety and performance aspects of specific products or processes – such as standards for infusion pumps, X-ray machines, blood glucose meters for self-testing and IVDs (29).

At the expanded-level regulatory controls, the NRA should establish a procedure to identify national versions of recognized international standards that it regards as providing a presumption of conformity to specific essential principles (that is, a recognized standard) (46). Preference for such recognition should be given to international standards such as those of the International Organization for Standardization (ISO), the International Electrotechnical Commission (IEC) and other international standards development organizations (SDOs). If no standards are available from international SDOs, the NRA may consider standards from regional or national SDOs. Where feasible, members of SDOs (such as ISO and IEC) should participate in standards development and in the adoption of international standards by national SDOs in a timely manner. It is also important that national standards correspond to the current versions of international standards. As international standards are periodically revised, national recognition and adoption of the updated editions will have to take place accordingly, and the NRA should establish a transition period for manufacturers to adopt and implement 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. These documents can then be revised and updated to stay current much faster than legislation can be.

6.3.1.4 Select and implement a medical device nomenclature system

An internationally recognized medical device nomenclature system (70) includes a framework for standardizing the use of internationally recognized nomenclatures for regulatory purposes. It supports collaboration between current

systems among key stakeholders to ensure convergence towards the widespread use of an international coding and classification of medical devices.⁷²

A nomenclature system provides for the consistent and accurate identification of medical devices with similar characteristics by a variety of stakeholders, including policy-makers, regulators, manufacturers, trade and customs officials, insurance companies, the health care sector and users. A nomenclature system is intended to improve product distribution and use, and supports timely and accurate post-market surveillance activities and medical record keeping.

For example, the identification and investigation of a potential medical device safety issue will depend on:

- correct and timely medical record keeping by the health care provider;
- exchange of information on adverse events and incidents between the health care provider and the manufacturer and/or NRA;
- comprehensive data analyses of all adverse events and incidents for a particular device type by the manufacturer and/or regulator;
- dialogue between the manufacturer and NRA regarding any performance concerns and appropriate next steps; and
- communication to health care providers of the precautions to take with a particular device type.

Several nomenclature systems exist for identifying medical devices to support regulatory decision-making, procurement and supply, and international trade and customs, as well as inventory and maintenance management. The benefits of a nomenclature system can only be realized when the same nomenclature system is used consistently and accurately by all relevant stakeholders and that nomenclature is globally harmonized. To this end, the selection of an internationally recognized nomenclature should reflect the needs of each stakeholder both individually (for example, the Ministry of Health, regulator, manufacturer, health care industry, health care providers, trade and customs officials and patients) and as a system.

The use of an internationally recognized nomenclature supports the aggregation and analysis of information – not only within a given jurisdiction but also internationally (71). An internationally recognized nomenclature system is particularly relevant for low- and middle-income countries (LMIC) who are the

⁷² 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 7 February 2023).

recipients of medical devices from well-resourced settings (72, 73). If countries have their own nomenclature systems that are jurisdiction-specific, then device traceability in a health care system will be significantly hindered.

Fig. 6.1 and Fig. 6.2 provide 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 three nomenclature systems most commonly used by countries:

- European Medical Device Nomenclature (EMDN)⁷³
- Global Medical Device Nomenclature (GMDN)⁷⁴
- Universal Medical Device Nomenclature System (UMDNS).⁷⁵

6.3.1.4.1 *Selecting a nomenclature system*

Considerations in selecting a nomenclature system include:

- Harmonization (74): the selection of a nomenclature system should consider whether the system is harmonized between various countries, regionally or internationally, to allow for pooling of data and exchange of information. Currently, several nomenclature systems are available. Selection should first be limited to those nomenclature systems that are internationally recognized, meaning that the nomenclature agency is actively contributing their terms and codes towards ongoing harmonization efforts (75) – for example, by mapping codes and terms with other nomenclature systems – and that the nomenclature contains a hierarchical structure grouped into categories.
- Accessibility and ease of use: the selection of a nomenclature system should balance the needs of all stakeholders in the health care landscape to enable consistent implementation. The required terms, codes and definitions should be publicly available and free to users.
- Governance: the selection of a nomenclature system should consider whether the system is managed in a transparent manner with a process for obtaining feedback from all stakeholders, and a quality

⁷³ EMDN (<https://webgate.ec.europa.eu/dyna2/emdn/>, accessed 7 February 2023).

⁷⁴ GMDN (<https://www.gmdnagency.org/>, accessed 7 February 2023).

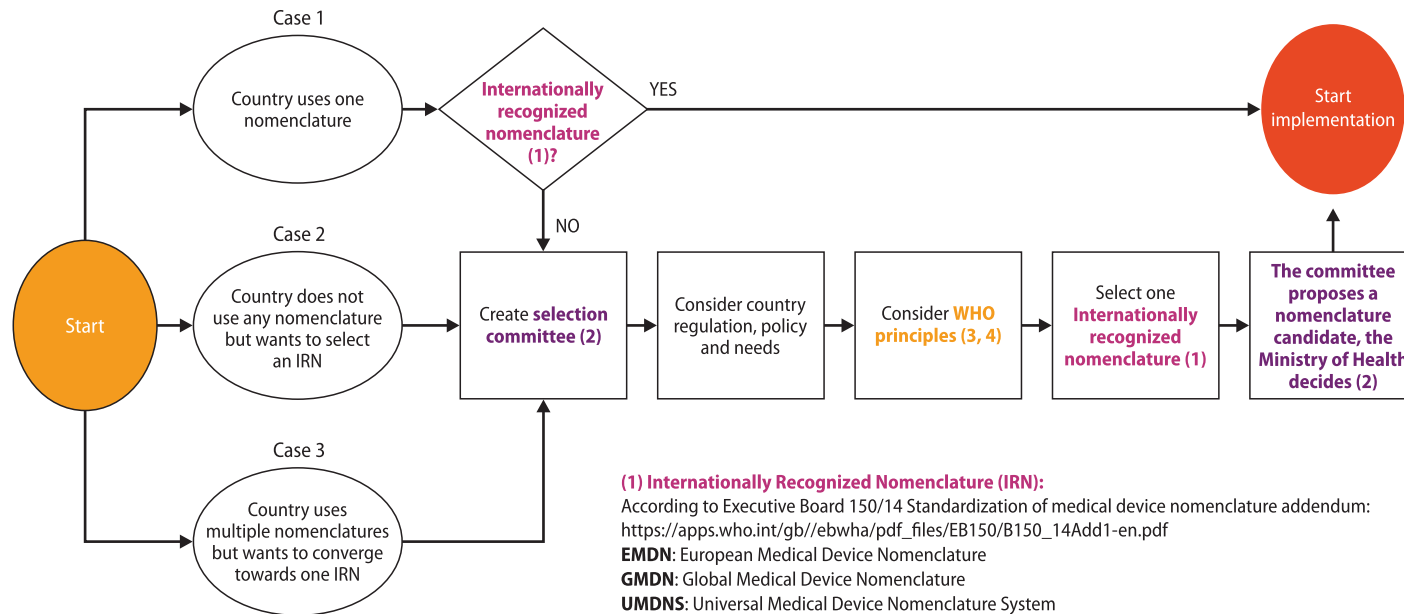
⁷⁵ UMDNS (<https://www.ecri.org/solutions/umdns>, accessed 7 February 2023).

system for managing changes to terminology. Organizational and review structures should be in place to ensure that all stakeholders are able to provide feedback according to their needs. Processes should use a transparent methodology for the establishment and coding of nomenclature terms.

- **Timely updates:** the selection of a nomenclature system should consider the mechanism and periodicity of updates to medical device terms (for example, once a year). The frequency of updates should accommodate innovation in new generic types of medical devices and allow for the clear and consistent implementation of new terms by all stakeholders.
- **Used in source jurisdictions:** the selection of a nomenclature system should consider the systems used in jurisdictions that are the predominant sources of imported devices. If UDI regulations (see section 6.3.1.5 below) are in place or proposed, consideration should be given to the nomenclature requirements associated with UDI in the source jurisdiction.
- **Language:** the selection of a nomenclature system should consider the availability of versions in multiple languages, especially those used in the jurisdiction of the NRA. If an appropriate language version is not available, then the selection committee should consider the possibility of translation.
- **Transferability and interoperability:** the selection of a nomenclature system should take into account whether the nomenclature is compatible and can be shared and fully used in other public systems such as national device lists, procurement systems, inventory and maintenance systems, and electronic health care records. Its interoperability, traceability, configuration control, maintenance and quality assurance should be assessed. Terms and related descriptive information should be accessible through simple and intuitive search functions. A key element is that the nomenclature system should support a UDI system (see section 6.3.1.5 below).

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 in the Ministry who will then communicate the decision to all respective stakeholders for implementation.

Fig. 6.1
Selection of an internationally recognized nomenclature (IRN)



(1) Internationally Recognized Nomenclature (IRN):

According to Executive Board 150/14 Standardization of medical device nomenclature addendum:
https://apps.who.int/gb/ebwha/pdf_files/EB150/B150_14Add1-en.pdf

EMDN: European Medical Device Nomenclature

GMDN: Global Medical Device Nomenclature

UMDNS: Universal Medical Device Nomenclature System

For more information visit the WHO nomenclature website: <https://www.who.int/teams/health-product-policy-and-standards/assistive-and-medical-technology/medical-devices/nomenclature>

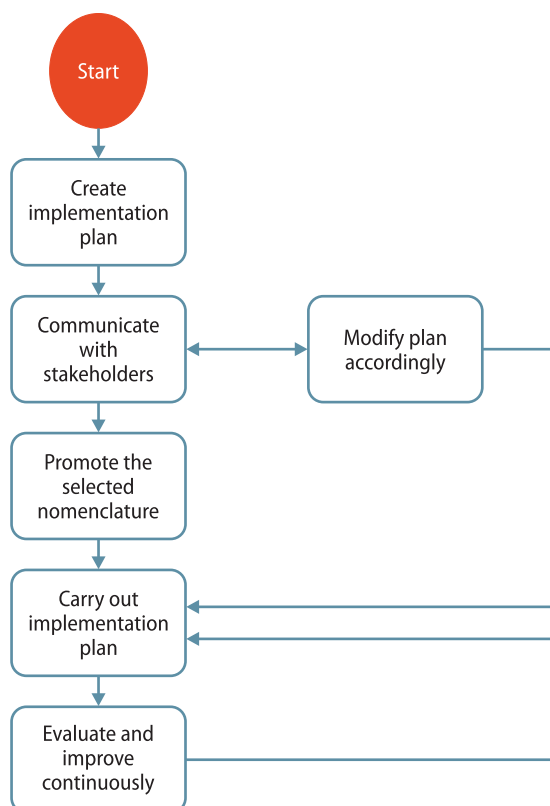
(2) Selection Committee to include stakeholders, i.e. members from Health Council, Ministry of Health, NRA, Health Service providers, Insurance, Med tech Industry and patients organizations.

(3) WHO Principles

According to Executive Board 150/14 - Standardization of Medical Device Nomenclature:
https://apps.who.int/gb/ebwha/pdf_files/EB150/B150_14-en.pdf

(4) Internationally Recognized Nomenclatures compared against WHO principles and other characteristics (as of June 2022)

Fig. 6.2

Country implementation of a nomenclature for medical devices**6.3.1.4.2 Implementing a nomenclature**

Successful implementation of a medical device nomenclature system requires significant resources, planning and coordination. Steps to consider when developing and executing an implementation plan include:

- identify which stakeholders are responsible for which aspects of implementation and how the actions of each stakeholder will affect the others. For example, a manufacturer's ability to identify the correct term for a device impacts a health care provider's ability to input correct information into a medical record;
- map the selected nomenclature system to existing national nomenclature systems used in the country and provide the map to stakeholders to enable adoption;

- define a transition plan to have only one nomenclature system in the country – the plan will describe which stakeholders are expected to use which aspects of the nomenclature system by what dates, and should balance the time required for each stakeholder to complete the necessary tasks against the benefits of complete implementation;
- obtain feedback from stakeholders on anticipated challenges regarding the proposed plan and adjust the plan as needed;
- execute the plan, providing clear, consistent and timely communication to all stakeholders; and
- evaluate the effectiveness of implementation, and update the implementation plan and related policies as needed.

6.3.1.5 Unique device identification (UDI) system

A UDI system provides a single, harmonized system for the positive identification of medical devices sold on the market – from manufacturing through to the distribution chain and to the patient. Health care professionals and patients would then no longer need to access multiple, inconsistent and incomplete sources in order to correctly identify a medical device and its key attributes.⁷⁶

A globally harmonized and consistent approach to a UDI system is expected to increase patient safety and improve patient care by facilitating:

- traceability of medical devices throughout their life-cycle, especially for FSCA;
- identification of medical devices through their distribution and use;
- identification of medical devices associated with adverse events;
- reductions in medical errors;
- the documenting and capture of data on medical device use over time; and
- detection of SF medical devices.

UDI itself is only one component of a UDI system. The system will also include a framework requiring device manufacturers to apply UDI to the device label and to submit data elements associated with the UDI device identifier (UDI-DI) to a public UDI database (UDID). To ensure that UDI will facilitate the exchange and interoperability of device information, NRAs should adopt international best practices when creating a new jurisdiction-specific UDI system or when using an existing UDI system. UDI guidance – unique device identification (UDI) of medical devices (23) provides an internationally

⁷⁶ UDI basics. United States Food and Drug Administration (<https://www.fda.gov/medical-devices/unique-device-identification-system-udi-system/udi-basics#format>, accessed 7 February 2023).

harmonized framework for NRAs intending to develop their UDI systems, while the unique device identification system (UDI system) application guide (76) provides the necessary details and specifications.

UDI consists of two components – the UDI-DI and the UDI production identifier (UDI-PI) – and is assigned to a medical device by the manufacturer at the time of production. The UDI-DI is a unique numeric or alphanumeric code specific to a model of medical device. The UDI-PI is a numeric or alphanumeric code that identifies the unit of device production. The different types of UDI-PI include serial number, lot/batch number, SaMD version and manufacturing and/or expiry date.

The UDID is a designated repository and source of identifying information and other elements associated with a specific medical device.

A UDI system has three interrelated requirements:

1. UDI must be based on the technical specifications of government-recognized UDI-DI issuing agencies;
2. UDI must be applied to the label of a medical device and its associated packaging; and
3. UDI-DIs along with specific information about the medical device must be submitted to a UDID for the purpose of making it publicly available and to promote data sharing between regulators and other stakeholders.

Use of UDI should be one of the regulatory requirements for placing a medical device on the market. The NRA should accredit an issuing agency (such as GS1,⁷⁷ HIBCC,⁷⁸ ICCBBA⁷⁹ or IFA⁸⁰) to operate a system for assigning UDI that complies with national and international requirements (23, 76).

