

Life cycle of medical devices: regulations in a worldwide market

Carmelo De Maria





What is a medical device?



What is a Medical Device?

MDR 2017/745 – Article 2 (1)

“medical device” means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

diagnosis, prevention,
monitoring, prediction,
prognosis, treatment or
alleviation of disease,

diagnosis, monitoring,
treatment, alleviation of, or
compensation for, an injury
or disability,

providing information by
means of in vitro
examination of specimens
derived from the human
body, including organ, blood
and tissue donations,

investigation, replacement or
modification of the anatomy
or of a physiological or
pathological process or state,

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

Comments

- Identified by means of its INTENDED PURPOSE
- Use on humans (or animals on a lower grade of regulation)
- Intended to have a MEDICAL purpose, excluding devices intended for
 - Aesthetic purposes
 - Research not aimed to marketing of the device
- Multiple ways of interacting with the human body
 - Implant to NO corporeal interaction (medical SW)
 - Temporary or permanent
 - Acute or chronic
 - Energy or substance exchange
- Performance: technical performance + clinical effectiveness (SAFE and EFFECTIVE)

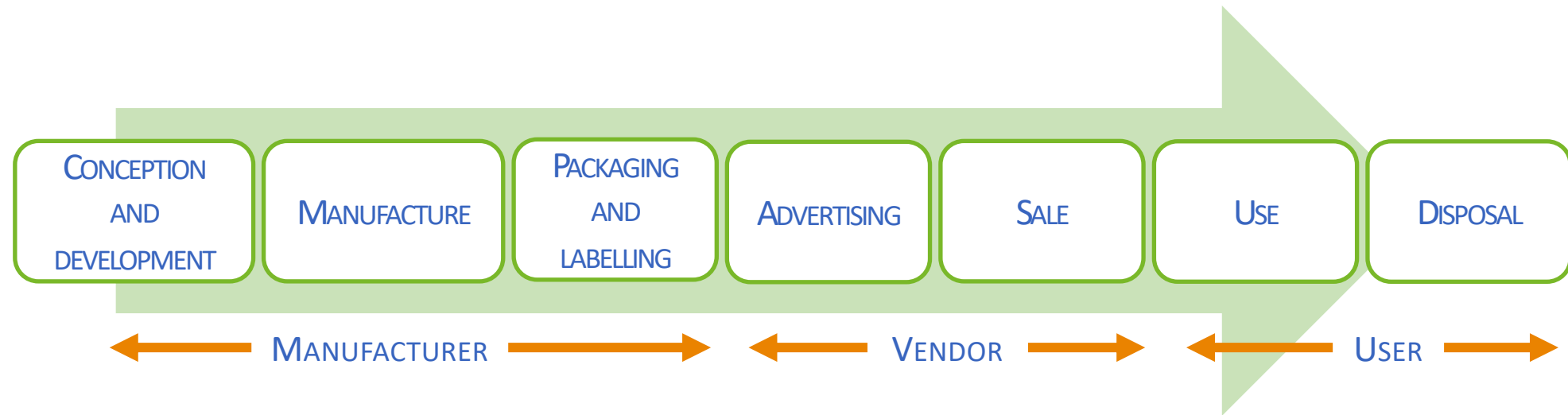
- How much does it cost to bring a low to moderate-risk device from concept to market?
 - <1 M\$
 - 1 to 10 M\$
 - 10 to 50 M\$
 - > 50 M\$



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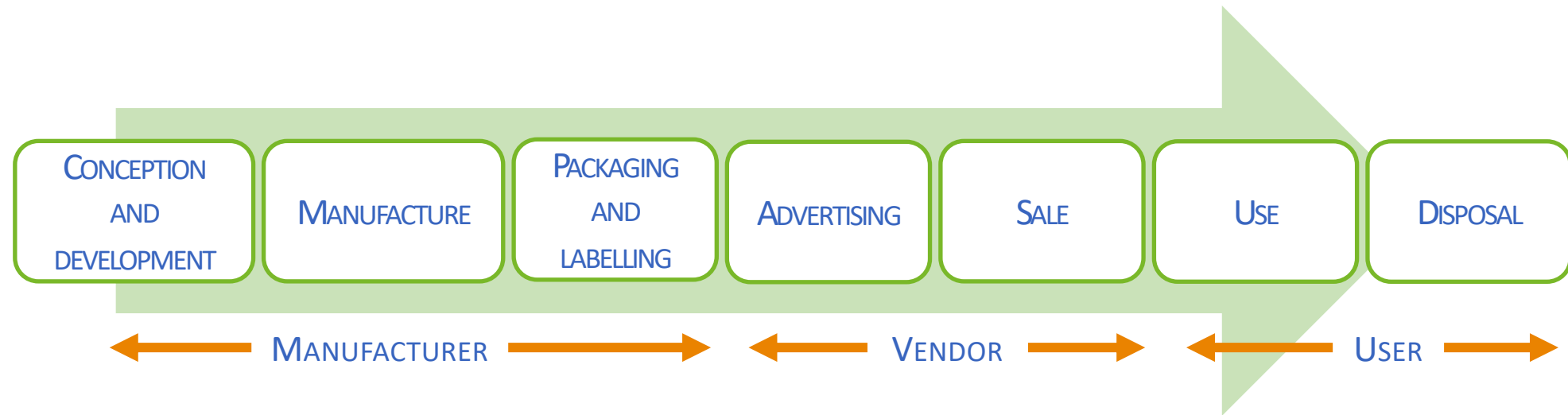


Life cycle of a medical device



- Stakeholders: Manufacturer, Vendor, User, Public/Patient, Government

Life cycle of a medical device



- The necessary quality assurance in all these steps leads to high costs
- Developing a medical device from the idea to the market has a cost of around \$31 million for a low-to moderate-risk device, and around \$94 million for high-risk products

Medical Device Safety

- Ensuring safety of patients, users, bystanders, healthcare providers, environment
- Absolute safety cannot be guaranteed
- It is a **risk management** issue
- It is closely aligned with device effectiveness/performance
- It must be considered throughout the life span of the device
- It requires shared responsibility among the stakeholders

Regulation of medical devices

An efficient regulation system means:

- Safety for patients and workers
- Higher quality of devices
- Reliability in diagnostic exams
- Healthcare for the whole community
- Fair competition in healthcare industries

Regulation of medical devices



Regulation of medical devices

- "Zero risk" does not exist
 - Risk management design
- Up-to-date technologies and requirements
 - Use of "standards"

Standards & Regulations

- Regulations

- Legislation
- Use is mandatory
- Available to the public
- Developed by an authority under public observation
- Provide technical specifications either directly or by reference, e.g. to standards
- Adopted by an authority

- Standards

- Recommendations
- Use is voluntary
- Available to the public
- Established by consensus of all parties concerned
- Based on consolidated results of science, technology and experience
- Approved and published by recognized standardisation body

Regulation of medical devices

- Regulatory measures should be implemented in all phases of a medical device life span:
 - a) “Pre-market” regulation including:
 - Definition of a medical device.
 - Risk classification.
 - Essential principles of safety and performance.
 - b) “Placing on the market” regulation including:
 - Registration of establishments.
 - Listing of medical devices.
 - Import controls.
 - c) “Post-market” regulation:
 - Adverse event reporting.

