Biomedical regulation for product safety and manufacturing quality in Europe

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Topics:

• European Union Regulation for Medical Devices
• Bringing your medical device to the EU market: CE-marking step-by-step
  • What is the product?
  • Classification
  • Meet Safety and Performance Requirements
  • Conformity Assessment Procedure
  • Assemble Technical Documentation
  • Affix a CE Marking
  • Draw up a Declaration of conformity
Legislation on Medical Device in the European Union
What do they have in common?
Yesterday – Medical Device Directive

• Three Directives ("current directives")
  • Council directive 93/42/EEC of 14 June 1993 concerning medical devices ("MDD")
  • Council directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the member states relating to active implantable medical devices ("AIMD")

The Medical Device Directive is a law that regulates the marketing of Medical Devices in the EU
Covered Medical Devices (1/3)

Medical Devices (MD)
(Directive 93/42/EEC)

“Medical Device means any instrument, apparatus, appliance, software, material or other article (...) including the software (...) intended by the manufacturer to be used for human beings “ for several purposes such as diagnosis, monitoring, treatment and “which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means”;

Active Implantable Medical Devices (AIMD) (Directive 90/385/EEC)

«Any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure;”

Example: heart pacemakers

NB: “active” = relying for its functioning on a source of electrical energy or any source of power
Covered Medical Devices (3/3)

In Vitro Diagnostic Medical Devices (IVD)
(Directive 98/79/EEC)

“Reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system (...) intended by the manufacturer to be used in vitro for the examination of specimens (...) derived from the human body (...) for the purpose of providing information” concerning a pathological state, a congenital abnormality, or to determine the compatibility with potential recipients, or to monitor therapeutic measures.
Today – Medical Devices Regulations

- Directive 90/385/EEC on active implantable medical devices
- Directive 93/42/EEC on medical devices

**Regulation on medical devices:** Regulation (EU) 2017/745

- Directive 98/79/EC on in vitro diagnostic medical devices

**Regulation on in vitro diagnostic medical devices:** Regulation (EU) 2017/746

The Medical Device Regulation is a **law** that regulates the marketing of Medical Devices in the EU
Transitional period: MDR and IVDR (1/2)

- Entry into force ("EIF") of both regulations takes place 20 days after their publication ➔ As of 25 May 2017

- The regulations do not apply directly ("Application Date"):  
  - MDR applies 3 years after EIF
  - IVDR applies 5 years after EIF
Transitional period: MDR and IVDR (2/2)
Bringing your medical device to the EU market:
CE-marking step-by-step
Step 1: what is the product? (1/2)

- Is the product a medical device according to the medical devices directives/regulations?
- What kind of medical device is the product (IVD, AIMD, MD)?

Depends on the intended purpose and whether the product fits the definition of the directives.
Step 1: what is the product? (2/2)

Borderline issues

It may sometimes be difficult to determine:

• If a product is a medical device (whether MD, IVD or AIMD)
  *Examples: thermomixers intended to control the temperature of liquids in closed micro test tubes, gold implants for treatment of osteoarthritis...*

• If a medical device is an MD, or an IVD, or an AIMD:
  *Example: bone-anchored hearing aids...*
Step 2: classification (1/10)

• Medical devices (MD, IVC and AIMD) fall into various risk categories

Compliance procedures depend on classification →
Important to classify properly

NB. US and EU classification system don’t match perfectly
Step 2: classification (2/10)

Classification of MD

- A ‘risk based’ system based on the vulnerability of the human body
- Four risk classes:

Risk
Step 2: classification (3/10)

Annex IX of Medical Device Directive 93/42/EEC contains the classification rules for the Medical Device

Annex VIII of Medical Device Regulation 2017/745 contains the classification rules

Step 2: classification (4/10)

Class I

All invasive devices with respect to body orifices, other than surgically invasive devices, which are not intended for connection to an active device or which are intended for connection to a class I active device if they are intended for transient use;

All non-invasive devices which come into contact with injured skin or mucous membrane if they are intended to be used as a mechanical barrier, for compression or for absorption of exudates;

All invasive devices with respect to body orifices, other than surgically invasive devices, which are not intended for connection to an active device or which are intended for connection to a class I active device for transient use;
Step 2: classification (5/10)

<table>
<thead>
<tr>
<th>Class IIA</th>
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</thead>
<tbody>
<tr>
<td>All invasive devices in relation with body orifices, other than surgically invasive devices, which are not intended for connection to an active device or which are intended for connection to a class I active device.</td>
</tr>
<tr>
<td>All surgically invasive devices intended for transient use.</td>
</tr>
<tr>
<td>All active therapeutic devices intended to administer or exchange energy.</td>
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<tr>
<td>Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes</td>
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<tr>
<td>All active devices intended to administer and/or remove medicinal products, body liquids or other substances to or from the body</td>
</tr>
<tr>
<td>All devices incorporating or consisting of nanomaterial with a negligible potential for internal exposure.</td>
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</table>
Step 2: classification (6/10)

Class IIb

All non-invasive devices intended for modifying the biological or chemical composition of human tissues or cells, blood, other body liquids or other liquids intended for implantation or administration into the body

All non-invasive devices which come into contact with injured skin or mucous membrane are classified as: class IIb if they are intended to be used principally for injuries to skin which have breached the dermis or mucous membrane and can only heal by secondary intent;

All implantable devices and long-term surgically invasive devices

All active devices intended to emit ionizing radiation for therapeutic purposes, including devices which control or monitor such devices, or which directly influence their performance

All devices used for contraception or prevention of the transmission of sexually transmitted