One key feature of UDI systems is the requirement to assign a specific medical device nomenclature term for each UDI-DI record in a UDID. IMDRF guidance (76) states that regulators should:

connect the device UDI-DI information with codes and terms of a nomenclature which would enable other stakeholders to: use the UDID data for activities like purchasing, stock handling, reimbursement or research; find UDID information related to similar devices or to enable regulatory authorities to effectively assess the safety and performance of product groups in the field.

⁷⁷ GS1 – <https://www.gs1.org/>.

⁷⁸ HIBCC – <https://www.hibcc.org/>.

⁷⁹ ICCBBA – <https://www.iccbba.org/>.

⁸⁰ IFA – <http://ifa-coding-system.eu/en/ifa-codingsystem/udi/budi-generator.html>.

Where the UDI identifies an individual device, the nomenclature assignments to UDI-DI records enable the grouping of products with the same or similar nomenclature assignments. Thus, the UDI system complements and helps to achieve the goal of a nomenclature system – that is, the accurate identification of medical devices with similar characteristics.

The benefits of UDI can only accrue if all stakeholders from the manufacturer to health care providers use UDI throughout their workflow systems. Therefore, it is imperative that stakeholders are educated on the development and use of a UDI system.

6.3.1.6 Control of advertising and promotion

As part of their market development efforts, manufacturers, importers and distributors generally seek to promote medical devices to health care professionals, users and/or patients. At a minimum, in all countries there should be a requirement that advertising and promotion materials should not be false, misleading or deceptive (36). The device's intended purpose as described in promotional materials should be consistent with that for which market authorization was granted. In countries where the presence of misleading and inaccurate advertisements is a particular problem, the NRA may expand its controls to include the review of advertising and promotional materials before their publication. The NRA should also consider a role for pre-clearance agencies, which act as independent entities to review advertising materials to ensure compliance with regulatory requirements. The NRA should also consider whether existing general rules for advertising to consumers (for example, fair competition rules), including through online promotions, are sufficient for application to medical devices. If not, they should consider whether specific guidance is required. If preventive measures against false, misleading or inaccurate promotional materials are ineffective, the NRA may consider enforcement actions such as the issuance of warning letters, seizure and/or disposal of devices, fines/penalties and court orders.

6.3.2 Expanded-level regulatory controls – placing on the market

6.3.2.1 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 to demonstrate 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 of regulatory control, this GMRF recommends that the law should require manufacturers of all classes of medical devices to establish and

maintain a QMS. As the NRA moves to enact expanded-level regulatory controls, the requirement in law should be supplemented by a regulation or ministerial decree that gives power to the NRA 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 13485:2016 (41), in most countries with established NRAs, they are generally not subject to inspection by the NRA prior to market approval nor routinely inspected by the NRA after the devices have been placed on the market (see Table 4.3 above for QMS requirements for medical devices in Classes B, C and D).

6.3.2.1.1 *QMS audit*

The NRA should establish means of verifying that the manufacturer conforms to the relevant QMS requirements (41). The law should include provisions for the NRA to designate or recognize CABs (see section 6.3.1.2 above) to perform QMS audits, or to 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 NRA to rely upon evidence (including QMS certificates) of the manufacturer's compliance with international guidelines and recognized standards, and with legal requirements in other jurisdictions. The receiving country thereby relies upon information from the QMS audit or recognizes the decision of the other jurisdiction regarding the QMS audit. The NRA 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 in the case of Class B, C and D medical devices. The NRA should verify that such certificates remain valid (typically for 3–5 years) and cover the scope of medical devices and activities appropriate for the devices being imported.

In the event of suspected non-compliance or problems with the product, the NRA may perform an inspection, regardless of whether a CAB has performed a QMS audit. In cases where the NRA chooses to conduct its own inspection of the QMS of a manufacturer, importer or distributor, the inspectors should be appropriately trained and qualified (58).

6.3.2.2 *Review submissions for compliance with essential principles*

The NRA makes a decision on market authorization based on transparent criteria established in a law, regulation and related guidance (see also section 5.1 above). The regulation 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 (7, 20, 37).

For basic-level regulatory controls, assessing the safety and performance of medical devices depends primarily on an assessment by a reference regulatory authority supported by the manufacturer's declaration of conformity (see section 6.2.2.2 above). At the expanded level of regulatory controls, the NRA may establish a requirement for its own pre-market review of a manufacturer's submission or may rely on an assessment by another NRA. Guidance on the process for application and approval should be provided. This will usually be through the completion of a prescribed form or access to the authority's web portal.

Internationally harmonized formats for the submission of technical documentation for conformity assessment purposes have been developed by various bodies – for example, the IMDRF Table of Contents (ToC)⁸¹ which provides a modular structure for such submissions in electronic form. Separate ToCs have been established for medical devices and IVDs (77, 78). The Association of Southeast Asian Nations (ASEAN) has also developed the Common Submission Dossier Template (CSDT) based on harmonized essential principles (79). These formats provide guidance on how to present evidence that a medical device conforms to the regulatory requirements for safety and performance.

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 may, in the judgment of the NRA, trigger a more extensive review of the technical documentation submitted by the manufacturer. For example, when:

- the device incorporates innovative technology – that is, a new or improved product or process whose technological characteristics differ significantly from earlier devices;
- an existing compliant device is being offered 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 and/or potentially hazardous materials;

⁸¹ The former harmonized format by GHTF was the Summary technical documentation for demonstrating conformity to the essential principles of safety and performance of medical devices (STED) – <https://www.imdrf.org/sites/default/files/docs/ghtf/archived/SG1/technical-docs/ghtf-sg1-n011-2008-principles-safety-performance-medical-devices-080221.pdf>, accessed 7 February 2023).

- the device type raises specific public health concerns (particularly for IVDs);
- the medical devices classification by the relying NRA is different from the manufacturer's assigned classification;
- the imported medical device has not been assessed and authorized by another NRA;
- the device type will be used by lay persons to support or sustain life; and
- the device is an IVD for self-testing.

The NRA should provide public guidance on the criteria for a more extensive review.

Once medical devices have been granted market authorization and placed on the market, the manufacturer may introduce changes to the product, its manufacturing process or location, or to the QMS under which it is produced. Such changes may range from minor changes (with little potential to impact the safety, performance and/or quality of the medical device) to substantial changes likely to affect the safety, performance and/or quality of the medical device. A substantial change is any change that could reasonably be expected to affect the safety or performance of a medical device or its conformity with the essential principles, and would include changes to any of the following:

- the manufacturing process, facility or equipment;
- the manufacturing quality control procedures, including the methods, tests and procedures used to control the quality 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 QMS as either substantial or not substantial (41, 80).

The NRA should establish guidance on changes (including a definition), and on the tools and processes used to handle such changes. The NRA should when possible, implement reliance and recognition principles when evaluating changes.

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

The NRA may be assisted in reaching its decision on pre-market assessment (or any other regulatory decision) by an expert medical device committee (see section 5.8 above), which may include experts from outside the NRA. Where advice from external experts is sought, the NRA should ensure that the necessary agreements for the exchange of confidential information are in place along with signed declarations of interests. The final regulatory decision rests at all times with the NRA.

6.3.3 Expanded-level regulatory controls – post-market

6.3.3.1 Establish within the NRA processes for reviewing manufacturer post-market surveillance – including the reporting of adverse events and incidents

For basic-level regulatory controls, a system for reporting adverse events and incidents involving medical devices to the NRA – particularly those resulting in death or serious deterioration in the health of a user, patient/client or other person – is established (see section 6.2.4.1 above). At the expanded level of regulatory controls, the role of the NRA may be extended to include reviewing, as part of QMS audits, the post-market surveillance system of the manufacturer or its authorized representative, and reviewing the manufacturer's investigation of user feedback. As a part of their QMS, manufacturers undertake post-market surveillance activities, including review of user feedback, to determine the need to report certain categories of adverse events and incidents to the NRA. The risk-management elements of the QMS require that manufacturers review the benefit–risk profile associated with the ongoing use of devices. Manufacturers may implement corrective actions to reduce the likelihood of recurrence of an event or incident. Properly structured post-market surveillance can identify serious problems in the safety, quality and/or performance of a medical device that may not have been foreseen or detected during product development or pre-market evaluation, and can provide for corrective action. This may include the international exchange of alerts through a standardized process (26).

NRAs should ensure that manufacturers have in place a system for post-market surveillance (for example, through an ISO 13485 audit) that includes the collection of user feedback, reporting of certain adverse events and incidents to the NRA, and evaluating the need for corrective actions. The responsibilities of the NRA should encompass:

- handling of adverse event and incident reports and user feedback (including complaints) reported by the manufacturer, and setting out clear responsibilities for the manufacturer, authorized representative, importer and distributors;
- collecting and reviewing of adverse events and incidents reported by the manufacturer;
- ensuring maintenance by parties in the distribution chain (importers and distributors) of appropriate records of user feedback (including complaints) and actions taken; and
- reviewing the implementation of corrective or preventive actions, including FSCA, by the manufacturer or its authorized representative, when appropriate.

Where the manufacturer is located outside the jurisdiction of the NRA, there should be an agreement between the manufacturer and its authorized representative defining who fulfils the national regulatory requirements and maintains records of the distribution of the device. The agreement should require the authorized representative to report all incidents and adverse events and user feedback, including complaints, to the manufacturer for investigation and possible corrective action.

To the extent that investigation and information management resources allow, the NRA should establish a mandatory requirement for the timely reporting, by the authorized representative or manufacturer, of any adverse events, incidents and serious public health threats associated with the use of medical devices in the jurisdiction. It should define the threshold for reporting, reporting time limits, required information and which party (or parties) shall report. In general, such criteria should be consistent with WHO and IMDRF guidance (8–11).

6.3.3.2 **Develop a system for market surveillance (see also section 6.2.4.5 above)**

In addition to adverse event and incident reporting by the manufacturer, the NRA may develop a system for market surveillance. The system will include the receiving of feedback from users and patients, analyzing of data from regulatory investigations or audits, and, possibly, the targeted testing of specific medical devices on the market. The NRA assesses reports from users and may forward these reports to the manufacturer or its authorized representative for follow-up and investigation. For a systematic approach to market surveillance, the NRA may develop a risk-based plan based on data from regulatory checks on medical devices already on the market. Sampling and testing may be part of market surveillance if applied in a focused and cost-effective manner. However, the resources needed to acquire expertise and maintain testing facilities covering

the broad spectrum of medical devices are often beyond the reach of NRAs and testing laboratories. Collaborating with laboratories on a national or regional level will promote the building of expertise and improved use of resources (11).

6.3.3.3 Inspections of registered establishments

The NRA should have the power and authority to inspect, scheduled or unannounced, all registered establishments of manufacturers, importers and distributors to confirm that they have the facilities, procedures and records in place to allow them to comply with regulatory requirements. Where possible, the NRA is encouraged to rely on facility inspections or audits performed by reference regulatory authorities, CABs or other trusted institutions such as WHO. However, the NRA should retain the right to inspect all registered establishments in its jurisdiction. Inspections or audits should be based on a risk-based approach (for example, first inspect or audit higher risk-class products, facilities with recent adverse inspection or audit findings, and facilities not previously inspected or audited by the NRA). Additionally, the NRA may issue licences to registered establishments, renewable on a periodic basis. The registration – or licence if such has been issued – may be withdrawn or suspended if significant non-conformities are found during inspection and not corrected.

6.3.3.3.1 Distribution of medical devices

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

- select and contract appropriately qualified distributors (for example, those with 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; and
- periodically verify the conformity of distributors with the contractual requirements.

Post-market surveillance activities, including the collection of customer feedback and implementation of corrective actions, will generally be conducted by the manufacturer through cooperation with its authorized representative and distributors.

Distributors should implement a basic QMS covering the scope of their activities. With the continuing increase in global trade in medical devices, new suppliers enter the field often without much experience or relevant qualifications. This may allow for the supply of non-conforming medical devices or, in some cases, SF medical products.⁸² Parties within the distribution chain should comply with good practice guidelines, such as a code of good distribution practice (GDP). Fulfilment of the requirements of GDP may be enabled by the implementation of a QMS in accordance with ISO 13485:2016. Because the scope of activities covered by ISO 13485:2016 is broader than the activities of most distributors and importers, the Asian Harmonization Working Party (AHWP, now GHWP) published guidance on the application of ISO 13485:2016 in an organization that distributes or imports medical devices (66). Widespread adoption and implementation of GDP in the medical device supply chain is an important element in preventing the spread and use of SF medical products.

6.3.3.4 Local production

Local production of quality medical devices can lead to more accessible and affordable products which will be critical for the provision of quality health services (81–83). As well as ensuring the safety, quality and performance of medical devices, governments have legitimate policy interests in promoting and encouraging the development of local development and manufacturing capacity. Local production potentially offers a cost-effective pathway to improving access to health care and medical devices. While local production is one approach to increasing access to medical devices, additional research on technology transfer will be needed to create an environment that will benefit public health. In addition, local production requires a multisectoral approach to put in place policies to ensure the manufacture of quality products. The government should ensure transparency, predictability, non-discrimination, consistency of requirements, impartiality and respect for proprietary confidential information (that is, GRP) (4). The government will play an important role in establishing the local production of medical devices including through policies, resources, mobilization of relevant government bodies and stakeholders, promoting a conducive business environment for the local production of medical devices, and the establishment of a strong NRA.

The NRA should be equipped to:

- advise the government on the preparation of appropriate policies to facilitate local production of medical devices;

⁸² Substandard and falsified medical products. Key facts (<http://www.who.int/entity/mediacentre/factsheets/fs275/en/>, accessed 8 February 2023).

- ensure adoption of relevant international standards as national standards, and to publish reference lists of standards recognized by the NRA for the purpose of demonstrating conformity with regulatory requirements;
- provide appropriate and impartial technical support to manufacturers, whether domestic or foreign. Appropriate consultation mechanisms encourage compliance with regulatory requirements by resolving misunderstandings – this may help manufacturers gain proficiency in the production of quality and safe medical devices;
- ensure public availability of concise regulations and guidelines for assessment, market authorization and post-market surveillance, equally applicable to local and foreign manufacturers;
- implement risk-based assessments and issue timely market authorizations for both locally manufactured and imported medical devices; and
- support and participate in regional initiatives for the implementation of reliance and recognition mechanisms and regulatory cooperation.

In the interests of safeguarding public health, and to ensure quality, safety and performance, local manufacturers should be subject to the same regulatory controls as manufacturers and distributors of imported medical devices. These controls should be consistent, non-discriminatory and impartial regardless of the origin of medical devices. The NRA, in the pre-market phase, should provide clear guidance on the legal requirement for both foreign and local manufacturers to submit technical documentation for the different risk classes of medical devices. Support from regulatory authorities to local manufacturers should be made available on request and should take into account the fact that manufacturers will differ due to the diversity of medical devices, different risk classes and different levels of development of manufacturer capabilities. A voluntary pre-submission meeting between the NRA and manufacturer may cover national requirements, and is an opportunity to discuss the requirements for an application and to obtain NRA feedback before an intended pre-market submission.