The background of the slide features a blue-toned image of a person's hands holding a tablet. Overlaid on this are several semi-transparent hexagonal icons representing various medical fields: an eye, a heart, a person silhouette, a virus, a network diagram, a wheelchair, and a blood drop. A stethoscope is also visible, draped across the center. The text 'Insight into MDR 2017/745' is centered in white.

Insight into MDR 2017/745

EUROPEAN MEDICAL DEVICE LEGISLATION

Marketing of Medical Devices in the EU is regulated by:

- Regulation on medical devices: **Regulation (EU) 2017/745**
 - <http://eur-lex.europa.eu/legal-content/ENG/TXT/PDF/?uri=CELEX:32017R0745&from=EN>
 - Repeals the Directive 93/42/EEC on Medical Devices and the Directive 90/385/EEC on Active Implantable Medical Devices
- Regulation on in vitro diagnostic medical devices: **Regulation (EU) 2017/746**
 - <http://eur-lex.europa.eu/legal-content/ENG/TXT/PDF/?uri=CELEX:32017R0746&from=EN>
 - Repeals the Directive 98/79/EC on In Vitro Diagnostic Medical Devices

Medical Device Regulation (MDR)

- The MDR 2017/745 regulates the marketing of Medical Devices in the European Union:
- It details the device identification and classification
- It defines manufacturers responsibilities and duties
 - Safety and performance requirements
 - Surveillance
 - Gives powers to the Local Authorities to control the placing on the market of the devices

EU REGULATION 2017/745

- 101 Whereas...= WHY
- 10 Chapters of 123 Articles = WHAT
- XVII Annexes = HOW



- Chapter I – Scope and Definitions
- Chapter II – CE Marking, Economic Operators, Reprocessing
- Chapter III – Identification and Traceability of Devices
- Chapter IV – Notified Bodies
- Chapter V – Classification and Conformity Assessment
- Chapter VI – Clinical Evaluation and Investigation
- Chapter VII – Vigilance and Market Surveillance
- Chapter VIII – Cooperation between Member States
- Chapter IX – Confidentiality, Data Protection, Funding, Penalties
- Chapter X – Final Provisions

EU REGULATION 2017/745

- 101 Whereas...= WHY
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- Annex I – General safety and performance requirements
- Annex II – Technical Documentation
- Annex III – Technical Documentation on PMS
- Annex IV – EU Declaration of Conformity
- Annex V – CE Marking of Conformity
- Annex VI – European UDI System
- Annex VII – Requirements to be met by Notified Bodies
- Annex VIII – Classification Criteria
- Annex IX – Conformity Assessment – QMS and Technical Documentation
- Annex X – Conformity Assessment – Type Examination
- Annex XI – Conformity Assessment – Product Conformity Verification
- Annex XII – Procedure for Custom-made Devices
- Annex XIII – Certificates issued by a Notified Body
- Annex XIV – Clinical Evaluation and Post-market clinical follow-up
- Annex XV – Clinical Investigations
- Annex XVI – Products without an intended medical purpose
- Annex XVII – Correlation Table 90/385, 93/42 and Regulation

Use the EU REGULATION 2017/745

Intended use and device characteristics

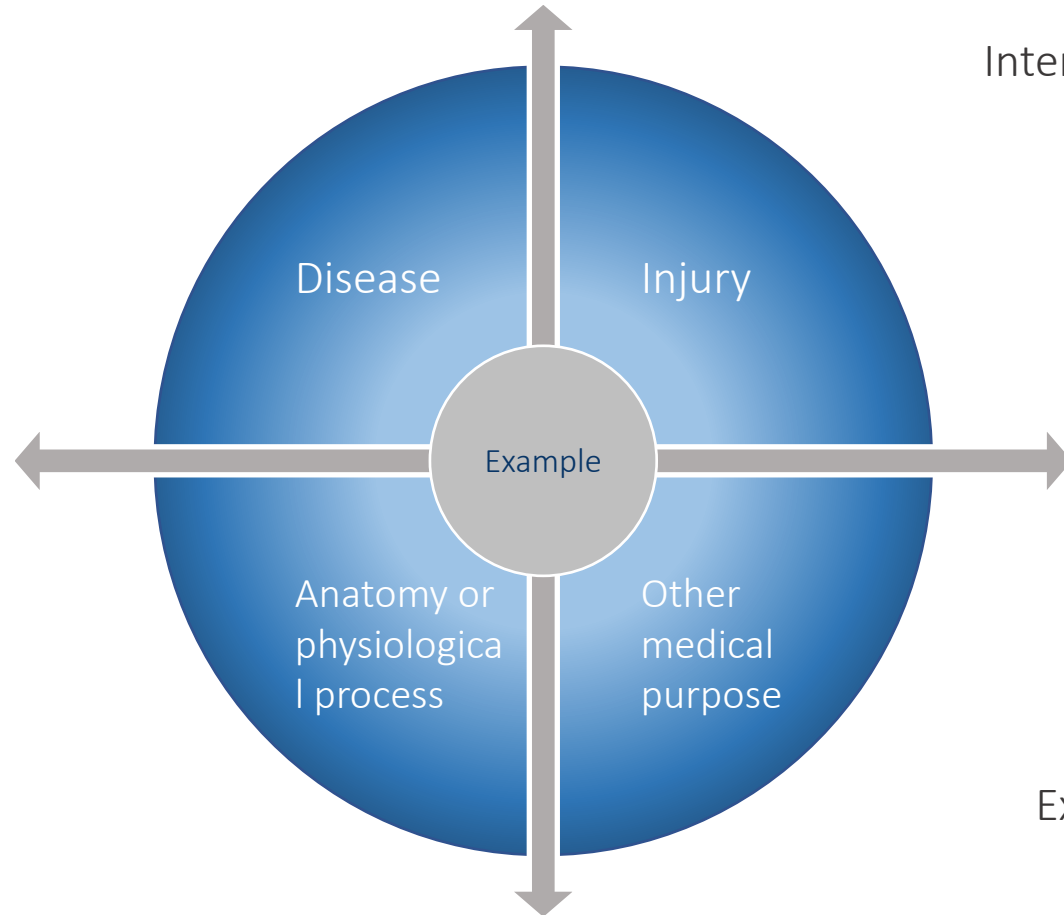
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graph TD; A[Intended use and device characteristics] --> B[Classification]; B --> C[Regulatory requirements]; C --> D[Regulatory submission process];
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Classification

