The New Medical Device Regulation and the Clinical Challenges in the EU

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New Medical Device Regulations – MDR

- 2008: Commission starts new draft
- 2009-2012: PIP, metal-on-metal endo-prostheses
- 2012-2013: EP deliberation (350 amendments)
- 2013-2015: Very long negotiations in the council
- Early 2016: Trialogue (Parliament, Council, Commission)
- June 2016: Consolidated version
- Final Version: February 22, 2017
- Reading in Council: March 7, 2017
- Acknowledgement in EP: March 14, 2017
- Final vote in EP: Early April 2017
- Official publication: April/May 2017
- MDR will become direct law 20 days later
- Transition period only 3 years

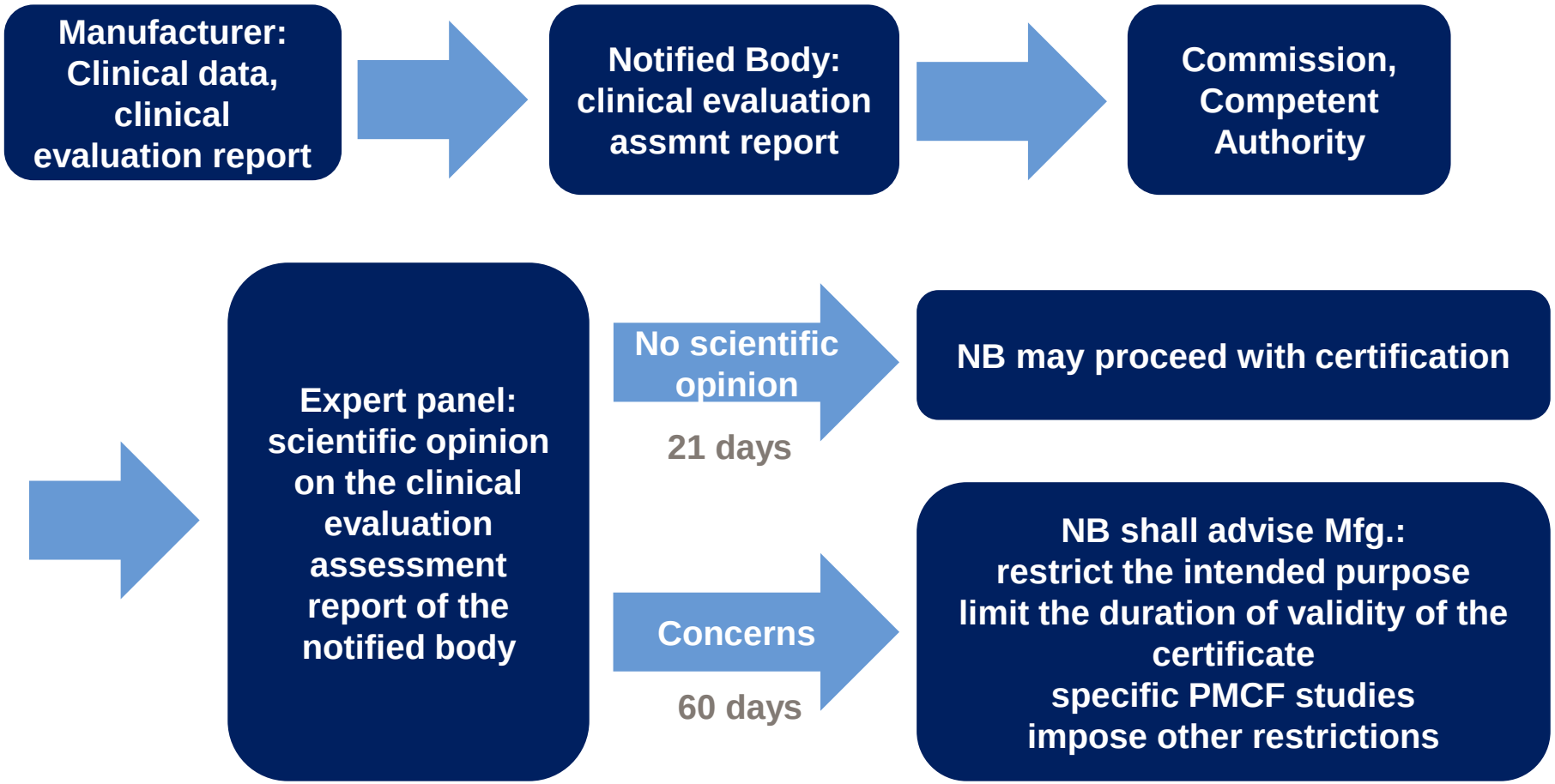
Medical Devices

- Great variability of risk potential and complexity
  - From crutches to fully implantable artificial hearts
- Many medical devices are tools
- Iterative improvements of established technologies
  - Significant differences to pharma research and development
- Numerous medical devices address small patient groups with specific needs
  - No regulatory equivalent to “orphan drugs”
- 95+% of all medical device companies are SMEs

MDR – Some Highlights

- Overreaching goal: Patient safety
- All medical devices including active implantable devices
  - IVD devices in a separate regulation
- Up-classification of several device groups
- Much tighter requirements for showing equivalence
  - For many devices effectively impossible
- New processes for class III and some class IIb
  - Class III implants
  - Class IIb administering medications
  - Scrutiny procedures involving expert panels
  - Consultation procedure