Where pre-market conformity assessments of higher risk-class medical devices, whether foreign or locally produced, are necessary, the NRA would generally conduct its own evaluations but may take into consideration (that is, rely upon) similar evaluations conducted by other authorities. Because a local manufacturer is physically located in the jurisdiction of the authority, the NRA would typically conduct its own QMS inspections or audits of the manufacturer's

plant(s) and warehouse(s). Reliance and recognition mechanisms would generally not apply in such cases unless a reference regulatory authority or CAB has previously conducted such audits of the facility. Requirements for the 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, including those for which a pre-market assessment is not required (that is, Class A medical devices).

In the post-market phase, the NRA undertakes market surveillance and imposes enforcement measures, if appropriate. The reporting system for adverse events and incidents is identical both for locally manufactured medical devices and imported medical devices. When serious public health threats occur for locally manufactured medical devices the NRA enforces corrective action by the manufacturer, whereas for imported medical devices the NRA enforces corrective action by the authorized representative and distributor.

In the case of adverse events, or incident reports or FSCA involving locally produced devices exported to other countries, the NRA may be called upon to investigate the manufacturer/exporter and/or to coordinate with foreign authorities. Local adverse event and incident reports or FSCA involving locally produced devices would be investigated and monitored by the NRA, but may still involve coordination with other relevant stakeholders.

In the case of inspections or audits to investigate suspected noncompliance or problems with products, the NRA would likely undertake the inspection. Based on the outcomes of the inspection or audit, the NRA may either allow the local manufacturer to continue its operations with corrective actions, or issue citations for non-conforming activities. Depending on the significance of the non-conformance, a warning letter, product withdrawal or even shutdown of the local manufacturing site are possible.

NRA activities such as assessing the technical dossier, performing on-site inspections and enforcing post-market requirements require specific capacity-building efforts. Development of the required expertise and competencies is vital if NRA staff are to perform these tasks effectively and responsibly (see section 9.3 below).

6.3.3.5 Regulatory testing of medical devices

In general, the routine testing of medical devices including IVDs (either imported or locally produced) by the NRA is not a cost-effective use of limited resources and is not recommended. The manufacturer has the primary responsibility for demonstrating that a device conforms to the essential principles of safety and performance, quality requirements, and all applicable national laws and regulations. Under the manufacturer's QMS this includes any testing and documentation, all of which is subject to auditing and review by the

NRA or CAB either before market introduction or on demand. All such testing is covered by, and forms part of the basis for, the manufacturer's declaration of conformity. As with other evidence of conformity held or submitted by the manufacturer, the testing evidence is subject to review by the NRA.

The manufacturer is also responsible for any testing that may be required as part of investigating product complaints, or adverse event and incident reports, as well for testing to verify the effectiveness of corrective and preventive actions.

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

- examination and testing of suspected SF medical devices (see section 8.5 below);
- investigation of devices allegedly involved in an adverse event;
- investigation of devices sent to the NRA by lay persons;
- systematic post-market testing of specific devices (either imported or locally produced) according to specific national public health priorities based on a plan (11);
- post-shipment lot verification of an IVD; and
- providing support for law enforcement investigations.

Given the diversity of medical devices, and the large number of medical devices in circulation, it is unlikely that an NRA will have the necessary resources to test all categories of medical devices including IVDs when testing is deemed necessary to verify their safety and performance. The work of the NRA may be supplemented through access to an independent accredited test laboratory (or laboratories). Testing of medical devices may be conducted by the national control laboratory (which is usually located within the NRA), the national reference laboratory, other external testing laboratories within or outside the country or by the medical device manufacturer in accordance with appropriate recognized international standards and guidelines.

The national regulations should include the option to outsource testing to competent laboratories. The organizational and governance structure, communications channels and responsibilities of entities conducting laboratory testing activities should be defined in the regulations. A memorandum of understanding with all stakeholders should be agreed upon and signed.

The competence of any testing laboratory should be evaluated by an accreditation body, and the NRA should further verify its competence before entering into the agreement. The national policy should also emphasize the need for provision of adequate funding for the human resources and infrastructure of testing laboratories. Countries that do not have well-resourced and accredited

testing laboratories are encouraged to adopt the mechanism of reliance on laboratory testing from other regulatory authorities or expert laboratories.

The NRA should establish criteria for the selection of testing laboratories. These criteria will include competent staff; adequate testing facilities; access to testing specimens, controls and reference materials; and analyte-specific accreditation to publicly available international standards such as ISO/IEC 17025:2017 (33) or ISO 15189:2022 (84) or equivalent. The integrity of laboratory testing should be maintained through effective implementation of an established QMS that includes policies and procedures for validation and verification of test methods and transfer of validated test methods, established standard procedures for the receipt, handling, storage and retention of samples received for quality testing and a management system for all laboratory records.

6.4 Stepwise approach – harmonization, reliance and recognition

Resolution WHA67.20 (1) emphasizes the importance of collaboration and harmonization and requests the Director-General of WHO:

... to prioritize support for establishing and strengthening regional and subregional networks of regulatory authorities, as appropriate, including strengthening areas of regulation of health products that are the least developed, such as regulation of medical devices including diagnostics.

and:

... to promote the greater participation of Member States in existing international and regional initiatives for collaboration and cooperation in accordance with WHO principles and guidelines.

The national regulation of medical devices takes place in an era of significant demographic changes, growing demand for access to affordable medical technologies at all levels of society in more countries, and an increasingly globalized world. These trends create a need for closer alignment of regulatory requirements and practices. Accordingly, countries that align their medical device regulations with existing harmonization guidance documents will help to advance the necessary regulatory convergence.

Resolution WHA67.20 also urges Member States to:

... engage in global, regional and subregional networks of national regulatory authorities, as appropriate, recognizing the importance of collaboration to pool regulatory capacities to promote greater access to quality, safe, efficacious and affordable medical products.

and to:

... promote international cooperation, as appropriate, for collaboration and information sharing, including through electronic platforms.

Harmonization, reliance and recognition will contribute to more effective regulatory systems, both directly and by supporting NRA capacity-building and the pooling of competence among authorities. These essential components of health system strengthening will contribute significantly towards better public health outcomes.

Table 6.3 illustrates which elements of basic-level and expanded-level regulatory controls are covered by existing international regulatory harmonization guidance (in red) and which may be implemented through reliance or recognition (in blue).

Table 6.3
Elements of regulatory controls for which international regulatory guidance has been developed and those that may be implemented through reliance or recognition

Expanded level controls and enforcement		
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 adverse events and incidents by manufacturers
Adopt standards		Inspection of registered establishments
Adopt medical device nomenclature system		Provide for testing laboratories
Control advertising and promotion		

Table 6.3 *continued*

Basic level controls and enforcement		
Pre-market	Placing on the market	Post-market
Publish law including definitions and regulations with transition period	Registration of establishments	Establish a system for reporting adverse events and incidents
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		

Note: 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.

7. Regulatory pathways

7.1 Regulatory pathways for pre-market conformity assessment of medical devices according to risk class

The regulatory pathways shown in Fig. 7.1 illustrate the steps required for the routine assessment of an application for market authorization for a medical device according to its risk class. Although determining the correct risk class of a medical device is primarily the responsibility of the manufacturer, a determination may be overruled by the NRA either before or after a device is placed on the market. The degree of scrutiny by the NRA or CAB of a device's conformity with regulatory requirements depends on the risk class of the medical device. Regardless of the classification and any market authorization by the NRA,

the manufacturer retains responsibility for ensuring the safety, performance and quality of the medical device, as evidenced by the declaration of conformity and supporting documents.

Fig. 7.1
Regulatory pathway according to risk class (see also Table 4.3 above)

	A	B	C	D
	↓	↓	↓	↓
Preparatory stage: collecting evidence of the safety and performance of the medical device	Device classification is determined according to the classification rules.			
	↓	↓	↓	↓
	Registration of establishment (manufacturer, authorized representative and/or importer or distributor)*			
	↓	↓	↓	↓
	Preparation and maintenance of the technical documentation according to requirements			
	↓	↓	↓	↓
	Evidence of effective implementation of QMS and declaration of conformity			
	ISO 13485 certificate or inspection/audit from an accredited organization is required			
	↓	↓	↓	↓
Market authorization procedure	Listing submission to the regulatory authority	Submission of technical documentation/dossier to the Authority/CAB (including clinical evidence and evaluation)		
	↓	↓	↓	↓
	Usually**, no review is required. Only notification to the regulatory authority is required.	Usually, administrative review only	Technical review	In-depth technical review
		Review is conducted, including a technical and administrative review. Novel and high-risk products may also be subject to an Expert Panel consultation.		
	↓	↓	↓	↓
				In-depth review of clinical evidence (may require clinical investigation)
	↓	↓	↓	↓
Approval				
	NRA lists the medical device	NRA issues market authorization when all requirements are fulfilled or sends notice of deficiencies or rejection.		

* Overseas manufacturer shall assign an authorized representative.
** Except for Class A devices that are sterile or have a measuring function: regulatory audit can be considered.

The length of the pre-market review process will vary depending on factors such as risk class of device, amount and nature of submitted evidence to be reviewed, complexity of device, degree of novelty of the device and/or its mode of action and/or its intended use, and on the availability of appropriate review staff. Fig. 7.2 shows the duration of key elements of the approval process by risk class based on best practices. The review periods shown are indicative and the NRA may consider applying different time limits. Where a jurisdiction does not require the periodic renewal of a market authorization, the indicative renewal times shown in Fig. 7.2 will not apply. Renewal intervals and review time for QMS certificates may also differ.

Fig. 7.2
Duration of key elements of the approval process, by 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
Validit period for device registrations		3–5 years	3–5 years	3–5 years
Market authorization renewal should be started this far in advance		6 months	6 months	6 months

7.2 Regulatory pathways for pre-market conformity assessment of medical devices based on reliance

Reliance is a process that may apply to several regulatory activities and decisions. Examples include reliance on assessments of technical dossiers or reports of inspections or audits performed by another NRA or a CAB, and on the evaluation of incidents made by another NRA where such incidents also affect the domestic market of the NRA. Acceptance and use of the results of tests conducted by collaborating laboratories in other jurisdictions may also be considered to be reliance. Fig. 7.3 outlines the steps to market authorization for a medical device based on reliance.

Fig. 7.3
Regulatory pathways based on reliance, by risk class

	A	B	C	D
	↓	↓	↓	↓
Preparatory stage: collecting evidence of the safety and performance of the medical device	Device classification is determined according to the classification rules.			
	↓	↓	↓	↓
	Registration of establishment (manufacturer, authorized representative and/or importer or distributor)*			
	↓	↓	↓	↓
	The applicant assesses sameness** of the products, submits application and other relevant documentation based on requirements of the reference institution.			
	↓	↓	↓	↓
	Evidence for an effective QMS implementation and declaration of conformity	Upon manufacturer consent, reference regulatory authority or other trusted institution exchange assessment reports with the relying NRA.		
Market authorization	↓	↓	↓	↓
	Usually***, no review is required. Only notification to the regulatory authority is required.	Relying NRA conducts abbreviated assessment of the shared reports based on national requirements.		
	↓	↓	↓	↓
Approval	NRA lists the medical device.	NRA issues market authorization when all requirements are fulfilled or sends notice of deficiencies or rejection.		

* Overseas manufacturer shall assign an authorized representative.

** 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 reliance practices.

*** Except for Class A devices that are sterile or have a measuring function: regulatory audit can be considered.

Fig. 7.4 shows the duration of key elements of an approval process based on reliance, by risk class and according to best practices. The NRA may consider applying different time limits. Where a jurisdiction does not require the periodic renewal of a market authorization, the indicative renewal times shown in Fig. 7.4 will not apply. Renewal intervals and review time for QMS certificates may also differ.

Fig. 7.4
Duration of key elements of an approval process based on reliance, by risk class

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
Validit period for device registrations		3 years	3 years	3 years
Market authorization renewal should be started this far in advance		6 months	6 months	6 months

7.3 Regulatory pathway for emergency use authorization or derogation

Public health emergencies often stress the entire health care system. NRAs play an important role in responding to emergencies by enabling the timely availability of medical devices intended to help address the public health threat (85–93).

The NRA should establish policies and processes to allow emergency authorization of previously unmarketed medical devices, or derogation from the routine assessment procedure for previously unmarketed devices that are considered essential in managing public health emergencies. The adoption of such mechanisms enables regulatory agility in responding to an emergency and should be a critical component of national emergency preparedness.

The main purpose of an emergency regulatory authorization mechanism or derogation procedure is to allow the use of previously unmarketed medical devices during a public health emergency where the available evidence reasonably suggests a potential benefit, some minimal criteria have been met and a basic regulatory review has been performed.

Reviews should support risk-based regulatory decisions, weighing the potential risks of a previously unmarketed device against the potential risks posed by the public health emergency. Such decisions should be based on the evidence submitted to support the emergency authorization request, supplemented with additional monitoring after authorization and ongoing review of safety and performance evidence to adjust the regulatory decisions as necessary and as more evidence becomes available.

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

1. The medical device is needed:
 - to treat or diagnose any medical condition resulting from a public health emergency;
 - to prevent the spread or possible outbreak of an infectious disease;
 - to treat or diagnose an infectious disease or any medical condition associated with an infectious disease, where the medical condition or infectious disease is potentially serious or life threatening; and
 - no safe and effective alternatives have previously been authorized or are reasonably available.
2. In the understanding of the NRA, there is:
 - preliminary scientific evidence that the medical device has the potential:
 - to treat or diagnose the medical condition resulting from the public health emergency,
 - to prevent the spread or possible outbreak of an infectious disease, and
 - to treat or diagnose an infectious disease or any medical condition associated with an infectious disease.
 - continued scientific evidence that the potential benefits of the medical device outweigh the known risks of the medical device to a person on whom the medical device is used, and;
 - a strong post-market surveillance structure and market surveillance system to monitor product safety and performance, update the benefit–risk assessment and reduce the chance of SF products reaching the market.

The applicant⁸³ is required to actively seek and submit more evidence as it becomes available.

To develop and establish the minimum criteria for evaluating the safety and performance of such emergency use medical devices, the NRA should consult with experts at the national, regional or, in some cases, global level before such products are placed on the market.

Any emergency authorization strategy should provide for transparent disclosure of the evidence requirements and evaluation criteria. The NRA should also establish a limited validity period for such measures and for the

⁸³ The legal person or institution that applies for registration of a product on behalf of the manufacturer (140).