Regulatory requirements

Regulatory submission process

MDR 2017/745 – Intended use

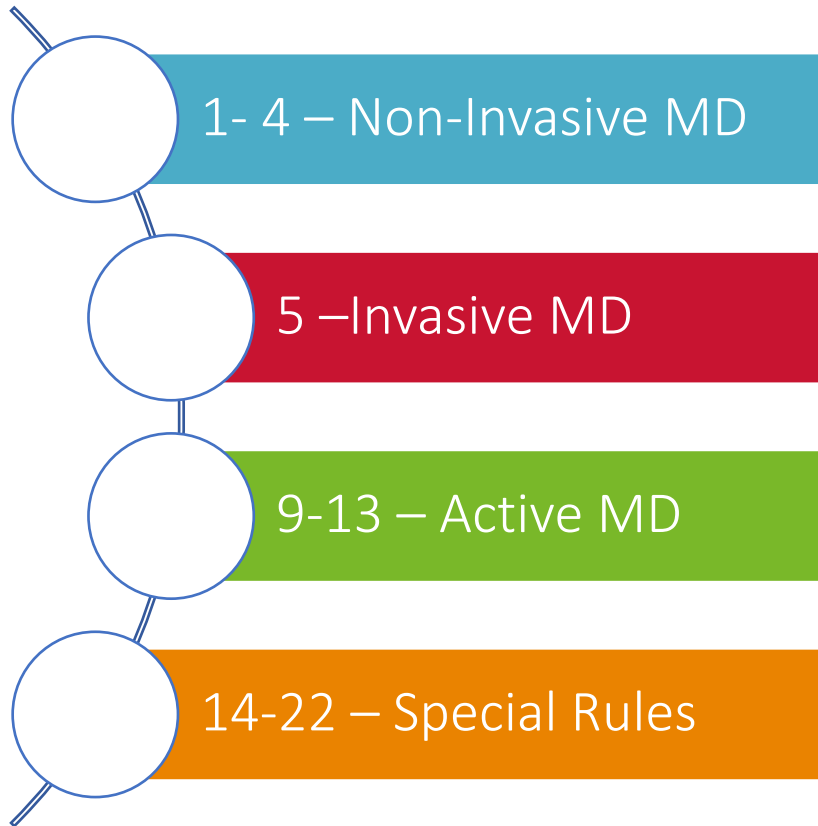


Intended use The general purpose of the medical device or its function (what you “claim” the medical device does)



Example: is a diagnostic x-ray system for generation of x-rays for examination of various anatomical regions

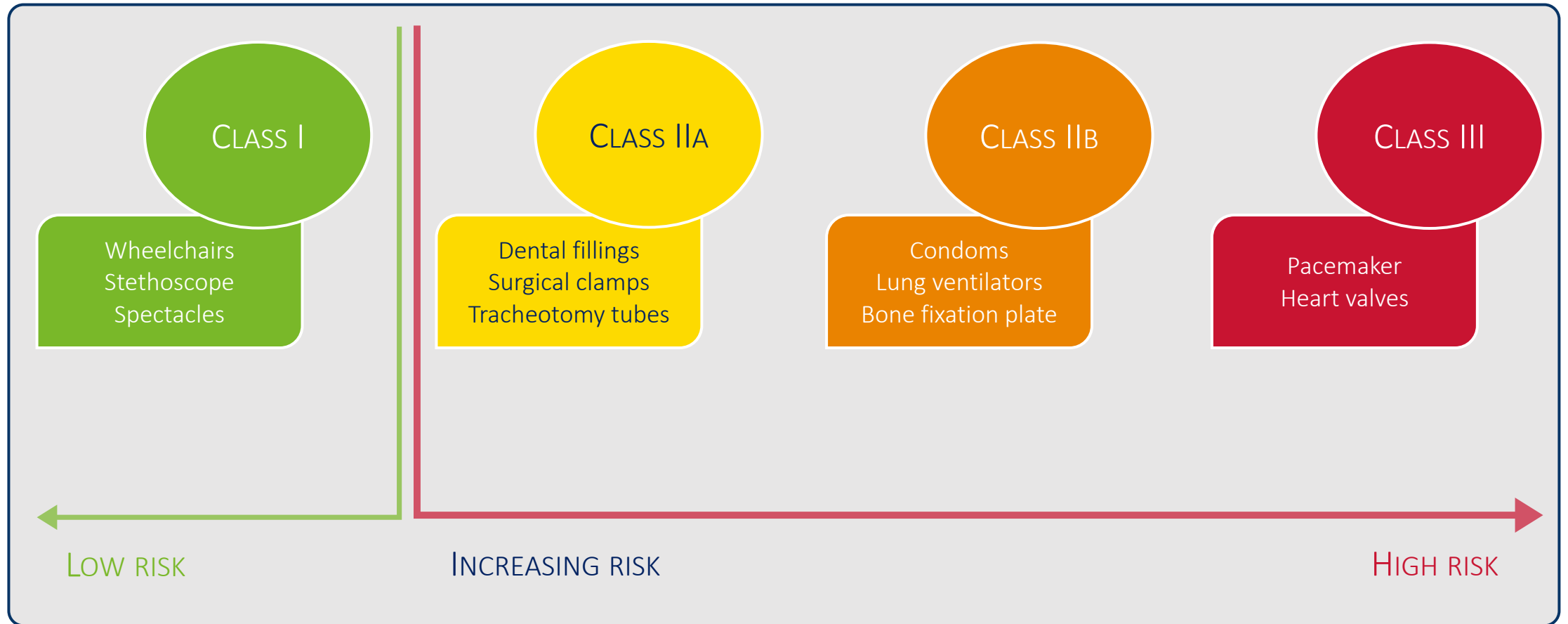
MDR 2017/745 - CLASSIFICATION



ANNEX VIII

22 CLASSIFICATION RULES

MDR 2017/745 – CLASS RISK



Annex VIII - Classification

Some new rules, new definitions, some clarifications, some upclassifications...

