Transition to European Medical Device Regulation (MDR) *Ongoing Challenges*

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Ongoing Challenges

- Device (risk) classes (some up-classifications)
- Emphasis on clinical evaluation of all medical devices
- Strict rules for equivalence
- More clinical data needed (how to generate)
- Some non-clinical challenges (few examples)

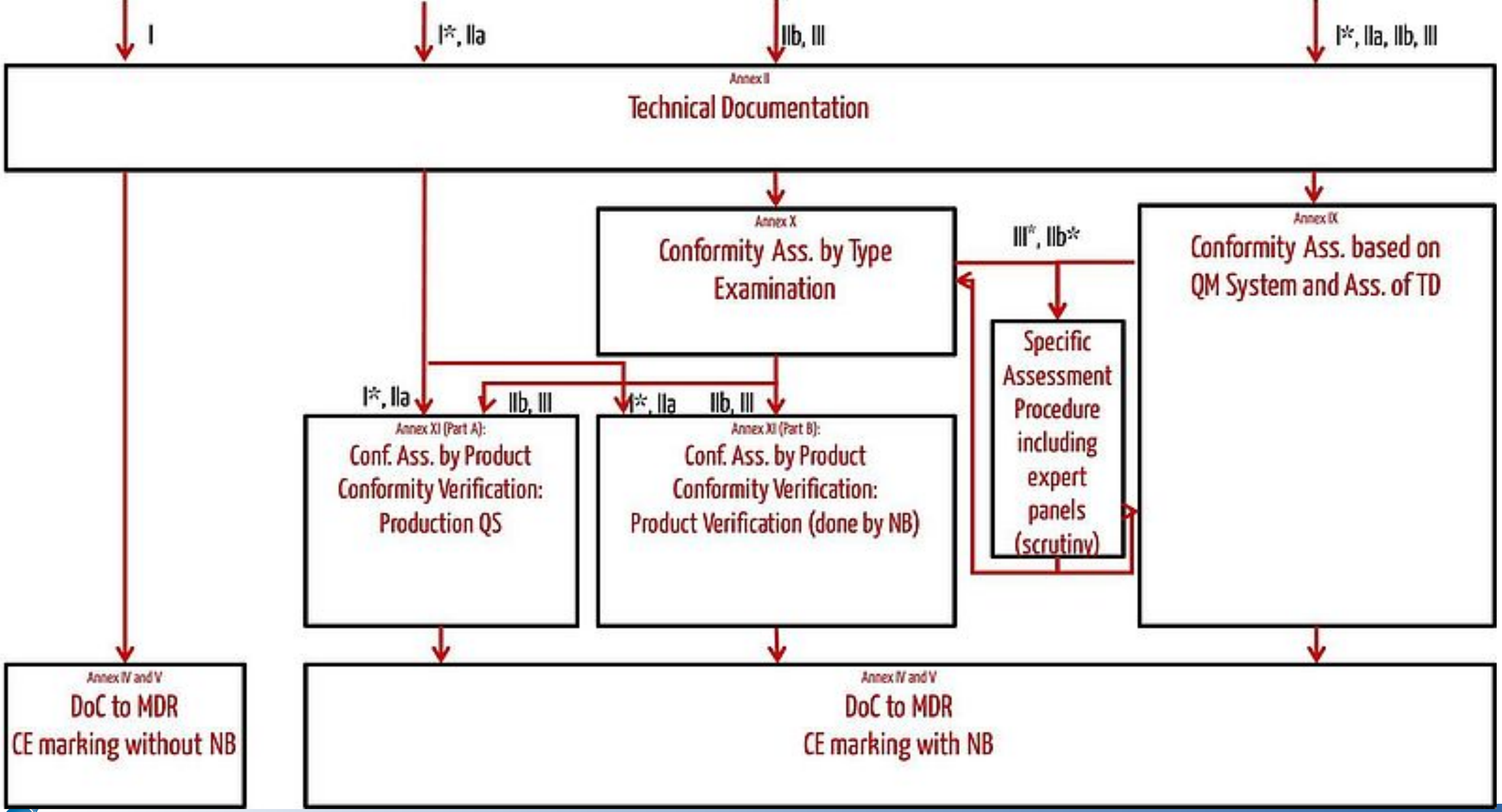
- Brief overview of the European way of placing medical devices on the market

The European Way (several players involved)

- European Commission
  - *Executive branch of the European Union*
  - Medical Device Regulation; Guidance Documents
  - Accreditation and control of notified bodies
- Notified bodies
  - *Notified bodies are government accredited, mostly private companies that take over sovereign tasks on behalf of national authorities.*
  - Certification quality management systems according to ISO 13485 and to the Annexes of the Medical Device Regulation
  - Assessment of conformity of the medical devices (clinical evaluations, risk management, etc.)
- Competent authorities
  - *National authority (in each country), typically reporting to the ministry of health*
  - Vigilance
  - Approval of pre-market clinical investigations
  - Final classification decisions