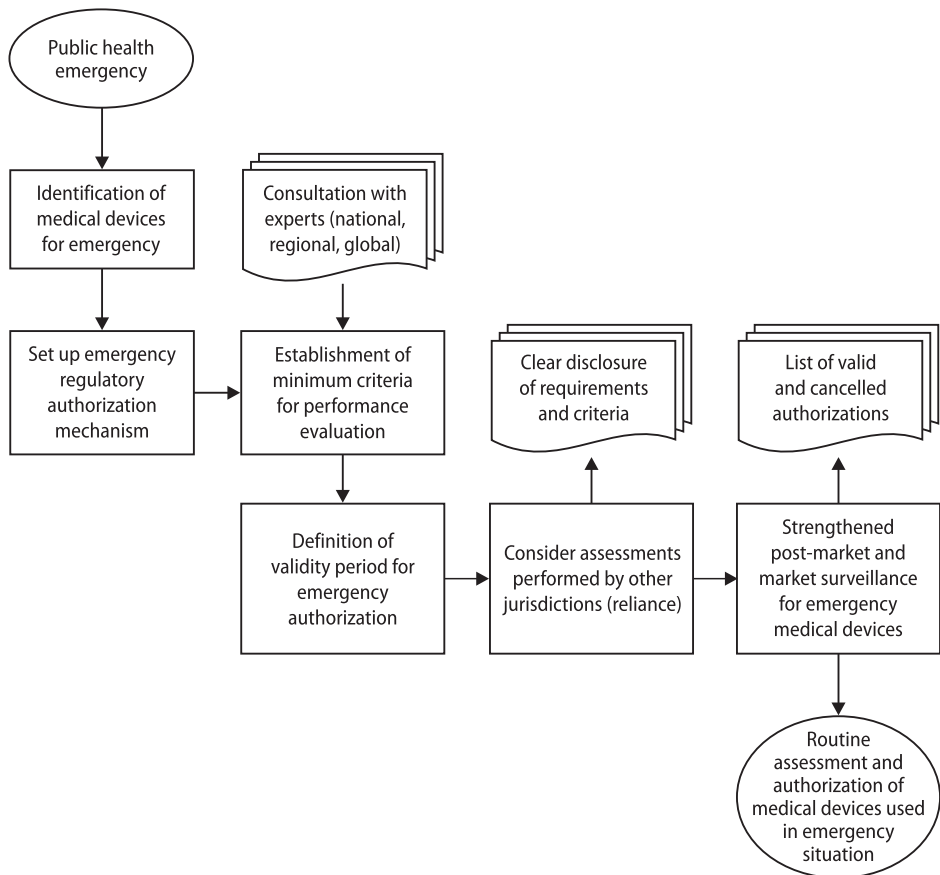
authorized medical device so that the evidence assessed during the emergency period may be proved, disproved or strengthened. The period of validity of the data assessed for authorization should be clearly disclosed so that health services and professionals do not purchase or use products for which emergency authorizations have expired or been cancelled.

As part of post-market surveillance, manufacturers should continuously monitor post-market data on the safety and performance of the medical device as such evidence becomes available. When adequate supporting data have been compiled, a complete assessment of the product using routine review procedures should be conducted by the NRA.

A diagrammatic summary of these and other steps in the emergency use authorization process is shown in Fig. 7.5.

Fig. 7.5

Process for emergency use authorization



7.4 Regulatory pathway for borderline products

The field of borderline products⁸⁴ is becoming more complex due to advances in technology, conflicting regulatory decisions and changing regulations in different jurisdictions. A lack of clarity in such cases may lead to difficulty in determining appropriate regulatory requirements. In some jurisdictions, no separate regulation or specific guidance for such medical products exist. It is in the public interest to ensure the safety, quality and performance of all borderline products through appropriate regulatory controls, either those used for medical devices or those used in other regulated products sectors.

7.4.1 Background information and approaches to improve the regulation of borderline products

Although many products are used in the delivery of health care, not all fit exclusively within the existing definition of a single category of medical product, and more specifically that of a medical device. An increasing number of products are characterized as borderline – an ambiguity that exists for either innovative products that do not clearly fall under current regulations or those that fall within the overlaps of existing regulations. For reasons of transparency, predictability and proportionate regulatory control, it is important to have established demarcation lines between different product categories. This will allow for the identification of appropriate regulatory requirements and authorization pathways under legislation most appropriate for such products (94–100).

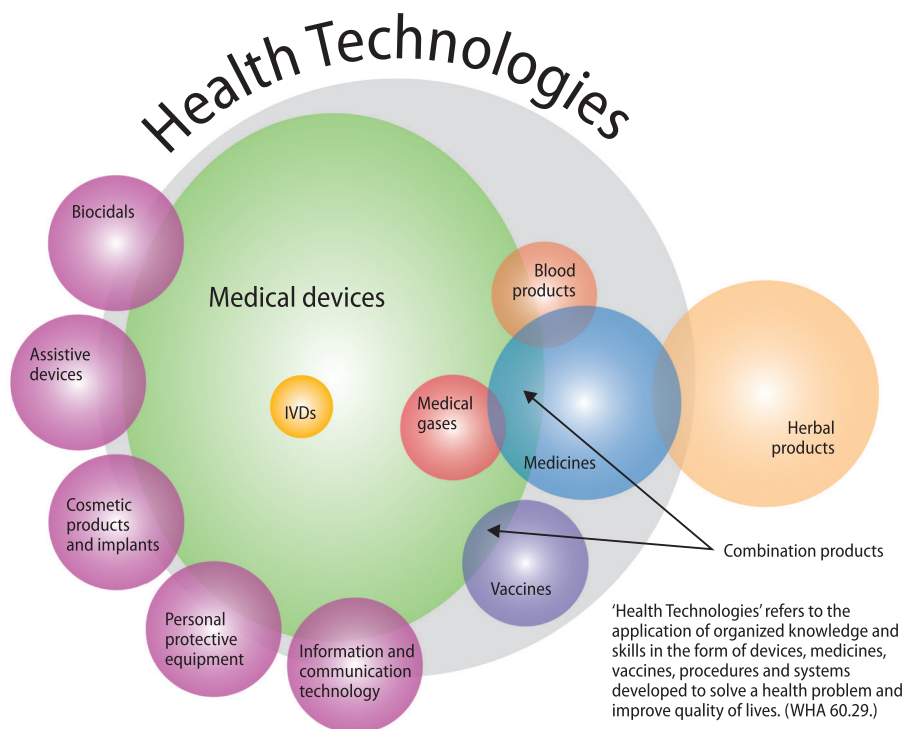
Borderline products are considered to be products where it is not immediately clear whether a given product is to be regulated as a medical device or as something else (Fig. 7.6). In the absence of internationally harmonized guidance, these products often pose a challenge to medical device regulators across the world.

Some medical devices have characteristics that place them near the definitional borderlines with medicines, cosmetic products and implants, air purifiers, PPE, biocidals, blood products, herbal products, information and communication technology products, assistive devices and medical gases, as well as products for general laboratory use, products used for hospital support or infrastructure, products for personal or home use, and products for common use employed as parts or accessories of health care products.⁸⁵

⁸⁴ Borderline products are generally (medical) products that have characteristics covered by at least two bodies of legislation (for example, both medical device and medicine), where the primary or lead legislation within a jurisdiction may be unclear. In the context of use in combination with other medical products or components, some products that appear to be borderline may instead be considered to be combination products (see also section 7.5 below).

⁸⁵ This is not intended to be an exhaustive list of borderline products but rather to provide illustrative examples.

Fig. 7.6
Examples of borderline products



A product may be considered to be a medical device in some countries but not necessarily in others. Manufacturers should always refer to the definitions of a medical device and other relevant regulations in the country in which an application is planned (101–103).

To ensure predictability and transparency, the NRA should develop criteria and mechanisms for determining the appropriate regulatory regime for borderline products through established guidance. It should describe the considerations and 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 manufacturer(s) concerned. It may also take into account regulatory decisions made by the 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 a medical device. Such a designation may be 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, and intended use and indications for use of the product (for example, cosmetic contact lenses, wound-healing gel, etc.).

NRAs may take decisions on a case-by-case basis, considering all the characteristics of the product and its medical purpose. A committee or working group on borderline products may be appointed to advise the NRA when deciding on the designation of a product. The decision of the NRA on the regulatory status of a given product should be published and the option of appeal provided should the applicant disagree with the decision.

7.4.2 Points to consider in determining whether a product is a medical device

NRAs should refer to the medical device definition when making any borderline product determinations (6). It is important to note that not all equipment used in health care settings or by a health care professional meets the definition of a medical device.

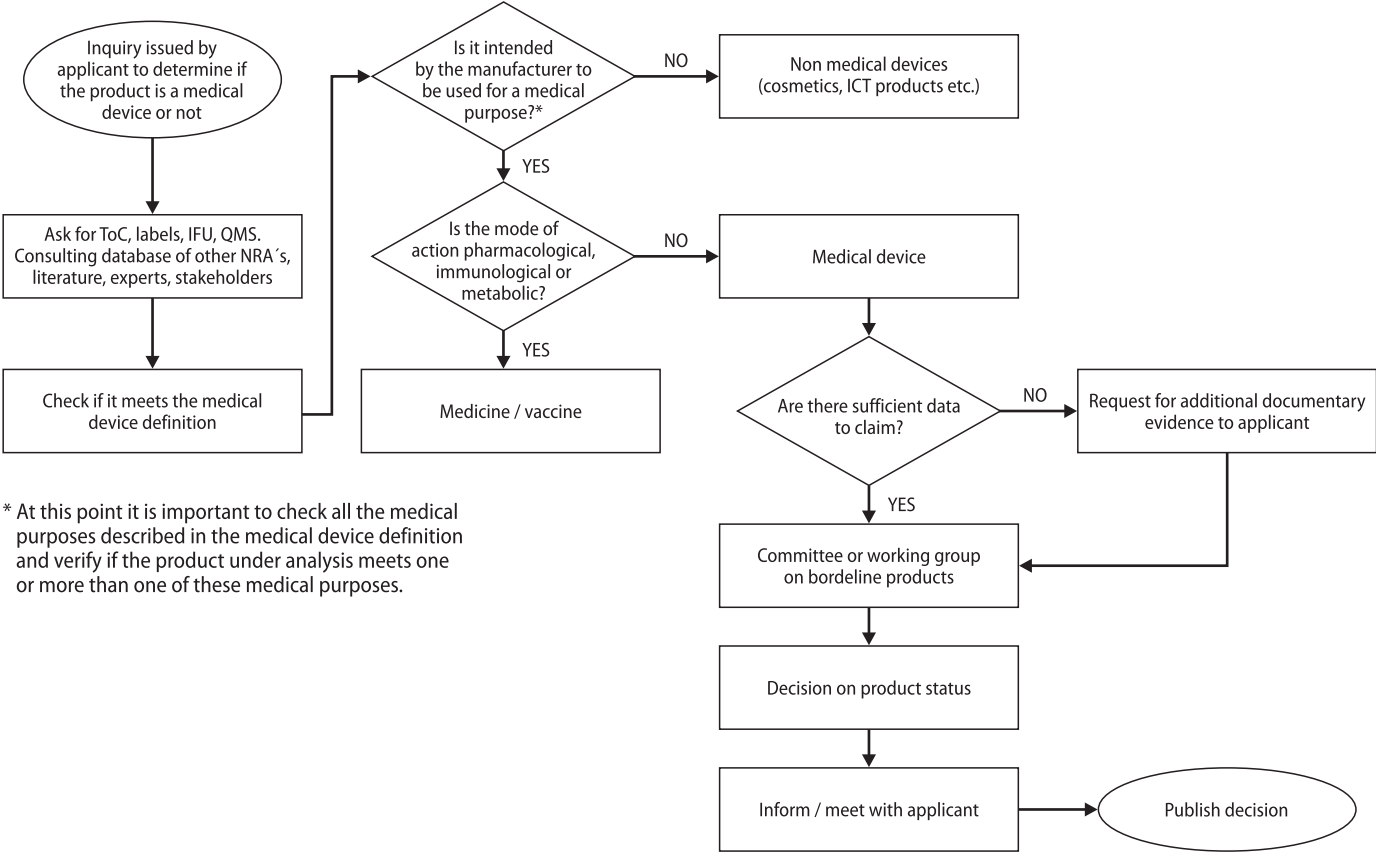
In order to decide whether a product is a medical device, the NRA should consider:

- how the product is presented to the NRA and to the market in terms of labelling, packaging, promotional literature and advertisements, including on websites;
- the intended purpose of the product, as declared by the manufacturer, including the claims made (both explicit and implicit);
- the claimed “medical purpose” as outlined in the definition of a medical device given in section 4.1 of this GMRF;
- the mode of action – medical devices do not attain their primary mode of action through pharmacological, immunological or metabolic means, but may be assisted by such means; and
- whether there are any similar products on the local market and how they are being regulated.

Some of this information may be obtained by consulting with regulatory authorities for other product categories. If available, the applicant may submit evidence of product classification and market authorization by a reference regulatory authority. A proposed process for making a borderline product determination is shown in Fig. 7.7.

Fig. 7.7

Process for borderline product determination



7.5 Regulatory pathway for combination products

There is no internationally harmonized definition of a combination product.⁸⁶ If defined, the definition may vary across regulatory jurisdictions, especially as the field continues to evolve. A combination product is typically defined⁸⁷ as a product consisting of two or more different types of medical products (that is, a combination of a medicine, device and/or biological product). The medicines, devices and biological products included in combination products are referred to as the constituent parts of the combination product. The medicine constituent of a combination product may be a pharmaceutical, radiopharmaceutical, natural health product, biological, cell, tissue, organ, gene therapy or human blood and its components.

Some jurisdictions have distinct definitions for medicines and biologicals. As a result, there may be both medicine-device and biological-device combination products.

The evolution of medicines and medical technologies worldwide has created a broad spectrum of medicine-device combination products that range from long-established and relatively simple in nature to highly complex. Examples of medicine-device combination products include drug-eluting stents, pre-filled syringes, transdermal medicine patches, metered dose inhalers, heparin-coated vascular catheters and orthopaedic bone cement containing antibiotics.

Combination products constitute a distinct category of medical product subject to specific regulatory requirements. The requirements for combination products arise from and combine elements of the separate statutory and regulatory requirements applicable to medicines, devices and biological products. These requirements may need to be adapted when applied to the constituent parts of a combination product, either alone or in combination. Specific regulatory requirements for combination products are generally designed to address the risk-based considerations raised by the combined use of the constituent parts. These may include the overlaps and distinctions between the requirements applicable to the drug, device and biological product constituent parts that constitute them, and specific requirements for their use in combination (104, 105).

⁸⁶ A combination product is defined by many jurisdictions as a product comprising two or more different types of medical products (that is, 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.

⁸⁷ For example, by Health Canada (<https://www.canada.ca/en/health-canada/programs/consultation-issue-identification-paper-drug-device-combination-products-draft/document.html>), accessed 9 February 2023) and USFDA (<https://www.fda.gov/combination-products>, accessed 9 February 2023).