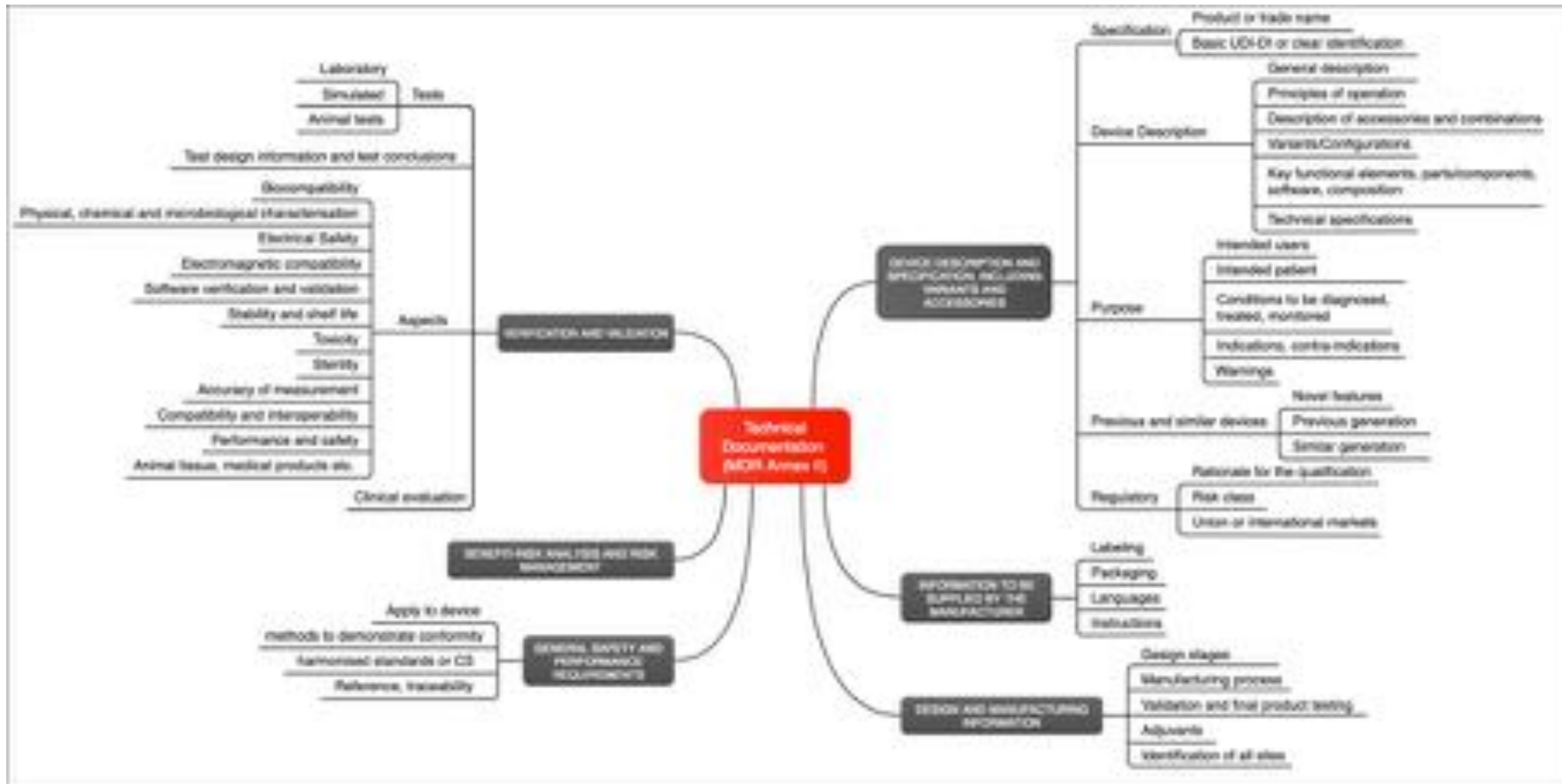
- ✓ **Rule 3:** Upclassification of IVF media/solutions for organ storage to Class III
- ✓ **Rule 8:** Upclassification of surgical meshes and spinal devices to Class III .
- ✓ **Rule 9:** Active devices intended for controlling, monitoring or directly influencing the performance of active implantable devices are Class III.
- ✓ **Rule 11:** Upclassification of some software (decision making SW, monitoring of physiological parameters) from Class I to IIa.
- ✓ **Rule 19:** Nanomaterials – Class IIa/IIb/III
- ✓ **Rule 20:** Invasive devices with respect to body orifices, [...] intended to administer medicinal products by inhalation are classified as Class IIa, unless their mode of action has an essential impact on the efficacy and safety of the administered medicinal product or they are intended to treat life-threatening conditions, in which case they are classified as Class IIb
- ✓ **Rule 21:** Devices that are composed of substances or combinations of substances that are intended to be introduced into the human body via a body orifice, or applied on skin and that are absorbed by or locally dispersed in the human body – Class IIa/IIb/III.
- ✓ **Rule 22:** Active therapeutic devices with an integrated or incorporated diagnostic function which significantly determines the patient management by the device, such as closed loop systems or automated external defibrillators, are classified as Class III - Upclassification from Class IIb to Class III



What requirements need to be met for a conformity assessment?

1. General Safety and Performance Requirements (Annex I MDR):
 - Benefits must outweigh risks and achieve claimed performance supported by clinical evidence and investigation
 - Chemical, physical and biological properties for medical devices disclosed [Performance characteristics for IVDs disclosed]
 - Information supplied by manufacturer with the device; e.g. Instruction For Use and correct device labelling
 - 23 requirements
2. Technical documentation (Annex II MDR)
3. Procedures for conformity assessment (Annexes IX, X and XI)

Technical Documentation



Harmonised standards

Article 8 – MDR 2017/745

*“Devices that are in conformity with the relevant **harmonised standards**, or the relevant parts of those standards, the references of which have been published in the Official Journal of the European Union, shall be presumed to be in conformity with the requirements of this Regulation covered by those standards or parts thereof.” (1)*