MDR – Scrutiny Procedure



MDR – Some Highlights

- Increased documentation and reporting
- Comprehensive control and auditing of suppliers by manufacturer
- Increased depth of assessment of the technical documentation
- More clinical data for performance, safety and patient benefit
- Compulsory clinical studies for many devices
  - Implants, class III, some class IIb
- Much stricter certification of Notified Bodies
  - Less notified bodies (some countries w/o NBs)
  - NBs stretched to the limit
  - NBs do not accept new clients
- Special NBs for certain product groups

MDR – New Classification Rules

Now in Class III

- Implants:
  - Direct contact to heart, central vasc. system, CNS
  - Biological effect, absorption, resorption
  - Drug delivery
  - Active implants (previously AIMDD)
  - Breast implants, surgical meshes
  - All joint replacements
  - Spinal disc/column implants
- Drug-device combinations
- Cells/tissues of human or animal origin (except skin contact)
- Nanomaterials with a high or medium potential for internal exposure
- Closed-loop controllers, AEDs, etc.

MDR – Clinical Evaluation

- The term “Clinical Evaluation” is mentioned
  - 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)
- MEDDEV 2.7/1 Revision 4
  - Guidance document for clinical evaluations
  - New revision since July 1, 2016, without transition period
  - Effectively binding, although “only” a guidance document
  - MDR requirements for clinical evaluations
  - Inconsistent interpretation between notified bodies

MEDDEV 2.7/1 Revision 4

- Clinical evaluation from start of development to end of marketing
- Strong emphasis on clinical benefit from all medical devices
- Much tighter requirements for equivalence
- More clinical data (and studies) needed
- Much higher demands for data analysis (especially data from literature)
- Increased requirements for PMS, PMCF
- Excessive requirements for author qualification
- Overlap (inconsistent!) with other MEDDEVs and industry standards
  - Risk management
  - Clinical studies

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 for 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 with ERs
  - Identify needs for PMS/PMCF

Equivalence

- Alle relevant aspects of equivalence must be shown in ONE medical device!
  - Partial equivalence from different products not acceptable
  - Only CE-marked devices
- Detailed comparison of the level of development and production details.
  - Clinical properties (application, intended use, mode of operation, etc.)
  - Technical properaties (incl. production process)
  - Biological properties (e.g. materals in contact with patient)
- For implants and class III de facto only products from own production

Risk-Benefit Analysis

- Increasing emphasis on risk-benefit 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 risk-benefit profile
- Changes over time have to be considered.

Clinical Data – New Requirements

- All data from within and outside the EU:
  - Studies, publications, literature, PMS data
  - Exhaustively described and evaluated
- Literature searches:
  - Description of the state of the art
  - Description of performance, safety and benefit of the evaluated device and (if claimed) equivalent products
  - Separate search protocols and results reports
  - At least Medline and EMBASE (other database as needed)
- Other sources:
  - Complaint data, register data, field safety action
  - Data from all countries where the device is marketed

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.*

Example 1 – Vascular Implant (class III)

- Large patient population, established therapeutic principles
- Direct competitor (5 years longer in market)
- One RCT with own product (< 2 years follow-up)
- State of the Art / medical alternatives:
  - Numerous recent guidelines
  - Many meta-analyses with moderate to very high quality
- Clinical benefit
  - Own RCT
  - Long-term follow-up of direct competitor (equivalence claimed)
- Clinical risks
  - Established therapy concept
  - Moderate number of publications with (potentials) AEs
  - Comprehensive complaitn data (own product, competitor)
- Unambiguous risk-benefit analysis

Example 2 – Patient Monitoring (class IIb)

- Numerous products in market
- Established technology for the last 50+ years
- Universal use (no specific patient populations)
- State of the art / medical alternatives
  - Guidelines very general
  - Systematic studies only in special patient populations
- Performance and safety comprehensively defined in industry standards
- Clinical benefit
  - Clinical benefit results only from medical action triggered by monitoring!
  - Example: Perioperative pulse oximetry ➔ outcome benefit cannot be shown
- Risk-benefit analysis unclear (and not really appropriate)

Example 3 – documentation software (class IIa)

- Alternative to paper-based patient record
- Established application for 2,000+ years
- Universal use (every patient), indispensible
- State of the art / medical alternatives:
  - Documentation legally required, in guidelines requested
  - Method of technical implementation not required/regulated
- Clinical benefit
  - Without documentation no consistent patient care
  - No clinical studies into the benefit of documenation
- Clinical risks
  - Decision making influenced by missing/erroneous data (technical risk)
  - Literature search de facto not feasible
- Risk-benefit analysis not feasible and not meaningful

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 (PMS annually)
  - Class IIa: every 2-5 years (PMS every 2 years)
  - Class I: every 5 years (PMS when necessary)
- If the evidence for the product changes (e.g, by new medical alternatives) it may need to be taken off the market

Authors – New Requirements

- Knowledge of the technology and application of the device
- Knowledge of scientific work
- Knowledge of the design of clinical investigations
- Knowledge in biostatistics
- Knowledge of the disease to be treated/diagnosed with respective clinical experience
- Experience in use of databases and in medical writing
- Regulatory knowledge
- ➔ more than one author required?!

Summary and Outlook

- The new MDR is a game changer
- Strong emphasis on clinical benefit from all medical devices
- Up-classification of several device groups
- Stricter requirements for showing equivalence
- Massively increased requirements for data analysis
- More clinical data needed
- More clinical investigations needed
- The lower the risk class the higher the incremental effort
- More frequent updates required
- Cost and time for conformity assessment will increase (have already increased)