7.5.1 Considerations in regulating combination products

In the interests of consistency, transparency and predictability, the NRA should publish the guidance it has adopted on how to:

- determine what qualifies as a combination product;
- designate an appropriate regulatory pathway; and
- establish suitable pre- and post-authorization requirements.⁸⁸

The NRA should publish designation criteria and establish a process by which an applicant may obtain a designation decision from the NRA. Where necessary, the process may allow for consultation with subject matter experts as well as with regulators from other product sectors, and with the manufacturer or authorized representative concerned. Regulators may also take into account determinations made by the NRAs of other jurisdictions. The NRA may take decisions on a case-by-case basis, taking into account all of the characteristics of the product. The decision of the NRA on the designation of a given product should offer the option of appeal should the applicant disagree with the decision.

The NRA should designate a product that combines a medicine, a biological product and/or a device as a combination product. Some combination products will be designated as primarily subject to the regulatory requirements for medicines and others to the requirements for medical devices. The designation may be based on the primary mode of action (40) 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 requirements. Where the principal action is not achieved by pharmacological, immunological or metabolic means, but may be assisted in that action by such means, the combination product should be primarily subject to medical device regulatory requirements.⁸⁹ Elements of both medicine and medical device regulations may be applicable (106, 107).

Product designation should lead to the development of a single product-specific pathway for market authorization, combining elements of both sets of requirements. Creating such a single regulatory pathway will help streamline effective product review, while taking into account the particulars

⁸⁸ Good manufacturing practice/QMS requirements may be developed specifically for combination products (for example, <https://www.fda.gov/media/90425/download>, accessed 9 February 2023) or should follow the regulatory requirements of the constituent parts of the combination product.

⁸⁹ If a medicine is incorporated in a medical device, according to the IMDRF classification rules, it is always a Class D medical device (<https://www.imdrf.org/sites/default/files/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n15-2006-guidance-classification-060627.pdf>, accessed April 2022).

of each constituent part. It will also reduce any overlapping administrative requirements. The pathway will determine both the type of application, data requirements and type of market authorization review process required for the combination product, with the criteria for review differing depending on whether the product is designated as predominantly a medicine or as a medical device.

In addition to directing the combination product into the appropriate regulatory pathway, the NRA should also decide on the extent of the requirements to apply to its constituent parts. For example, the safety and performance of the medical device that contains a medicinal substance should be verified as a whole, along with the identity, safety, quality and efficacy of the medicinal substance in its intended function in the specific combination product (108). The pathway should provide for timely and appropriate consultations and information exchange between medical device and medicines technical experts during the process of reviewing the market authorization application.

Beyond the pre-market evaluation requirements, the NRA should establish specific requirements for the manufacturing, quality assurance, testing and distribution of the combination product. These requirements would generally be based on established medicines good manufacturing practices (GMP) or medical device QMS requirements, adapted as appropriate to the product designation. The NRA should also establish requirements for inspections and audits, either by the NRA or CAB. Depending on product designation, the NRA should also establish specific requirements for post-market surveillance and adverse event and incident reporting, adapted as appropriate from the respective medicines and medical device requirements. As both the medicines and medical device NRA departments will have an interest in adverse events and post-market surveillance field performance information, an effective coordination mechanism should be implemented.

The use of reliance and recognition in evaluations of medicine-device combination products may be more difficult due to the diversity and complexity of such products and to differences in regulations between jurisdictions. General reliance principles (see section 5.9 above) should be applied. As there is currently no international harmonization guidance for combination products, NRAs using reliance or recognition should consider which requirements in other benchmark jurisdictions would best serve their country's needs. Given the current challenges in the regulation of combination products, medical devices stakeholders should support and encourage international regulatory harmonization forums in pursuing convergence and harmonization efforts in this field.

7.6 Regulatory pathway for donated medical devices

Donations to LMIC of medical devices including IVDs can be very helpful and may improve the efficiency of health facilities, save on the costs of purchasing new medical devices, and make some diagnoses or therapies accessible to patients, especially in resource-limited settings. Although donations may thus be beneficial, they can also pose health risks if the safety and performance of the donated medical devices are not verified and/or the devices do not correspond to the clinical needs, use environment and skills of end-users and local technical staff. Other potential challenges include the lack of clear documentation, appropriate labels and labelling on the donated medical device, and data on its state, origin and technical and service history. There is also often a lack of clarity regarding the responsibilities of donors (109).

Quality and other problems associated with donated medical devices have been reported in many countries (110, 111). Such problems have included short or outdated expiry dates, defective medical devices⁹⁰ and gifts or donation of unnecessary items not requested by the recipient. These factors often result in the receiving countries incurring unwanted costs for the maintenance and disposal of the donated medical devices. Donations may also create the impression that the medical devices are “substandard” or even waste that donors have “dumped”⁹¹ on receiving countries (110–112). For these reasons, some countries have banned the donation of used equipment. Before donating medical devices including IVDs, WHO recommends (112) that a number of core principles be taken into account, including that donated devices should:

- address an expressed request from the end-users, corresponding to a real clinical need;
- be authorized by the regulatory authorities of the receiving country and/or meet current international safety standards;
- have all their necessary parts and accessories;
- be accompanied by documentation in a language understood in the receiving setting;
- be adapted to the local context, such as the electrical power supply;
- match the operating and maintenance human resources, skills and capacities and/or be accompanied by training; and

⁹⁰ Donated used durable medical equipment is often not accompanied by documentation of its 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.

⁹¹ The dumping of obsolete equipment by high-income countries has been described as “morally reprehensible” (111).

- be imported with a plan for their 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.⁹²

Authorities in countries from which donations originate are urged to develop policies, regulations and guidelines on the exportation of donated medical devices to other countries, particularly to prevent the export of waste or hazardous medical devices to LMIC. A national policy for donations in the receiving country is also vital for guiding all parties involved so that they may develop their own institution-level operational donation guidelines and standard operating procedures based on this policy.

Policy on donations should cover the following three phases:

1. Pre-donation phase – assessment and identification of potential recipient(s), familiarization with requirements, donation proposals, agreement between donor and recipient, application to obtain authorization to export/import donated medical devices, commitment letter confirming their safety and performance, and application to import/export.
2. Donation phase – importation, document verification, physical inspection, sample collection (where applicable) and verification studies (where applicable).
3. Post-donation phase – installation and commissioning, verification of functioning status and post-market surveillance;⁹³ this implies feedback to the donor on device performance and post-market surveillance data.

To safeguard public health, medical devices imported as donations should comply with all regulatory requirements on safety, quality and performance, and should not differ in this regard from devices imported through a regular supply chain. It is the responsibility of the donor, charity organization, private person or medical devices company – in consultation with the recipient and vice versa – to ensure that medical devices intended for donation are in compliance with the

⁹² Upon arrival, the remaining shelf-life of the medical devices (specifically IVDs) should be reasonable and should allow for the use of the entire donated lot according to the specifications set between donor and recipient (<https://apps.who.int/iris/bitstream/handle/10665/255577/9789241512558-eng.pdf>, accessed 15 January 2023).

⁹³ 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.

regulatory requirements of the receiving country. This also applies to donations made within a jurisdiction. Even during emergency situations (such as natural disasters, pandemics, etc.) public safety takes precedence and recipients should therefore still take action according to the national guidance on donations.

Regulatory authorities should establish a mechanism to verify and authorize the importation of donated medical devices. Institutions that intend to donate devices should communicate with the recipient to determine their needs, make relevant donation proposals and obtain their approval before the products are shipped. To avoid delay and additional expense, importation documents and supporting documents must be submitted to the NRA of the recipient's country for assessment and authorization before shipment of the consignment. These documents will typically include but are not limited to: (a) a list of the products to be donated; (b) each product's (package) label; (c) name and address of the manufacturer(s) of the products; (d) evidence that the products are approved/authorized in the donor's country or the manufacturer's QMS certificate (for high risk class medical devices); (e) expiry dates (if applicable); and (f) a commitment letter confirming the safety and performance of the devices to be donated, along with all documentation of proof of proper functioning (112). All donors are required to familiarize themselves with the donation requirements in force in the receiving country before they decide to donate medical devices. Donations that do not comply with the requirements should be rejected and sent back to the donor at the donor's expense. The typical steps and stakeholder responsibilities in the donation of medical devices are shown in Fig. 7.8.

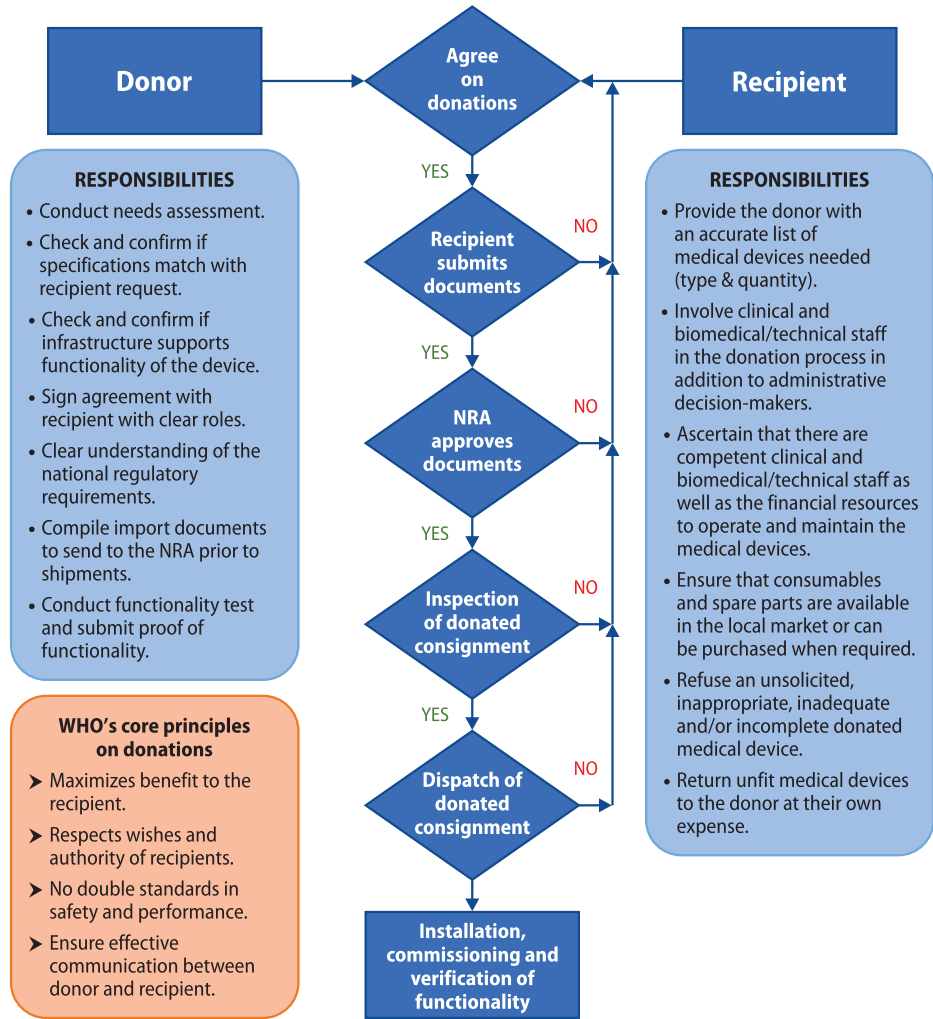
8. Additional topics

Beyond the general elements covered in earlier sections of this GMRF there are also a number of specific topics that must be considered when developing and implementing regulations for medical devices. This section explains the relevance of these topics and provides guidance for regulators on ensuring that they are appropriately addressed.

8.1 Disposal

A medical device that reaches the end of its intended life-cycle 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 to ensure that it will not be re-used if it is confirmed that the device can no longer perform its function properly and may present a hazard to users or patients.

Fig. 7.8
Steps and stakeholder responsibilities in the donation of medical devices



The 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 or potentially pathological materials such as human organs or unused blood products. Medical device labelling and the IFU or e-labelling should include instructions on the proper decontamination and disposal a device at the end of its life-cycle. Where the NRA has identified SF

medical products, it shall itself document a procedure for their local disposal (for example, mandatory destruction at an approved facility).⁹⁴ This will ensure that such SF 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 IVDs, decontamination and proper waste management practices according to the manufacturer's instructions should be followed based on national and international standards.⁹⁵ The responsible NRA, in coordination with other concerned governmental bodies, should establish criteria for replacement and decommissioning based on the manufacturer's recommendations. Consultation between the user and manufacturer is critical, especially for high-technology and complicated products, in order to decide upon the best way to dispose of them. Separate guidance is to be provided to the health care system by the Ministry of Health on the disposal of hospital waste.

8.2 Reprocessing of single-use medical devices⁹⁶

In general, regulatory and public health concerns about the reprocessing and re-use of devices labelled by their original manufacturer as single-use medical devices (SUMDs) include: lack of regulatory controls and oversight, responsibilities for reprocessing not established, variability in reprocessing methods, risk assessment not performed, and reprocessing not performed under a QMS, which all lead to lack of control with regard to cross-infection, contamination, residues of disinfectants, mechanical failure, endotoxins and labelling.

The perceived advantages to health care practices of cost-effectiveness and waste reduction measures 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 that could pose a risk to patients. Exposure to repeated sterilization processes may also change the properties of, or degrade, the device material. The high temperatures and harsh chemicals sometimes

⁹⁴ An example of specific guidance on the disposal of unfit products can be found at: [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) accessed 10 February 2023).

⁹⁵ For example, the Waste Electrical and Electronic Equipment (WEEE) EU directive: https://ec.europa.eu/environment/topics/waste-and-recycling/waste-electrical-and-electronic-equipment-weee_en accessed 10 February 2023.

⁹⁶ Single-use medical devices (SUMDs) are also referred to as disposable devices or single-use devices (SUDs).

used during reprocessing may also 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 also arise. They include potentially exposing a patient, with or without informed consent, to harms to which they would not otherwise have been exposed, and 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. For regulatory and liability purposes, the entity that reprocesses a medical device becomes the new manufacturer with all the associated responsibilities. If fully accounted for, the costs of reprocessing an SUMD using a controlled and validated process are such that the claimed savings may not be realized.

A device designated by the original manufacturer and labelled as single-use should not be re-used, except in extremely rare and dire situations, and then only as subject to specified controls (see next paragraph below). SUMDs are not intended to be reprocessed and used again, even for the same patient. They should only be used in or on an individual patient during a single procedure and then discarded. SUMDs are not provided with appropriate instructions for cleaning, disinfecting or sterilizing after use, and the manufacturer generally has not investigated deterioration in safety and device performance if subject to reprocessing. Because device conformity to its original specifications for safety, quality and performance cannot be assured, a patient or user may be endangered when SUMDs are reprocessed and used more than once.