International Standards Organization



International
Organization for
Standardization



INTERNATIONAL
ELECTROTECHNICAL
COMMISSION



European Standards Organization



CENELEC



Official Journal of the European Union

L 117



English edition

Legislation

Volume 60

1 May 2017

Contents

II – Legislative acts

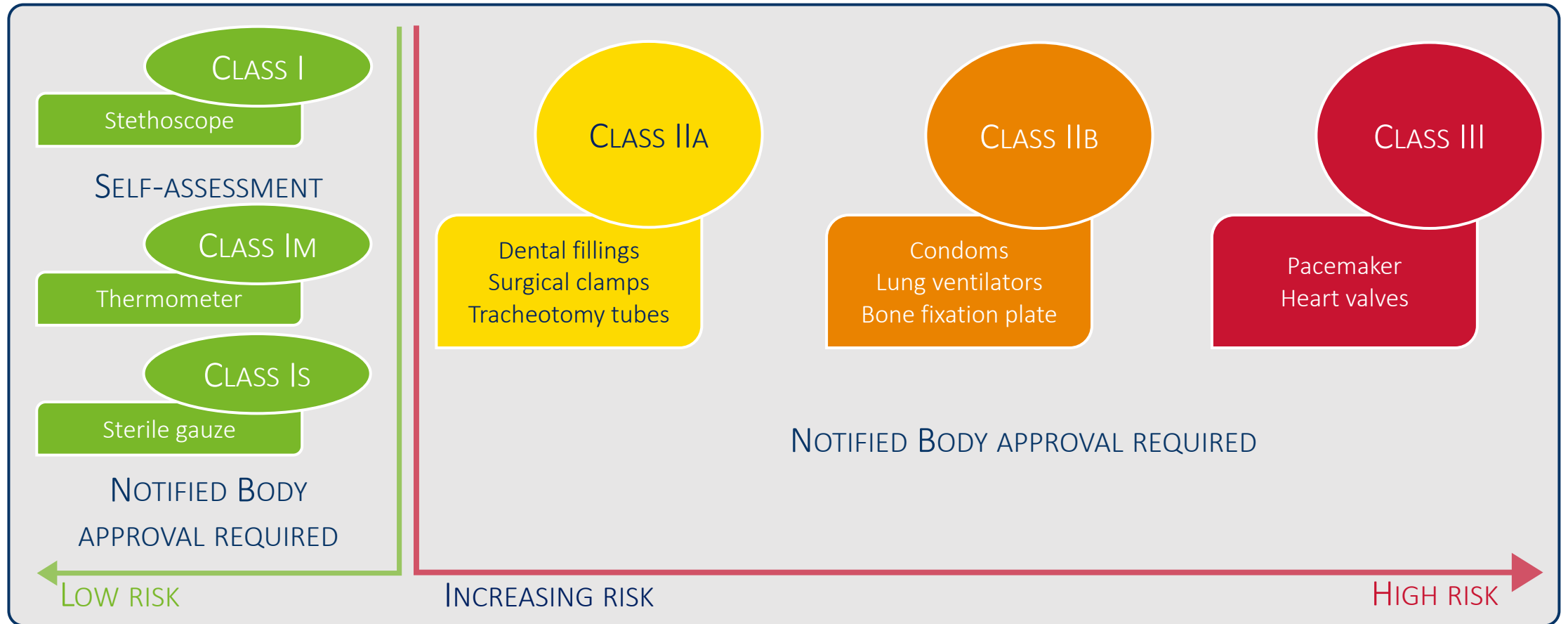
REGULATIONS

- Regulation (EU) 2017/1445 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EU) No 178/2002 and Regulation (EU) No 1275/2007 and repealing Council Directive 90/269/EEC and 93/42/EEC
- Regulation (EU) 2017/1446 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2003/228/EC

Some Key Standards

- EN ISO 13485:2016 – Medical devices – Quality management systems – Requirements for regulatory purposes
specifies requirements for a quality management system where an organization needs to demonstrate its ability to provide medical devices and related services that consistently meet customer and applicable regulatory requirements
- EN ISO 14971:2016 – Medical devices – Application of risk management to medical devices
specifies a process for a manufacturer to identify the hazards associated with medical devices, including in vitro diagnostic (IVD) medical devices, to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls.
- EN ISO 15223-1:2016 Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements
identifies requirements for symbols used in medical device labelling that convey information on the safe and effective use of medical devices. It also lists symbols that satisfy the requirements of this document.
- IEC 60601-1:2018 Medical Electrical Equipment -- Part 1: General requirements for basic safety and essential performance
contains requirements concerning basic safety and essential performance that are generally applicable to medical electrical equipment.

MDR 2017/745 – CLASS RISK



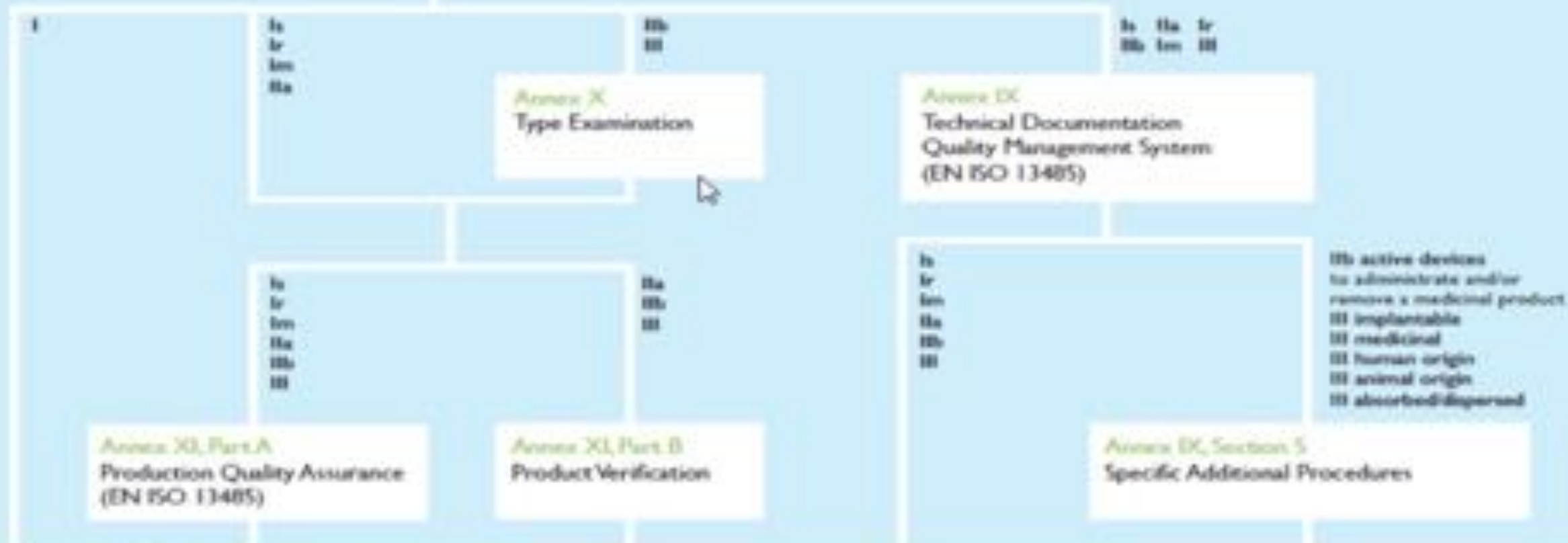
MDR conformity assessment

- ✓ Approval is required for Class IIA, IIB and III medical devices.
- ✓ Some Class I devices will require notified body approval for parts of the manufacturing process that relates to sterility or metrology, if the medical device includes sterile products or a measuring functions.
- ✓ Manufactures can certify their products with any notified body within the EU

Conformity assessment is the method by which a manufacturer demonstrates that their devices comply with the requirements of MDR 2017/745. The classification of the medical device will have an impact on the conformity assessment route that the manufacturer should follow in order to affix the CE marking on the medical device.