The European Way (the conformity assessment)

- The manufacturer must prove compliance with the General Safety and Performance Requirements of the Medical Device Regulation
- ‘Conformity Assessment’ means the process demonstrating whether the requirements of this Regulation relating to a device have been fulfilled
- Involvement of a notified body:
  - For medical devices that fall into class I, the conformity assessment does not involve a notified body.
  - For all other classes (I*, IIa, IIb, III) a notified body must be involved in the conformity assessment leading towards the CE-mark.
  - This CE-mark has to be renewed on a regular basis


I
I*, IIa
IIb, III
I*, IIa, IIb, III
Annex II
Technical Documentation
Annex X
Conformity Ass. by Type Examination
III*, IIb*
Annex IX
Conformity Ass. based on QM System and Ass. of TD
Specific Assessment Procedure including expert panels (scrutiny)
I*, IIa
IIb, III
I*, IIa
IIb, III
Annex XI (Part A):
Conf. Ass. by Product Conformity Verification: Production QS
Annex XI (Part B):
Conf. Ass. by Product Conformity Verification: Product Verification (done by NB)
Annex IV and V
DoC to MDR
CE marking without NB
Annex IV and V
DoC to MDR
CE marking with NB

The Device Classification

FDA

- Class I
- Class II
- Class III

The Device Classification

EU MDR

- Class I
- Class Im (*measurement*), Is (*sterile*), Ir (*reusable*)
- Class IIa (e.g. blood pressure monitors)
- Class IIb (e.g. ventilators)
- Class IIb [high riks] (e.g., implants, drug delivery)
- Class III (e.g. joint replacement, pacemakers)

FDA

- Class I
- Class II
- Class III

Challenges of Device Classification

- More implants in class III
- New rules for materials of human origin (III), nanomaterials (IIa – III) and devices intended for absorption by the human body (mostly III)
- Combination products (all III)
- Consideration of new technologies like treatment of cells or tissues in vitro before subsequent infusion or implantation (mostly III)
- Risk-based approach for classification of stand-alone software (classes IIa, IIb, III)

MDR Annex VIII

Clinical Evaluations – Clinical Data

- The term “Clinical Evaluation” is mentioned in the Medical Device Regulation
  - Total: 132 / 355 pages
    - Rationale: 49 / 28 pages
    - Articles: 49 / 174 pages
    - Annexes: 70 / 153 pages
- Medical Device Directive (for comparison):
  - Total: 7 / 65 pages (version 2007)
  - Total: 1 / 37 pages (version 1993)

General Principles of Clinical Evaluation

- Clinical evaluation is conducted throughout the life cycle of a medical device, as an ongoing process.
- Clinical evaluation is mandatory for initial CE-marking and it must be actively updated thereafter.
- Clinical evaluation undertaken during the development of a medical device
  - Definition of need regarding clinical safety and performance
  - Identify equivalent devices and their clinical data
  - Gap analysis ➔ data to be generated from clinical investigations
- Clinical evaluation for initial CE-marking
  - Sufficient evidence to show conformity to the General Safety and Performance Requirements
  - Identify needs for Post-Market Surveillance and Post-Market Clinical Follow-up

Benefit-Risk Analysis

- Strong emphasis on benefit-risk analysis

  Note: Benefit does not equal performance!

- Assessment of patient benefit from device
- Quantification of patient benefit
- Assessment of clinical risks from device
- Assessment of the acceptability of the benefit-risk profile
- Changes in medical alternatives have to be considered
  - Results of the benefit-risk analysis may change over time!

Updates of Clinical Evaluations

- Whenever new relevant information from PMS
- At least annually, if the device carries significant risks or is not yet well established; or
- Every 2 to 5 years, if the device is not expected to carry significant risks and is well established, a justification should be provided.
- Translation:
  - Class III: at least annually
  - Class IIb implants, drug administration: annually
  - Class IIb: every 2 years
  - Class IIa: every 2-5 years
  - Class I: every 5 years
- If the evidence for the product changes (e.g, by new medical alternatives) it may need to be taken off the market

Equivalence

- All relevant aspects of equivalence must be shown in ONE medical device!
  - Partial equivalence from different products not acceptable
  - Only CE-marked devices
- Detailed comparison on the level of development and production details
  - Clinical properties (application, intended use, operation mode, etc.)
  - Technical properties (incl. production process)
  - Biological properties (e.g. materials in contact with patient)
- *BUT: For all modifications and concomitant claims of equivalence, there must be no additional risks or potential of negatively altered performance related to the introduced modifications.*
- *If there are technical differences, but the function is the same, equivalence may be claimed.*
- For implants and class III de facto only products from own production (vs. competitor devices); a contract between manufacturers would be required!