In exceptional situations, the NRA, after considering all potential risks and benefits, may opt to allow the reprocessing of specified SUMDs (43, 113, 114). In extremely rare and dire situations, such as a global pandemic, reprocessing may be permitted even if the devices do not fully meet the specifications of the original manufacturer (115, 116). The conditions applicable to these situations are restricted to specific medical devices, for example single-use surgical masks and respirators,⁹⁷ for a limited period of time and only after performing a validation of the reprocessing process. In such circumstances, the NRA should develop specific guidance that describes the conditions applicable to the reprocessing and labelling of SUMDs, whether by a third-party manufacturer or a health care facility.

In adopting a policy on the reprocessing of SUMDs in non-emergency situations, the NRA should require that 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 the manufacturer

⁹⁷ <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 February 2022.

for regulatory purposes (43, 113, 117) and assumes all the obligations of a manufacturer, including assuring safety, quality and performance, labelling, the declaration of conformity, post-market surveillance and incident reporting. That entity also takes on the obligations to: (a) conduct a risk assessment (including analysis of device construction and materials, and use of procedures to detect changes in the design of the original device, as well as in its planned application after reprocessing); (b) validate the reprocessing process; (c) establish a QMS; and (d) ensure traceability after product release (117, 118). The original manufacturer should be identified in the technical dossier submitted to the NRA. The label of the reprocessed SUMD does not necessarily carry the name of the original manufacturer – however it should carry the name of the entity reprocessing the SUMD and should clearly indicate that the SUMD has been reprocessed (119).

8.2.1 Reprocessing SUMDs – health care facilities

Regulatory requirements for reprocessing should also apply to a health care facility reprocessing SUMDs for re-use within its own facility. The reprocessing of an SUMD in a health care institution must be performed so as to ensure the safety, quality and performance of the reprocessed medical device. This would include: (a) conducting a risk assessment (including analysis of device construction and materials, and use of procedures to detect changes in the design of the original device); (b) validating procedures for the entire process, including cleaning steps, product release and performance testing; (c) establishing a QMS; (d) reporting incidents involving reprocessed devices; and (e) ensuring the traceability of reprocessed devices (36). If a health care facility is not able to meet these conditions, it shall refrain from reprocessing SUMDs (120, 121).

If a hospital performs SUMD reprocessing for sale or transfer to another entity, then it must conform to the regulatory requirements applied to commercial third-party reprocessors.

8.2.2 Post-market surveillance of SUMDs

Post-market surveillance requirements apply to all medical devices, including reprocessed SUMDs regardless of the entity that reprocessed the SUMD – whether this is the original manufacturer, commercial reprocessor or health care facility. When investigating incidents and adverse events, the NRA should consider the possibility that the reprocessing of SUMDs may have been a contributing factor.

8.3 Refurbishing medical devices

Some durable electromedical devices or mechanical medical devices are meant to be re-used many times over a long design life. To assure their continued safety and performance, preventive maintenance, service, calibration and repairs are

often required once a device is placed into service. In some cases, devices may also be subject to refurbishing by an organization or entity other than the original manufacturer to extend their service life, often for economic reasons, either for the original purchaser or for sale to another party.

Refurbishing may be described as the restoration of a device to a condition of safety and performance that is comparable to its condition when new (42, 122–124). This includes reconditioning, installation of software and/or hardware updates that do not change the intended use of the original device, and replacements of worn parts or parts with known limited service lives. Refurbished medical devices should be identified as such on the labelling and in commercial documents. Spare parts supplied for the replacement of existing components of a medical device that has already been put into service are not usually considered to be medical devices. If, however, those parts are likely to significantly change the intended purpose, characteristics or performance of the finished device then their installation may be considered as a change to the medical device and should be assessed accordingly.

In adopting a policy on refurbishing, the NRA should clearly state that the entity responsible for refurbishing and the refurbished device itself 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, including the QMS certificate, technical documentation and declaration of conformity, as manufacturers of new devices. Insofar as they may affect the safety, quality, performance and/or conformity of the finished device, the NRA should also clearly state the role of the original equipment manufacturer in providing information to facilitate device maintenance, service and repair, as well as decommissioning at the end of service life (125). For regulatory purposes, the routine maintenance and repair of a device and replacement of parts should not be considered refurbishment.

8.4 **New medical device technologies – software as a medical device (SaMD) and software in a medical device (SiMD)**

Medical devices and health care are increasingly incorporating emerging technologies, including computing platforms, connectivity, software and sensors in diverse and interoperable systems. These technologies hold the promise of improved safety, performance and reliability, smaller size, energy efficiency, remote use by less-skilled operators, and new therapeutic and diagnostic capabilities. Current examples of such technologies include standalone software for medical purposes, networked systems, computational modelling and simulation, machine learning (ML) and artificial intelligence (AI). A decision to regulate SaMD depends on whether it meets the requirements of the statutory definition of a medical device.

The IMDRF defines medical purpose software as generally including:

- software as a medical device (SaMD); and
- software in a medical device (SiMD) – sometimes referred to as “embedded” or “part of”.

SaMD may have requirements and limitations defined by the platforms on which it is intended to be deployed, and on the broader connected systems in which it may be used. SiMD may have similar considerations to SaMD but may also have functional requirements that are driven by the relationship between the software and hardware components of the device (45).

AI is a branch of computer science, statistics and engineering that uses algorithms or models to perform tasks and exhibit behaviours such as learning, making decisions and making predictions (126). ML is a subset of AI that allows systems to “learn” through data analysis without models being explicitly programmed. An ML-enabled medical device (MLMD) is a medical device that uses ML, in part or in whole, to achieve its intended medical purpose. For “traditional” medical devices, manufacturers generally make modifications by planning future changes and collecting data before performing a planned change request and, in some cases, obtaining a new market authorization. One potential of MLMDs is the ability to incorporate continuous learning, where the MLMD may be continuously exposed to new data such that its performance may change as it learns and adapts continuously over time, rather than being updated through discreet manufacturer-initiated modifications. While continuous learning has potential benefits in maintaining or improving the performance of MLMDs in real world use, such learning also presents unique risks and may require different approaches to oversight than other software or hardware medical devices (35, 127).

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 (128).

While medical device software may provide significant potential benefits in improving patient access and quality of health care, these technologies may also present different regulatory challenges than those associated with hardware medical devices. For example:

- Medical device software might behave differently when deployed in 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 themselves to perform updates than may generally be the case with hardware devices.
- Due to its non-physical nature (a key differentiating characteristic), medical device software may be duplicated in numerous copies and widely spread, often outside the control of the manufacturer (62, 127, 129).

A plan for clear and timely communication between manufacturers and device users over the life-cycle of the software may be a critical consideration when evaluating the safety and effectiveness of device software functions in the context of their use.

In addition to the general considerations of medical device safety, quality and performance, device software functions must also be secure to ensure their continued safe functionality. The need for effective cybersecurity has become more important with the increasing use of wireless, internet and network-connected devices. Several cybersecurity incidents have rendered medical devices and hospital networks inoperable, disrupting the delivery of patient care across health care facilities (130).

Regulatory systems must have the capacity, either directly or through reliance, to accommodate the diversity of both SaMD and SiMD, and to assure high levels of device safety, quality and performance. Consistent with GRP, regulatory controls should be proportionate to the risks and benefits, including those arising from the technologies incorporated in devices.

Using a risk-based approach based on the intended use of SaMD, IMDRF has published a proposed risk-categorization framework (51). The framework proposes that the intended use of SaMD can generally be described using two factors – “A: Significance of the information provided by the SaMD to the health care decision, and B: State of the health care situation or condition.” Based on these two axes, the framework proposes that SaMD can then be categorized into four categories (I–IV), with category IV devices considered to be of very high impact (51, 131).

Table 8.1
SaMD categories⁹⁸

State of health care situation or condition	Significance of information provided by SaMD to the health care decision		
	Treat or diagnose	Drive clinical management	Inform clinical management
Critical	IV	III	II
Serious	III	II	I
Non-serious	II	I	I

While applicable to device software functions broadly, the IMDRF notes that:

... a SaMD manufacturer is expected to implement on-going lifecycle processes to thoroughly evaluate the product's performance in its intended market (13).

It is important that, for both SaMD and SiMD, manufacturers demonstrate:

- 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) and corresponds accurately to the real world health care situation or condition identified in the SaMD definition statement;
- analytical validity – measures the ability of SaMD to accurately and reliably generate the intended technical output from the input data; and
- clinical performance – the ability of a device to yield results that are correlated with a particular clinical condition/physiological state in accordance with the target population and intended users (13).

The manufacturing of SaMD, which is a software-only product, is primarily based on development life-cycle activities and is often supported by automated software development tools. However, the principles in a QMS will continue to provide structure and support to the life-cycle processes, and QMS

⁹⁸ From Table 8.1 source document (51): The approach developed in this document is intended only to establish a common understanding for SaMD and can be used as reference. This document is not intended to replace or modify existing regulatory classification schemes or requirements.

activities will still be applicable and important in controlling the quality of SaMD (132, 133). NRAs and CABs should consider what relevant expertise is required for reviewers and QMS auditors of SaMD, and whether that expertise can best be acquired directly or through reliance on the work of reference regulatory authorities.

Increasingly, medical devices that employ SaMD and SiMD, including MLMD, are being made available in regions with limited regulatory systems and capacities, and that are primarily dependent on imported products. The NRA or CAB should verify that the data used in development, verification and ML databases are representative of the local population and conditions. Data quality assurance and data management should be taken into consideration as part of the manufacturer's QMS and requirements for evaluating dataset quality should be established. Training datasets and test datasets should be maintained independently of each other. Monitoring of the MLMD post-deployment will help to ensure its continued safety and performance, as potential variations in real-world data may impact upon the robustness and generalizability of algorithms (132).

Policy-makers and NRAs in 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 placing on the market in countries or regions with mature regulatory systems may not be the most appropriate use of limited local resources. The NRA in countries with less developed regulatory systems should consider whether reliance could be used to provide evidence during the assessment of SaMD and SiMD, including evidence of the safety, performance and quality of MLMDs. Local review should focus on, for example, the local burden of disease and the applicability of the device to local population(s). It should also consider the need for regular software updates, the adequacy and appropriateness of labelling and promotional materials in the local language, local distribution practices, appropriateness for local conditions of use and maintenance, user training, and local post-market surveillance requirements. Because SaMD can be placed on the market quickly, widely and in large numbers, appropriate requirements for post-market surveillance, clinical evaluation and risk management must be in place (13, 51, 132, 134). Beyond the general requirements for post-market surveillance, and adverse event and incident reporting, regulators should also consider establishing specialized protocols for the market surveillance of SaMD, SiMD and MLMDs that incorporate the collection of real-world evidence (11).

- Recognized international standards – as part of the pre-market conformity assessment process, the NRA should verify the extent to which the manufacturer and/or applicant have applied recognized international standards in device design, development, verification and manufacture. This is especially important in the case of software (either as a standalone device or incorporated into a device) and networked device systems as they generally cannot be verified by inspection or testing alone.
- Appropriateness to local populations and conditions – for MLMDs the NRA should consider whether the clinical study participants and datasets adequately reflect the intended patient populations (for example, with regard to age, sex, race and ethnicity, disease severity and co-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 NRA should examine how its continued safety, risks and benefits will be assured under local conditions. The expertise of data and computer scientists, as well as biomedical engineers or other professionals with appropriate engineering and clinical expertise, may be required to perform the assessment of risks.
- Health care professional intervention – in some cases, MLMDs are intended to supplement or take the place of a health care professional. The NRA should evaluate whether the MLMD has been designed for human interaction and oversight appropriate to its intended use in the local context.
- Data handling and network safety – the NRA 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 NRA'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 state-of-the-art technology – as much of the technical expertise in these device fields may lie outside its jurisdiction, the NRA should consider how to develop relevant regulatory knowledge and experience, either at national or regional level, perhaps through consultation with local academic institutions. The NRA should also follow the development of new international standards (for example, IEC, ISO, ITU and IEEE⁹⁹) and/or evolving harmonized regulatory

⁹⁹ IEEE – <https://www.ieee.org>, accessed 11 February 2023.

guidance – for example from IMDRF, EU, USFDA, Therapeutic Goods Administration (Australia), Health Canada, and the Ministry of Health, Labour and Welfare (Japan).

8.5 Substandard and falsified medical devices

Substandard and falsified (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, often difficult to detect and designed to deceive a health care provider or patient into falsely believing that the device is the genuine article and has been carefully assessed in terms of safety, quality and performance.

Reports of SF medical devices have emerged from all over the world. WHO publishes and regularly updates its list of Medical Product Alerts, which includes SF medical products.¹⁰⁰ Falsified facemasks, diagnostic tests and other products for the management of COVID-19 have been reported.¹⁰¹ Where a demand exists, those engaged in the manufacture and distribution of SF devices will respond, and will use online distribution channels as well as the legitimate 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 an SF product from the genuine version.

The established enforcement approach consists of prevention, detection and response. The existence of a legal framework providing for proportionate regulatory requirements and powers, including dissuasive sanctions, is essential. A regulatory system with effective oversight of importation, distribution and sale of all medical devices will help prevent SF devices reaching users and patients. Awareness-raising among consumers, health care providers and distributors can also help to minimize the threat posed by SF medical products, while retaining confidence in health technologies generally. It is important to make the general public aware of the crucial importance of buying only from reliable sources, particularly on the internet.

Effective market surveillance is important for detecting SF medical devices early. NRAs should establish mechanisms that enable and encourage the

¹⁰⁰ The full list of WHO Medical Product Alerts can be found at: <https://www.who.int/teams/regulation-prequalification/incidents-and-SF/full-list-of-who-medical-product-alerts>, accessed 11 February 2023.

¹⁰¹ For example, see: <https://www.cbp.gov/newsroom/local-media-release/cbp-baltimore-field-office-seizes-nearly-59000-counterfeit-covid-19>, accessed 11 February 2023; and <https://www.gov.uk/government/news/uk-medicines-and-medical-devices-regulator-investigating-14-cases-of-fake-or-unlicensed-covid-19-medical-products>, accessed 11 February 2023.

reporting of suspicious medical devices. Regulator engagement with relevant stakeholders, including public and private sector organizations, law enforcement, civil society, health care providers, consumer groups and patients will lead to increased reporting and earlier detection of SF products (135, 136). In addition, new technologies (including UDI and track-and-trace systems) can provide increased assurance of the integrity of the supply chain and can also lead to the early detection of SF products.

Strengthening capacity among regulatory authorities to respond transparently, consistently and proportionately to SF products will help to maintain confidence in health systems. International collaboration and 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 (25, 137–139).

8.6 Companion diagnostics

A “companion diagnostic” is an IVD that is essential for ensuring the safe and effective use of a corresponding medicinal product by:

- identifying, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
- identifying, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product¹⁰² (44, 62).