MDR Conformity Assessment Procedure **OVERVIEW**

- Annex I General Safety and Performance Requirements
- Annex II Technical Documentation
- Annex III Technical Documentation on Post Market Surveillance
- Annex IV EU Declaration of Conformity
- Annex VI UDI – Unique Device Identification
- Annex VIII Classification Rules



MDR 2017/745 – Custom-made MD

“custom-made device’ means any device specifically made in accordance with a written prescription of any person authorised by national law by virtue of this person's professional qualifications which gives, under his responsibility, specific design characteristics, and is intended for the sole use of a particular patient exclusively to meet their individual conditions and needs.” MDR 2017/745 Article 2 (3)



Mass-produced devices which need to be adapted to meet the specific requirements of any professional user and devices which are mass-produced by means of industrial manufacturing processes in accordance with the written prescriptions of any authorised person shall not be considered to be custom-made devices.

Example of Custom-Made MDs



DENTURES



MAXILLOFACIAL IMPLANTS



CUSTOM INSOLE

Custom-Made VS Customized

“CUSTOMIZED” IS NOT EQUAL TO CUSTOM-MADE MEDICAL DEVICE

An existing medical device that is adapted, altered, fashioned, modified or ‘customised’ to fit a patient is NOT a custom-made medical device (e.g. contact lenses, orthodontic braces)



KNEE REPLACEMENT

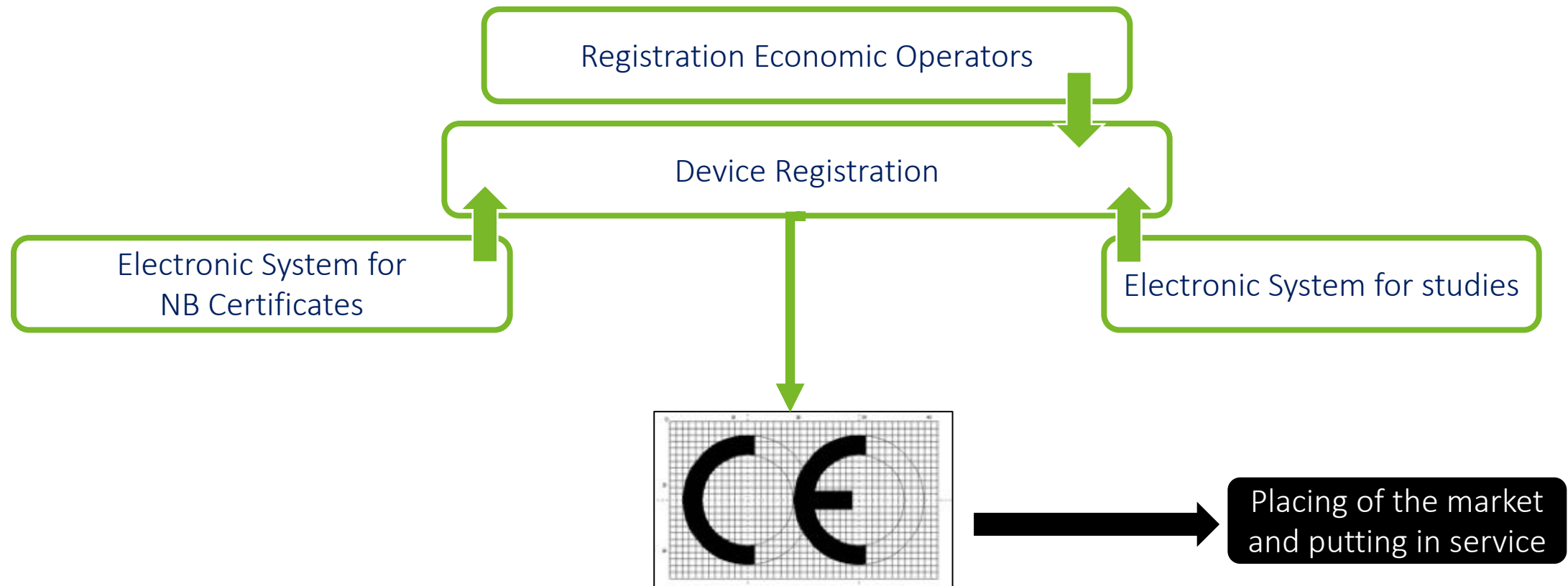


LUMBAR INTERBODY CAGES



PROSTHETIC LEGS

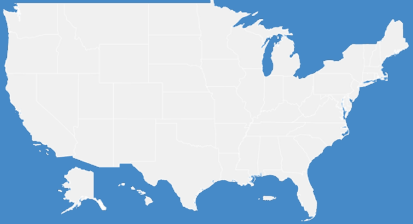
Registration



The background features a blue-toned image of a person in a white lab coat holding a smartphone. Overlaid on this is a grid of hexagonal icons representing various medical fields: an eye, a heart, a person silhouette, a virus, a wheelchair, a molecular structure, a blood drop, and a first aid kit. A stethoscope is also visible around the neck of the person in the lab coat.

Medical Device Regulation in U.S.A.

Medical Device Regulation in U.S.A



Medical Devices are regulated by the US FDA.

Some medical devices require premarket submissions depending on use and classification:

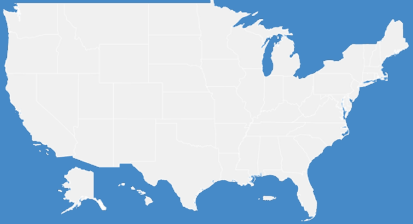
- [Premarket Notification \(510\(k\)\)](#)

A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is safe and effective, and substantially equivalent to a legally-marketed device that is not subject to Premarket Approval.

- [Premarket Approval \(PMA\)](#)

This is the FDA's process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices.

Medical Device Regulation in U.S.A



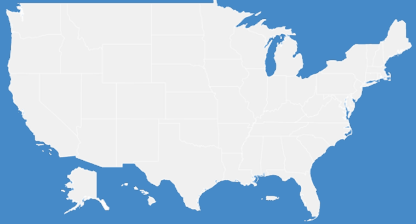
To determine if your device requires a 510(k) or PMA submission, you can [search the Product Classification Database](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm).