Clinical Evaluation – Ongoing Challenges

- Clinical evaluation along the entire product life cycle
- Strong emphasis on clinical benefit for all medical devices
- Strict requirements for equivalence
- More clinical data required, more clinical studies needed
- More emphasis on post-market surveillance (PMS) and post-market clinical follow-up (PMCF)
- More frequent updates required

Clinical Data

- Clinical investigations with the device or equivalent devices
- Other clinical studies with the device or equivalent devices
- Scientific literature (peer review) – performance, safety, benefit
  - Studies with the product, equivalent products
  - Studies with similar products (state of the art)

  Note: scientific literature is the preferred route for most devices
- Clinical data from post-market surveillance and post-market clinical follow-up

Clinical Investigations

- If gaps are present that cannot be addressed by other means, **clinical investigations** should be planned and carried out.
- **Implants and high-risk devices**, those based on technologies where there is **little or no experience**, and those that **extend the intended purpose of an existing technology** (i.e. a new clinical use) are most likely to **require clinical investigation data**.
- **Clinical investigations** may also be required for other devices, including for devices in **class I and class IIa, and for class IIb devices** that are not implantable.

- Gaps become wider due to the increased requirements for equivalence
- Further aggravation due to changes in classification rules in MDR

Clinical Trials

- Evidence of performance and safety in a prospective clinical study
  - (not yet) approved/certified medical device
  - expansion of the intended use
- Approval from the competent authority
  - (studies within the intended use)
- Clinical trial
  - Only after exhaustive preclinical studies (e.g. biomechanics, animal studies)
  - Complete risk management, etc.
- Strict requirements for study design and statistical planning
- Complex submission and approval procedures under MDR

PMCF Studies

- Possible designs post-market clinical follow-up studies
  - Registry studies
  - Retrospective analysis of prospectively acquired clinical data
  - User surveys (including proactive post-market surveillance)
  - Observational studies in case of open issues in the clinical evaluation
  - Prospective comparative studies in case of open issues in the clinical evaluation (also for already approved class III products)
- Challenges:
  - Often clinical data for established products may not be sufficient to show performance and safety as required by MDR
  - What was sufficient before, may not be enough today

Clinical Data – Ongoing Challenges

- Clinical data required for all medical devices
  - Including devices in classes IIb, IIa, and I
- Extensive literature searches and analyses
- Thus far sufficient clinical data may not be enough under MDR
- Not using clinical data requires a detailed rationale
- PMCF studies, proactive PMS
- Clinical trials may be necessary (even for existing products)
- Don’t be afraid of sponsor-initiated studies
  - Some may be required
- Coordination with FDA activities

Authorized Representative (AR)

- means any natural or legal person established within the Union who has received and accepted a written mandate from a manufacturer, located outside the Union, to act on the manufacturer's behalf in relation to specified tasks with regard to the latter's obligations under this Regulation;
- *Important: The manufacturer of the medical device CANNOT transfer (to the AR) his responsibilities for the devices or the fulfillment of the requirements according to the respective regulation.*
- *Requirements on the authorized representative are much higher under the new regulations.*

Person Responsible for Regulatory Compliance (PRRC)

Role and responsibilities:

<u>At the manufacturer:</u>

- Conformity of the devices is appropriately checked
- Technical documentation and Declaration of Conformity are drawn up and up to date
- Post-market surveillance system is implemented and kept up to date
- Vigilance obligations are fullfilled

<u>At the Authorized Representative (AR):</u>

- Ensuring that the tasks of an AR as specified in the mandate are fulfilled

- Each manufacturer must have at least **one PRRC** which has to be an **employee of the manufacturer's organisation**
- For manufacturers outside the EU, the PRRC must also be located **outside the EU**
- „Outsourcing" the responsibilities of the PRRC to a third party: **only for micro and small** manufacturers
- AR must have also at least one PRRC, which can be subcontracted to a third party but must be located in the EU → **The PRRC of the manufacturer and the PRRC of the AR must not be the same person**

Summary and Outlook

- The new MDR poses formidable challenges for all stakeholders
- Significant emphasis on clinical data to show performance, safety and benefit of the device
- More clinical data and clinical investigations needed
- Up-classification of several device groups
- Strict requirements for showing equivalence
- The lower the risk class the higher the incremental effort
- Conformity assessment literally begins with the start of development
- ***You may want some help!***

Thank You!

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