Companion diagnostics – regulated as IVDs and abbreviated “CDx” – increase the probability of clinical success of a medicine by identifying patients carrying predictive biomarkers and disease-specific therapeutic targets and can dramatically improve the safety and/or efficacy of the treatment.

The above 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 (44). However, on an exceptional

¹⁰² IMDRF 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 a 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 (<http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-wng64.pdf>, accessed 11 February 2023).

basis, an NRA may opt to classify individual CDx into a class other than that determined by the IMDRF IVD classification rules.

Depending on how an NRA classifies CDx, a more complex body of regulatory controls may apply to them.

The regulation of CDx should include clear pathways for the authorization of clinical studies involving both products (CDx and medicine), as well as for the coordinated review and approval of the technical documentation submitted for market authorization. This may include the issuing of guidance regarding the roles and responsibilities of parties bringing a CDx and medicine to market. To ensure compliance with regulatory requirements, the following controls should be implemented for CDx: authorization by the NRA of clinical performance studies, market authorization, audits and post-market surveillance.

Some CDx are developed for use with specific medicines where testing may be tied specifically to certain brand(s) of medicines. For such testing, a combined clinical study is performed of the CDx and the medicine together.¹⁰³ Regulatory requirements for the labelling of such a CDx should specify the corresponding medicine with which it is intended to be used.

In other cases CDx are developed as standalone, where the CDx may be used to support the use of various brands of medicine (with similar molecular targets). Clinical studies for such CDx are performed independently. In such cases, there is no requirement for simultaneous filing or synchronized approval for the CDx and the medicine. The regulatory controls (pre-market authorization and authorization of clinical performance studies) of the medicine and the device may not necessarily be performed at the same time. However, the assessors of the medicine and of the CDx may meet as appropriate to coordinate the two regulatory processes.

For adverse event and incident reporting, the determination of who should report and whether reporting to both medical device and medicine regulators is required will be based on the apparent cause of the adverse event or incident, and on the risk assessment performed by the respective manufacturers. For example, any reportable event arising from the failure of the CDx (such as inaccurate test results) should be reported to the medical device regulator. Based on the risk assessment, if failure of the test is assessed to potentially impact the safety and/or effectiveness of the corresponding medicine (for example, through incorrect dosage of medicine administered to patients) then a report to the medicine regulator by the medicine manufacturer will also be required.

Since not all countries have the capacity to perform all of the regulatory controls discussed here – especially those in the early stages of establishing

¹⁰³ For examples of CDx combined with specific medicines see: <https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools>, accessed 11 February 2023).

regulations for medical devices including IVDs – reliance may be used as an appropriate approach to ensure that the relevant requirements are fulfilled.

8.7 WHO prequalification of IVDs and male circumcision devices

Lack of access to quality health technologies, in particular IVDs, is reducing the opportunity to make progress in addressing high-burden diseases in certain countries. WHO prequalification of IVDs provides countries with appropriate technical support, tools and guidance on the provision of IVDs and laboratory services. This now includes the prequalification of male circumcision devices.¹⁰⁴ In addition to relying upon the work of reference regulatory authorities, the NRA may choose, for some medical devices, to rely upon assessments conducted for the WHO prequalification of IVDs and male circumcision devices. A focus is placed by WHO on IVDs for priority diseases (for example, HIV, malaria and hepatitis C) and their suitability for use in resource-limited settings.

WHO prequalification of IVDs and male circumcision devices is based on the use of a standardized procedure for determining whether a product meets WHO prequalification requirements. The assessment process consists of three components:

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

Prequalification requirements are based on best regulatory practices and are designed around the essential principles of safety and performance. As such, prequalification requirements reflect recognized international standards and guidance documents – including harmonized European standards, and ISO, Clinical and Laboratory Standards Institute (CLSI) standards, and IMDRF/GHTF standards – to ensure compliance with the essential principles. As is the case for WHO-listed authorities,¹⁰⁵ WHO review and prequalification assessments cover quality, safety and performance aspects.

Although prequalification requirements are thus aligned with the approach adopted by NRAs performing stringent reviews, they have also been designed in such a way as to best serve resource-limited settings. The following aspects are therefore reflected in the prequalification assessments:

- the device regulatory version marketed on the global market is assessed;

¹⁰⁴ WHO is intending to further extend the prequalification of medical devices to other categories.

¹⁰⁵ <https://www.who.int/initiatives/who-listed-authority-reg-authorities>, accessed 11 February 2023.

- the scrutiny level reflects individual and public health risks in resource-limited settings; and
- data submitted by the manufacturer are assessed from the perspective of resource-limited settings in order to reflect the environment and users in such settings.

Countries may benefit from the programme by relying on prequalification assessment outcomes. The WHO List of Prequalified IVDs and WHO List of Male Circumcision Devices, together with reports summarizing the assessment findings, are publicly available on the WHO website.¹⁰⁶

In addition to their regulatory purposes, the findings of the WHO prequalification of IVDs and male circumcision devices, in conjunction with other procurement criteria, are typically used by United Nations agencies, WHO Member States and other interested organizations to guide procurement decisions.

8.8 Collaborative registration procedure

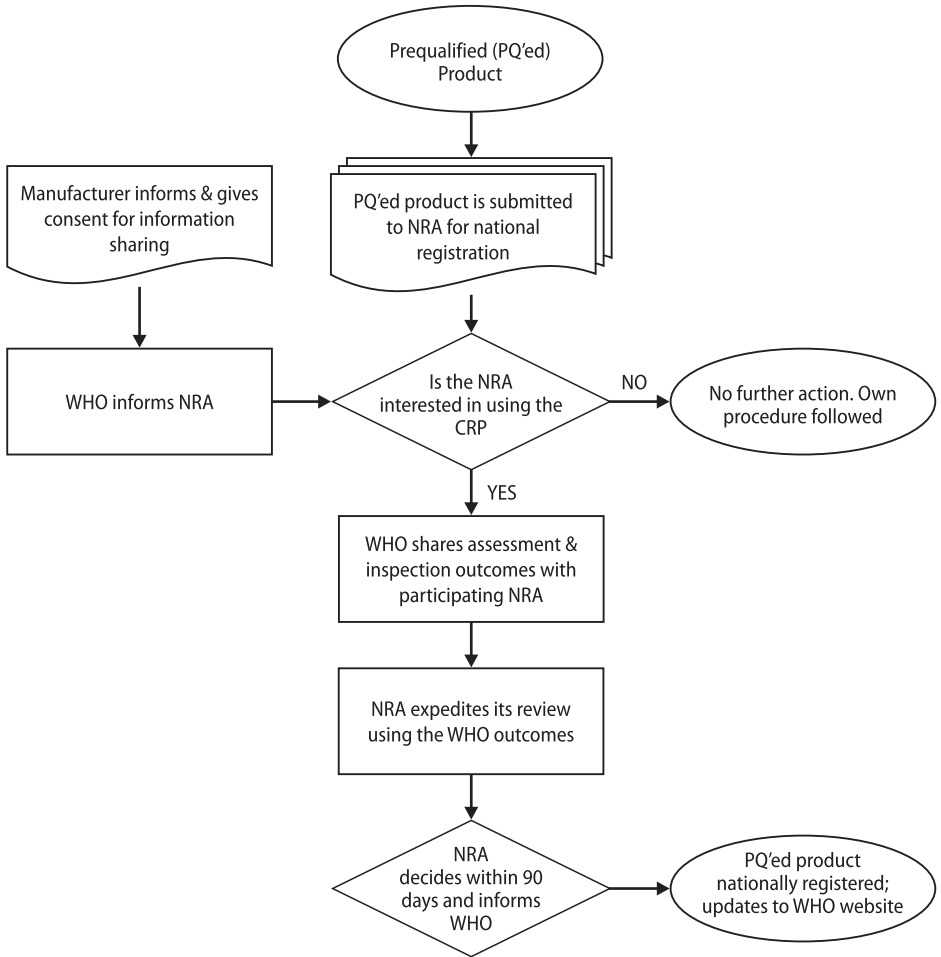
The collaborative registration procedure (CRP) was introduced to accelerate market authorization of eligible medical products in countries through information sharing between WHO and NRAs with the consent of a manufacturer of a WHO prequalified medical product. The CRP for IVDs was successfully piloted in 2019 and rolled out in May 2020 on the recommendation of the Expert Committee on Biological Standardization (140). The CRP for IVDs incorporates elements of capacity-building and regulatory harmonization. Successful application of the procedure is highly dependent on the ability and willingness of manufacturers (the applicants), NRAs and WHO to work together to meet public health goals. IVDs that are prequalified by WHO undergo a thorough evaluation (dossier assessment and laboratory performance evaluation) and a QMS audit of the manufacturing facilities according to international standards to confirm their quality, safety and performance (see section 8.7 above). Such products need to be approved by the NRAs for use in the countries for which market entry is being sought. Repeating the assessment, performance evaluation and quality audits for these products consumes scarce regulatory resources and unnecessarily prolongs the issuance of market authorization and the time needed to make them available to patients.

By leveraging assessment and inspection outputs already generated by WHO prequalification, and thereby eliminating duplicative regulatory work, the CRP speeds up the in-country market authorization of quality-assured products and contributes to their wider availability. The CRP is a typical

¹⁰⁶ <https://extranet.who.int/pqweb/vitro-diagnostics/vitro-diagnostics-lists>, accessed 11 February 2023.

reliance mechanism based on the three key principles of voluntary regulator and manufacturer participation, confirmation of the sameness of the product of interest and ensuring confidentiality of information. NRAs are expected to issue their decision on the market authorization of a given WHO prequalified product (whether positive or negative) within 90 calendar days of regulatory review time (Fig. 8.1).

Fig. 8.1
Steps in the procedure for national registration of a WHO prequalified IVD product (140)



8.9 Emergency use listing procedure

The WHO emergency use listing (EUL) procedure¹⁰⁷ (formerly the WHO emergency use assessment and listing (EUAL) procedure) is a risk-based procedure for assessing and listing 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 other public health emergencies (see section 7.3 above). During such times, communities and public health authorities may be willing to tolerate less certainty about the safety and performance of a product given the morbidity and/or mortality associated with the disease and the urgent need for diagnostics. The EUL procedure is based on an essential set of available quality, safety and performance data, and involves the following steps:

- QMS review and plan for post-market surveillance – desktop review of the manufacturer's QMS and its documentation, and specific manufacturing documents; and
- product dossier review – assessment of the documentary evidence of safety and performance; this evaluation is of limited scope and is intended to verify critical analytical and performance characteristics.

These reviews are conducted by one or more NRAs to which the manufacturer has made submissions, taking into account the outcomes of WHO assessments. Some submissions submitted for WHO EUL may have undergone a previous assessment through the other emergency mechanisms of a WHO-listed authority. Where this is the case, it is not the intention of WHO to undertake duplicative work if the review of the other emergency mechanism is deemed to be of a satisfactory standard.

¹⁰⁷ See: <https://extranet.who.int/pqweb/vitro-diagnostics/emergency-use-listing-procedure>, accessed 11 February 2023).

9. Implementation

9.1 Implementation – involving stakeholders in the regulatory process

To ensure that regulatory requirements and processes meet the objectives for which they are designed, it is important to determine their effects (benefits, costs and undesirable effects) in terms of the public health, economic and social impacts that they might have.

Likewise, such regulatory processes must take into consideration the limited resources of NRAs and the importance of avoiding duplication or the creation of barriers to achieving the objectives of the regulatory system. A key element in this will be the engaging and involving of stakeholders¹⁰⁸ in all stages of the regulatory process. Stakeholder groups are those that may be affected by the regulatory system, and include manufacturers, authorized representatives, importers, distributors, the health care sector, patients and users (4).

By working with stakeholders, policy-makers can help to determine risks and identify which regulatory controls will be the best option for addressing a public health problem. For example, the objective may best be achieved through laws (statutes and regulations), economic instruments (for example, market-based instruments such as taxes, fees, user charges, etc.), self-regulation, standards and other forms of voluntary actions, or information and education campaigns.

The introduction of medical device regulation should therefore be accompanied by the participation of stakeholders. This will facilitate, and may prevent delays in, the process of implementing regulatory controls. The NRA should establish a multidisciplinary team with experience of each stage of the life-cycle of the medical device, taking into consideration:

- who would be impacted by the regulatory controls, implementation process and policy, and in what way;
- who has or may have influence over the regulatory controls, implementation process and policy; and
- who has or may have an interest in whether regulatory control implementation is successful or unsuccessful (141).

Subsequently, a list of stakeholders should be drawn up for each of the different stages of the life-cycle – that is, pre-market, placing on the market and post-market (Fig. 9.1).

¹⁰⁸ A stakeholder is any individual or group that has an interest in any decision or activity of an organization. ISO 26000 (<https://iso26000.info/definitions/>, accessed 7 February 2023).

Fig. 9.1

Suggested stakeholders in the three phases of medical device regulation

The NRA multidisciplinary team should characterize each stakeholder, for example with regard to:

- Internal/external – internal stakeholders work within the organization promoting or implementing the policy; all other stakeholders are external.
- Knowledge of the policy – the exact level of knowledge that an actor has about the policy under analysis, and how each actor defines the policy in question.
- Position – whether the stakeholder supports, opposes or is neutral towards the policy; this will be key to establishing whether an actor will attempt to block policy implementation.
- Vested interest – the stakeholder's interest in the policy, or the advantages and disadvantages that implementing the policy may bring to the stakeholder or their organization. Determining the vested interests of stakeholders will help policy-makers and managers better understand their position and address their concerns.

- Alliances – organizations that collaborate to support or oppose policy. Alliances can strengthen a weak stakeholder or provide a way to influence several stakeholders by dealing with a key stakeholder.
- Resources – the resources (human, financial, technological, political and others) available to the actor and its capacity to mobilize them. This is an important characteristic that is summarized in a power indicator (see next point) and will determine the degree to which the actor can support or oppose the policy.
- Power – the stakeholder’s ability to affect the implementation of health reform policy.
- Leadership – the willingness to initiate, convene or lead an action for or against pro-health reform policy (142).

After characterizing the stakeholders, the NRA multidisciplinary team should develop a map of stakeholders in order to evaluate their expertise, positions, importance in the process, vested interests, potential impact and alliances. This will allow the NRA to interact appropriately with stakeholders to gain their support for the implementation of the proposed regulatory controls and avoid potential misunderstandings and delays.

Public consultation may help to improve both the quality of regulation and government responsiveness to its citizens and businesses. At the technical level, the use of consultation mechanisms and the introduction of a regulatory impact analysis (4) in particular will be pivotal in 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 social acceptance of decisions and, therefore, compliance. Stakeholder consultation is usually considered to be an integral part of ensuring regulatory quality. Stakeholders should therefore be involved when deciding, developing, reviewing, amending and soliciting feedback on:

- legislation;
- regulatory strategy, road map and policy;
- status of the NRA;
- regulations and guidelines;
- requirements for market authorization, and for post-market surveillance;
- transition period for implementing specific regulatory processes; and
- regulatory fees and timelines, and other factors as may be determined.