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm>



The FDA maintains public 510(k) and PMA databases. You can [search the releasable 510\(k\)](#) and [PMA databases](#) to obtain 510(k) and PMA information for a specific product.

Medical Device Regulation in U.S.A



Currently medical devices fall into one of three medical device classifications:

Class-1	Class-2	Class-3
No FDA approval needed* Must register device & company on FDA website.	FDA clearance required. Typically via 510 (K) Premarket notification submission.	FDA approval required. Typically via Premarket (PMA) approval process

Class I includes devices with the lowest risk and Class III includes those with the greatest risk.

Approval of Class-3 Devices is complicated and involves clinical trials.
Less than 10% of devices are considered Class-3 by the FDA.

The background of the slide features a blue-toned image of a person's hands holding a smartphone. Overlaid on this is a grid of hexagonal icons representing various medical fields: an eye, a heart, a person silhouette, a virus, a molecular structure, a wheelchair, a blood drop, and a first aid kit. A stethoscope is also visible, draped across the upper part of the image. The text 'Medical Device Regulation in China' is centered in white.

Medical Device Regulation in China

Medical Device Regulation in China



- The National Medical Products Administration (NMPA), previously the China Food and Drug Administration (CFDA), is the institution responsible for pharmaceuticals and medical devices regulations in China.
- The CFDA changed its name to NMPA in March 2018. The agency was established in 1998 and its main function was to regulate pharmaceuticals, medical devices, and, after 2003, also food.
- The NMPA, on the other hand, is focused only on the regulation of drugs and medical devices.



Medical Device Regulation in China



Class-1	Class-2	Class-3
Medical Devices are those for which safety and effectiveness can be ensured through routine administration.	Medical Devices are those for which further control is required to ensure their safety and effectiveness.	Medical Devices are those which are implanted into the human body, or used for life support or sustenance, or pose potential risk to the human body and thus must be strictly controlled in respect to safety and effectiveness.

Medical Device Regulation in China



- If a MDs company wants to register a device not manufactured in China, it has to provide device samples to the NMPA for testing.
- Chinese law requires each industrial product to have a Chinese national standard.
- The Chinese national standard is usually the same as the relevant international standard, although sometimes with minor modifications.
- Medical devices type testing must be based upon the **Chinese national standard**.
- However, if a national standard does not exist, an industry standard, or **a company-specified standard may be used**.
- Chinese testing laboratories work with companies to ensure that their company-specific standard are in-line with relevant national standards.

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Medical Device Regulation in Japan

Medical Device Regulation in Japan



- The PMDA is a division of the Ministry of Health Labor and Welfare (MHLW)
- Medical devices are approved by the Pharmaceuticals and Medical Devices Agency (PMDA)
- Pharmaceutical and Medical Device Act (PMD Act) – main medical device regulation



Medical Device Regulation in China



Class I	Class II	Class III	Class IV
Low risk	Medium-low risk	Medium-high risk	High risk

Regulatory route determined by JMDN Code (predicate device) and Classification

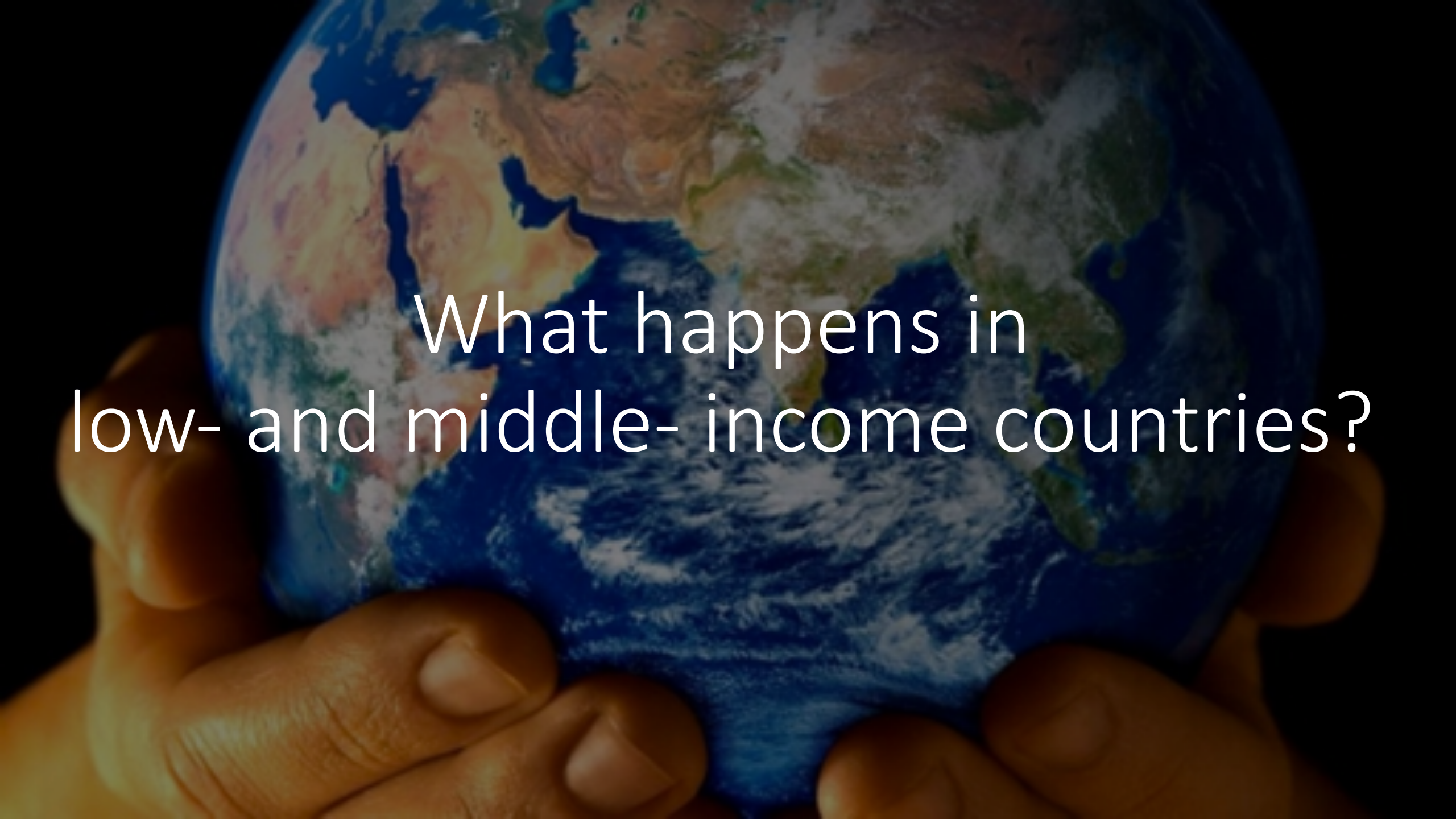
If no JMDN code is available, classification determined by risk to the human body