All devices intended specifically to be used for disinfecting, cleaning, rinsing or, where appropriate, hydrating contact lenses
### Step 2: classification (7/10)

<table>
<thead>
<tr>
<th>Class III</th>
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<tbody>
<tr>
<td>All surgically invasive devices in direct contact with the heart or central circulatory system or the central nervous system,</td>
</tr>
<tr>
<td>Active implantable devices or their accessories</td>
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<tr>
<td>Breast implants or surgical meshes</td>
</tr>
<tr>
<td>All active devices that are intended for controlling, monitoring or directly influencing the performance of active implantable devices</td>
</tr>
<tr>
<td>All devices incorporating or consisting of nanomaterial are classified as: — class III if they present a high or medium potential for internal exposure;</td>
</tr>
<tr>
<td>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,</td>
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</table>
Step 2: classification (8/10)

Classification of AIMD
High risk, invasive: one single risk class

Medical Device Directive 90/385/EEC contains the classification rules for the AIMD

Annex VIII of Medical Device Regulation 2017/745, Chapter III, Rule 8
Step 2: classification (9/10)
### Classification of IVD

<table>
<thead>
<tr>
<th>Class</th>
<th>Risk level</th>
<th>Device Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low Individual Risk and Low Public Health Risk</td>
<td>Clinical Chemistry Analyser, prepared selective culture media</td>
</tr>
<tr>
<td>B</td>
<td>Moderate Individual Risk and/or Low Public Health Risk</td>
<td>Vitamin B12, Pregnancy self testing, anti-Nuclear Antibody, Urine test strips</td>
</tr>
<tr>
<td>C</td>
<td>High Individual Risk and/or Moderate Public Health Risk</td>
<td>Blood glucose self testing, HLA typing, PSA screening, Rubella</td>
</tr>
<tr>
<td>D</td>
<td>High Individual Risk and High Public Health Risk</td>
<td>HIV Blood donor screening, HIV Blood Diagnostic</td>
</tr>
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</table>
Step 3: Meet Safety and Performance Requirements (1/4)

Safety and Performance requirements for the protection of health and safety

Form the core of the 2 Regulations.

- Are set out in general terms.
- Cover risks and hazards that may occur at the design, production and handling stages.
- Are listed in Annex I of each Regulation.

The Safety and Performance Requirements (SPRs) of the Medical Devices Regulation (MDR) replace the previous Directives' Essential Requirements (ERs) and outline the key areas to address within the Technical Documentation.
Step 3: Meet Safety and Performance Requirements (2/4)

EU-wide Harmonized standards

Compliance with harmonized standards provides a presumption of conformity with the corresponding requirements of the directive.

*Regulation (EU) 2017/745: «References in this Regulation to harmonised standards shall be understood as meaning harmonised standards the references of which have been published in the Official Journal of the European Union.»*
Step 3: Meet Safety and Performance Requirements (3/4)

A few examples EU-wide Harmonized standards

- EN ISO 14971:2009 (Risk management)
- EN 980:2008 (Symbols for use in the labeling of MD)

List of EU Harmonized Standards for MD/IVD/AIMD:
Language requirements

• Information to users plays a critical role in reducing risks.
• Detailed provisions for Instructions for Use (IFU) and label
• Use of symbol (standards)
• National language must be used for packaging, label and IFU
Step 4: Follow a CAP (1/5)

Conformity Assessment procedures (CAP)

- CAPs allow manufacturers to demonstrate the conformity of their device with the provisions of the regulation.
- The choice of the CAP is determined by the classification of the device and the preference of the manufacturer for a given CAP.
- CAPs address the design and production stages.
Step 4: Follow a CAP (2/5)

Range of CAP

• Low-risk products (e.g. class I MD) generally allow **self-certification**.

• CAPs applicable to higher-risk products will require the services of a **third party** ("EU Notified Body") depending on the classification of the device.
Step 4: Follow a CAP (3/5)

CAP for different Medical Device’s class
MDR 2017/745 (60)

The conformity assessment procedure for:

• **class I** devices should be carried out, as a general rule, under the sole responsibility of manufacturers in view of the low level of vulnerability associated with such devices.

• For **class IIa**, **class IIb** and **class III** devices, an appropriate level of involvement of a notified body should be compulsory.
Step 4: Follow a CAP (4/5)

Role of Notified Bodies (NBs)

- For all AIMD, certain IVD and MD (Class IIa and above).
- NB are accredited test laboratories based in the EU.
- Only an accredited EU NB can make the final assessment of conformity with the directives and deliver a certificate.
Step 4: Follow a CAP (5/5)

Quality Management System

- Required for all devices (except Class I non sterile/ non measuring).

- Most companies apply EN ISO 13485 to comply with QMS requirements (not mandatory).

- Implementation of a QMS may take 3-4 months to a year.
Step 5: Assemble the Technical Documentation

The Technical Documentation

- Contains all relevant information to support the claims of compliance with the requirements of the directive.
- Must be kept at the disposal of national surveillance authorities.
Step 6: Affix CE Marking

The **CE-marking symbol:**

- Is affixed to the device and accompanying documents.
- Demonstrates that the manufacturer has complied with the applicable directive(s)/regulation(s) and is not a quality sign.

*When a NB intervenes, its ID number must appear below/next to the CE-marking.*
Step 7: draw up a Declaration of Conformity

- For all devices

- One-page document on which the manufacturer of a medical device "declares" his product’s "conformity" with the:
  - Safety and Performance Requirements of the Regulation

- To be kept at the disposal of authorities.