Involving or informing stakeholders on the above factors may lead to:

- Transparency and access to information – stakeholder consultation can increase the transparency of the rule-making process because stakeholders have access to the process itself. Additionally, consultation enables policy-makers to make use of the stakeholder's experience and knowledge. Stakeholder engagement in rule making can increase support for regulatory requirements.
- Increased familiarity and compliance – engaging stakeholders and striving for consensus can help to increase the social acceptance of regulations. It can thus contribute to greater compliance and, therefore, reduced enforcement costs. Stakeholder engagement also promotes stakeholder education on rule making, and provides stakeholders with an opportunity to increase their regulatory knowledge.
- Legitimacy and improved conflict management – stakeholder consultation provides a mechanism for managing conflicts at an early stage. Greater stakeholder engagement also has the potential to create a source of legitimacy and proof of successful governance.
- Credibility, confidence and social cohesion – stakeholder consultation can help to establish stakeholder trust and government credibility by creating new and better ways to communicate with stakeholders.

It is important to define the stages in which the different parties will be involved. Involving stakeholders in the relevant stages of implementation will allow for the development not only of policies but also of processes, avoid repetition and lead to the placing on the market and availability of compliant medical devices.

With the active and objective participation of stakeholders, the implementation process may include:

- initial creation of the NRA multidisciplinary team to evaluate which stakeholders are interested in the regulatory process to be carried out;
- generating questionnaires for stakeholders to allow the multidisciplinary team to identify those with greater or lesser impact, and greater or lesser influence;
- establishing neutral spaces that allow collaboration among stakeholders so that those involved can listen to, discuss and learn from each other;

- conducting workshops;
- sending out documents for consultation and comments; and
- holding specific technical roundtables for each stage of the product life-cycle, allowing the appropriate stakeholders to be involved for each topic (143).

As part of GRP it is important to control the influence of stakeholders so that the development and implementation of regulatory controls is not prejudiced or biased by one or more of the stakeholders.

9.2 Implementation – developing a road map

The establishment of a new national medical device regulatory system, or significant changes to an existing system, requires thorough and careful planning. A comprehensive outline or “road map” is a visual way to quickly communicate a plan or strategy and will be helpful in its planning and implementation.

In preparing a road map, the first step will be to carry out a gap analysis (see section 5.2 above) in which the current local situation is compared with established medical device regulatory systems (benchmarks) based on WHO recommendations (3, 4, 5, 55, 144) and on international harmonization consensus guidance documents (64). It is important to consider the views of local stakeholders, including patient representatives. In addition, consideration should be given to public health priority 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, the NRA can then 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 step or in a very short time. This process requires a significant increase in the size and knowledge of the NRA, education of the regulated industry and health product purchasers and users, as well as high-level political commitment and long-term financial support. To achieve the above, WHO recommends that the implementation of such regulation be carried out in stages. At each stage, the principles of GRP for medical products should be applied (4). This GMRF outlines the basic-level regulatory controls that should be effectively implemented first. As resources permit, and according to national policy priorities, expanded-level regulatory controls may be implemented on the foundation of the basic-level regulatory controls.

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

The development of a prioritization matrix (see Table 9.1) in which the consequences of individual risks¹⁰⁹ are mapped to their probability of occurrence will make it possible to prioritize the identified objectives and actions (145).

Table 9.1
An example of a “probability–impact” matrix for risk ranking (145)

	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

Such a matrix may be used by policy-makers and the NRA in several ways when setting national priorities for the implementation of regulatory controls:

- The likelihood and severity of the national burden of disease may dictate regulatory priorities. For example, a high prevalence of a particularly severe disease or condition may justify a higher priority for access to certain medical devices, and development of the requisite regulatory and scientific expertise. If SF higher risk medical devices are known to be widespread, then a higher priority could be given to listing, registration, import controls and market surveillance.

¹⁰⁹ ISO 31000: Risk management defines “risk” as the effect of uncertainty on objectives (<https://www.iso.org/iso-31000-risk-management.html/>, accessed 7 February 2023).

- The stringency of regulatory controls should be proportionate to the consequence of the potential harm to be prevented. For harms of low consequence, even if relatively common, voluntary compliance by regulated medical device suppliers may be adequate. However, more stringent mandatory controls will be justified by potential harms with very severe consequences, even if infrequent. If resources prevent full implementation of a regulatory system for all devices at one time, a risk assessment may support the phased introduction of controls on higher risk-class devices before those for lower risk-class devices.
- Organizational risks include lack of consistent high-level political support, insufficient funding, misallocation of resources, inability to recruit and retain appropriately qualified staff, inadequate information systems or facilities, and loss of credibility and reputation as an effective enforcement body. The failure of an NRA to implement effective market surveillance mechanisms and/or of device manufacturers to properly report adverse events and incidents will impair the ability of the NRA to properly monitor and evaluate emerging device-related risks.

At this point, the necessary resources – human, technical, facilities, information technologies and economic – must be estimated. A realistic timeline must be established for the stepwise implementation of the plan in the short, medium and long term. Based on the proposed prioritization, detailed work plans must be prepared, along with the high-level road map laying out outcomes, responsibilities and timelines (Table 9.2).

The implementation plan will require continuous monitoring and evaluation of compliance with its objectives. To enable this, it is recommended that technical and other guidance documents are developed to make the established guidelines known to the stakeholders involved. It is recommended that these documents are based on international regulatory guidance adapted to the local context. The road map must also be updated on a regular basis.

Table 9.2
Example of a high-level road map

Objective	Responsible entity	Outcome/indicator	Information source	Interested stakeholder	Communication	Timeline
General						
Adopt law and regulations	MoH	Adopted legislation	Parliament	Manufacturers Importers Patients Health care sector		
Pre-market						
Define pre-market conformity	NRA	Regulations and guidance for stakeholders	NRA	Manufacturers Importers Authorized representatives	Meetings Workshops Internet	
System and resources for pre-market assessment	NRA	Number of market authorizations	NRA	Manufacturers Importers Authorized representatives	Meetings Workshops Internet	
Placing on the market						
Oversight: registration of establishments	NRA	Number of establishment registrations	NRA	Manufacturers Importers Distributors	Meetings Mailings Internet	
Oversight: listing of medical devices	NRA	Number of medical devices listed	NRA	Manufacturers Importers Distributors Authorized representatives	Meetings Mailings Internet	

Table 9.2 *continued*

Objective	Responsible entity	Outcome/ indicator	Information source	Interested stakeholder	Communication	Timeline
Post-market						
Establish system for review of adverse events and incidents reported by manufacturers	NRA	Number of reports of incidents reviewed compared to neighbouring countries	NRA	Manufacturers Distributors 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 sector Patients	Internet Mailings Media	

9.3 Implementation – regulatory capacity-building

The NRA should ensure the quality and integrity of the regulatory processes through the recruitment and retention of people with the necessary, skills, knowledge and experience. Capacity-building generally includes increasing organizational capacity, physical and communications infrastructure, and individual knowledge and skills. Regulatory capacities are related to the technical and scientific competence necessary to adapt to developments in national and international regulatory practices and standards. Regulatory capacities should also sufficiently support NRAs in implementing the legal framework, guidelines and procedures. Policies and measures for personal and career development (for example, training programmes or competitive remuneration schemes) are critical in attracting and retaining competent staff (4).

Due to the nature of their technologies, complex classification, and the wide and diverse range of product categories, medical devices including IVDs require knowledge and skills different to those needed for medicines. The NRA should be able to assess the quality, safety and performance of all product categories of medical devices including IVDs, calling upon outside experts and/or reliance on the work of other regulatory authorities as necessary.

Staff teams working in this area must be multidisciplinary to allow the NRA to assess medical devices for compliance with the national regulatory requirements during non-emergency situations, emergency situations, and when using reliance or recognition.

The development of regulatory capacities should begin by establishing regulatory processes for medical devices and identifying the associated competencies and skills required by the personnel involved. Regulatory capacities should be strengthened through institutional training programmes for developing and monitoring these competencies and skills.

The WHO global competency framework for regulators of medical products describes the competencies and underlying knowledge and skills needed (60, 146). Each NRA should specify the skills required in each position in the institutional organizational chart as mapped to these framework competencies.

9.3.1 Training plan for NRA staff

The training of NRA staff in regulatory functions must be aligned and maintained according to the competencies to be developed and implemented by the NRA. The NRA can then generate annual programmes based on the mapping of training needs, including training on specific topics. Based on this mapping, it is recommended that annual training plans are established for each staff member to address the specific topics to be covered. The annual training plans should be reviewed at least once every year (2).

The NRA should establish procedures for the formal selection, training, approval and assigning of personnel involved in regulatory reviews, QMS audits, market surveillance and enforcement functions (57, 59). The NRA should maintain evidence that the personnel have the required skills and competencies. Formal and informal exchanges of knowledge and experience with regulatory experts from other NRAs will promote collaboration and harmonization that may facilitate the use of reliance.

9.3.3.1 Competencies, skills and expertise

The eight general core competencies described in Table 9.3 should be evaluated depending on the objectives of the established programmes. The NRA should undertake continuous evaluation and monitoring programmes for the competencies, skills and expertise that will underpin the technical skills required of its staff.

Table 9.3

Core competencies for regulators (57)

Competency	Characteristics
Context analysis	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 the businesses and individuals that you interact with

Table 9.3 *continued*

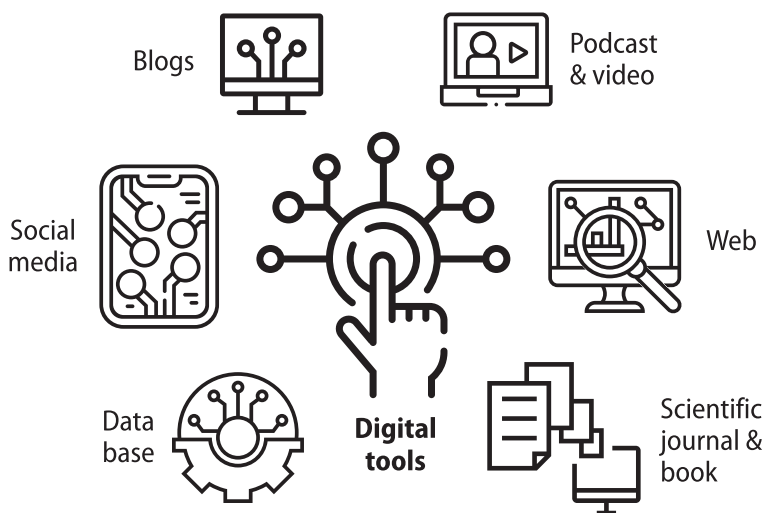
Competency	Characteristics
Planning of activities	<ul style="list-style-type: none"> • ability to act within your role and area(s) of responsibility • ability to make appropriate intervention choices, drawing on your understanding of the context in which you operate, of those that you regulate, and of 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 meet your responsibilities efficiently
Compliance	<ul style="list-style-type: none"> • 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 of compliance in an appropriate manner
Support for compliance	<ul style="list-style-type: none"> • understanding of the need for compliance support among 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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

9.3.3.2 Exploring training opportunities

Sources of training include workshops, courses, webinars, worktables and discussion, as well as evaluations of regulatory processes that indicate the improvements to be made in specific areas. E-learning and digital information resources will facilitate access to updated training options (Fig. 9.2).

Fig. 9.2

Digital sources to strengthen regulatory capacities



The NRA may choose to create alliances for capacity development with institutions that can support the strengthening and development of regulatory capacities, both at national and international level. Through regional harmonization initiatives or regional collaboration, regulators may opt to create regional Centres of Excellence (CoEs) to facilitate the training of regulators.

Several institutions and NRAs have generated programmes that focus not only on the NRA but are also applicable to the regulated industry – through innovation centres for educational purposes, organizing of virtual courses, cooperation agreements and inter-institutional training on building capacities.

To access expert input the following options may be considered:

- external expert policy;
- CABs;
- international organizations such as WHO;

- regional harmonization initiatives such as IMDRF,¹¹⁰ GHWP,¹¹¹ AMDF,¹¹² APEC RHSC;¹¹³
- internal portfolio of national and international experts; and
- academic institutions.

Such sources may provide expertise that can guide the actions of regulators within the NRA, and help to achieve a greater understanding of medical devices including IVDs and their regulation, especially in relation to new technologies.

Once implementation of the planning steps outlined above has begun, the NRA, under the oversight of the legislature or parliament, should periodically publish reports on the progress made towards policy goals and on the effectiveness of the measures taken. Such progress and effectiveness should be measured against national priorities and performance measurements, not only with regard to plan milestones, but also to indicate the compliance of regulated industry and the development of regulatory capacity.

The WHO GBT and GBT + medical devices (2, 3) were developed to enable WHO and NRAs to identify areas of strength as well as areas for improvement, facilitate the formulation of an institutional development plan (IDP) to build upon strengths and address the identified gaps, aid in the prioritization of investments in IDP implementation and to help monitor progress. The GBT also incorporates the concept of “maturity level” (adapted from ISO 9004), allowing WHO and NRAs to assess the overall maturity of the regulatory system on a scale of 1 (existence of some elements of a regulatory system) to 4 (operating at an advanced level of performance and continuous improvement).

Although it is acknowledged that not all countries will be able to move at the same speed or devote the same levels of resources, systematic assessment and continued progress in this area will lead to greater public confidence in the regulation – and safety, performance and quality – of medical devices including IVDs used in health systems.

¹¹⁰ IMDRF – <https://www.imdrf.org>, accessed 12 February 2023.

¹¹¹ GHWP – <http://www.ahwp.info>, accessed 12 February 2023.

¹¹² AMDF – <http://www.amdfnra.org>, accessed 12 February 2023.

¹¹³ APEC RHSC – <https://www.apec.org/rhsc>, accessed 12 February 2023.

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Appendix 1

Hierarchy of regulation

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

Table continued

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

^a Note that the term “Guidelines” as used above does not refer to guidelines in the sense of the WHO handbook for guideline development. Geneva: World Health Organization; 2014.

Appendix 2

Further reading

- Playbook for implementation of medical device regulatory frameworks. Asian Harmonization Working Party. 2014 (Document AHWPTC/OB/R001: 2014; <http://www.ahwp.info/sites/default/files/AHWP%20Playbook%20for%20Implementation%20of%20MD%20Reg%20Framework.pdf>, accessed 24 January 2023).
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- IMDRF International Medical Device Regulators Forum [website]. IMDRF (<http://www.imdrf.org/>, accessed 24 January 2023).
- GHWP Global Harmonization Working Party – towards medical device harmonization [website]. Global Harmonization Working Party (<http://www.ahwp.info>, accessed 24 January 2023).