Japan classification rules are based on Global Harmonization Task Force (GHTF) guidance

Medical Device Classification worldwide



GHTF	USA	China	EU	Australia, Canada	Japan	Associated risk
Class A	Class I	Class I	Class I	Class I	Class I	Low risk
Class B	Class II	Class II	Class IIa	Class II	Class II	Moderate low
Class C			Class IIb	Class III	Class III	Moderate high
Class D	Class III	Class III	Class III	Class IV	Class IV	High risk

A pair of hands, with fingers visible, gently cradles a small, realistic-looking globe of the Earth. The globe shows continents in shades of brown and green and oceans in deep blue. The background is dark, making the hands and globe stand out. Overlaid on the center of the globe is the text 'What happens in low- and middle- income countries?' in a white, sans-serif font.

What happens in
low- and middle- income countries?

Medical Device regulation in Africa



- In the majority of African countries, medical device regulations have an affinity to European Regulation/Directives, despite the fact that the latter are particularly strict.
- Several states have implemented or harmonized directives to medical device regulation, or have expressed interest in establishing them in their legislation
- Lack of investment and training limit the capacity to improve and maintain knowledge and skills of personnel for actuating these regulation



Journal of Biomedical Signals Processing and Control



Special issue on:

Biomedical and clinical engineering in resource-limited settings

Carmelo De Maria, University of Pisa, Italy

Philippa Ngaju Makobore, Uganda Industrial Research Institute, Uganda

Sudesh Sivarasu, University of Cape Town, South Africa

Davide Piaggio, University of Warwick, UK



Submissions featuring the following topics will be particularly welcome:

- Artificial intelligence, eHealth, mHealth
- Image and signal processing
- Closed-loop control applications
- Innovative sensors, Microfluidics
- Plug&play electronics
- Sustainable materials, Circular economy
- Medical device environmental impact
- Resilience of medical technologies
- Additive manufacturing
- Clinical engineering in context

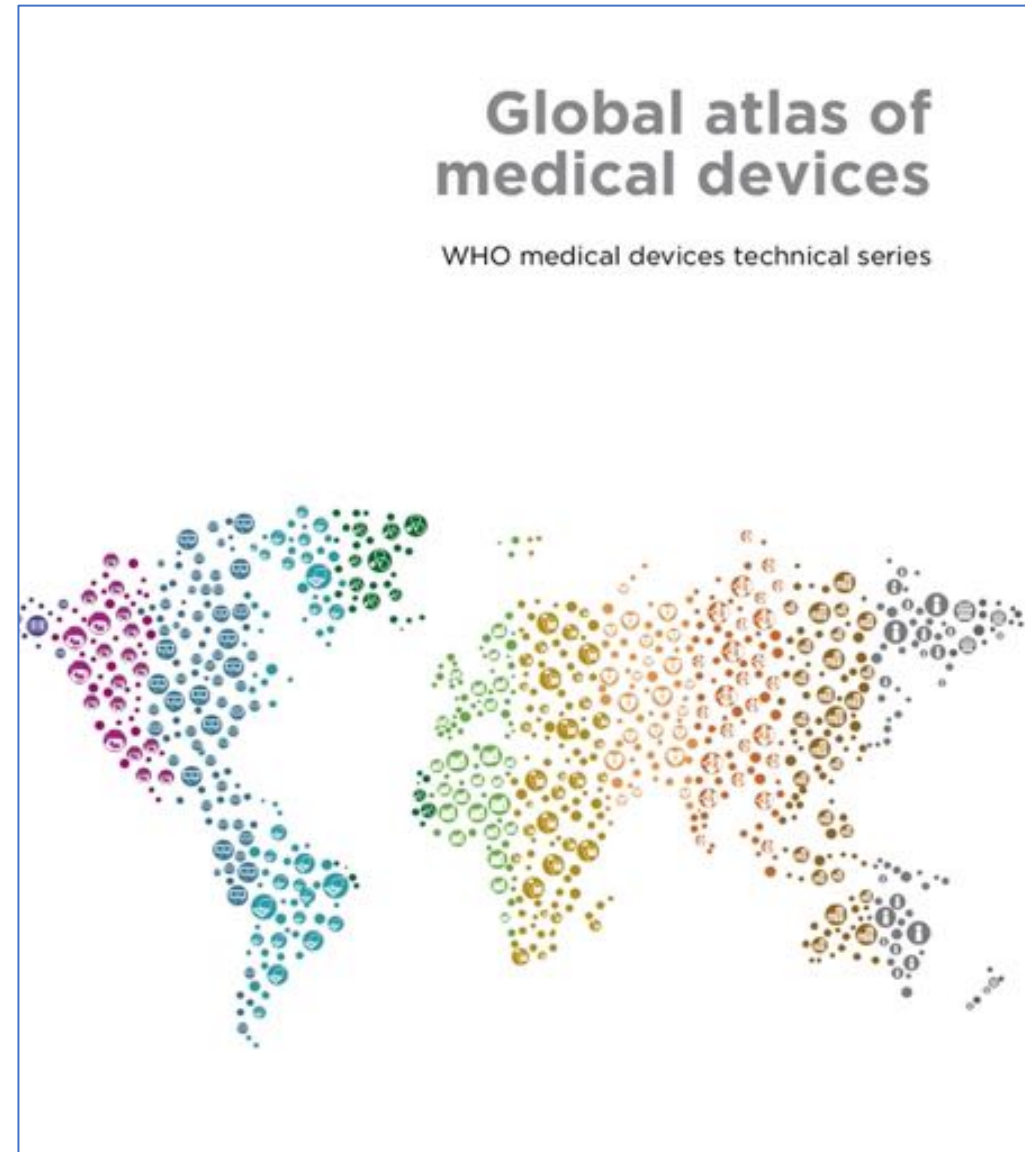
The submissions may range from prevention (primary and secondary), screening, diagnosis, treatment, rehabilitation, monitoring, end-of-life management, support and other interventions, with a priority to on-field studies.



Suggested readings

Global Atlas of Medical devices

[https://www.who.int/
medical_devices/publi
cations/global_atlas
meddev2017/en/](https://www.who.int/medical_devices/publications/global_atlas_meddev2017/en/)



Thank You!

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Dpt of Information Engineering & Research Center E. Piaggio