The new regulatory challenges in Europe

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Overview

- The new Medical Device Regulation (MDR) came into effect on May 26, 2017
- Transition period until May 25, 2020
- Dramatic changes from the old Medical Device Directive (MDD)
- Most aspects of notified body (NB) accreditation (by the European Commission (EC)) and of interaction between NB and medical device manufacturers have changed
- All aspects of the conformity assessment process are affected
- Highlights for today's presentation
  - Equivalence
  - Clinical Evaluations
  - Clinical Data

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)
- For implants and class III de facto only products from own production (vs. competitor devices)
- In general, equivalence is only accepted for effectively identical devices
- Data from “similar” devices may be used to define the state of the art (and for extended safety assessment)

Equivalence

- MDR Article 61 (5):
- A manufacturer of a device demonstrated to be equivalent to an already marketed device not manufactured by him, may also rely on paragraph 4 in order not to perform a clinical investigation provided that the following conditions are fulfilled in addition to what is required in that paragraph:
  - **the two manufacturers have a contract in place that explicitly allows the manufacturer of the second device full access to the technical documentation on an ongoing basis, and**
  - **the original clinical evaluation has been performed in compliance with the requirements of this Regulation,**
- and the manufacturer of the second device provides clear evidence thereof to the notified body.

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 with Essential Requirements (ER; *MDD*) / General Safety and Performance Requirements (GSPR; *MDR*)
  - Identify needs for Post-Market Surveillance (PMS) and Post-Market Clinical Follow-up (PMCF)

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 in medical alternatives have to be considered
  - Results of the risk-benefit analysis may change over time!

Risk-Benefit Analysis

- Requirements of MEDDEV 2.7/1 Rev 4 and MDR for the clinical evaluation
  - Assessment of risks
  - Assessment of risk-benefit ratio
  - Assessment of (not acceptable) side effects

- These are core competences of risk management!
- Risk management should be done at only ONE place in the tech file

➔Close coordination between risk management (RM) and clinical evaluation teams

Clinical Evaluation – New Challenges

- Clinical evaluation along the entire product life cycle
- Strong emphasis on clinical benefit for all medical devices
- Stricter requirements for equivalence
- Separate data searches and analyses for state of the art and the actual product
- Massively increased requirements for data analysis (esp. literature appraisal)
- More clinical data required
- More clinical studies needed

Clinical Evaluation – New Challenges

- More emphasis on PMS and PMCF
- More frequent updates required
- Strong focus on implants
- The lower the risk class the higher the incremental effort
- Extreme requirements for author qualifications
- MEDDEV and MDR overlap with other guidance documents and standards (e.g., RM, PMS, clinical studies)
- The MDR does not define the requirements for clinical evaluations in any detail

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
- Increasingly complex submission and approval procedures under MDR

Clinical Data – New Challenges

- Clinical data required for all medical devices
  - Including devices in classes IIb, IIa, and I
- Thus far sufficient clinical data may not be enough under MDR
- Alternative evidence (standards, animal studies) not considered under MDR/MEDDEV
- Not using clinical data requires a detailed rationale
- PMCF, proactive PMS
- Clinical trials may be necessary (even for existing products)
- Don’t be afraid of sponsor-initiated studies (ISO 14155, GCP)
  - Some are absolutely required
- Coordination with FDA activities

Example 1 – 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 2 – Vascular Implant (class III)

- Large patient population, established therapeutic principles
- State of the Art / medical alternatives:
  - Numerous recent guidelines
  - Many meta-analyses with moderate to very high quality
- Direct competitor (5 years longer in market)
  - Large RCT
  - Long-term follow-up
- One RCT with own product
  - < 2 years follow-up
- Unambiguous risk-benefit analysis
- Very low complaint rate, no serious adverse events
- Equivalence to competitor claimed
- Equivalence not accepted by NB
  - Minor structural differences (clinically not relevant)
  - No access to technical documentation
- Status after two years
  - Certificate not renewed
  - New clinical studies requested
  - Large registry study, or
  - New RCT with long-term follow-up (5+ years)

Authors – Example

- Vascular implant class III
- Main author
  - Board certified surgeon and intensivist
  - PhD in medical informatics and statistics
- Internal reviewer
  - Board certified vascular surgeon
- Literature searches
  - External specialist team
  - EMBASE database expert
- PMS Data
  - Internal complaint management team
- Close coordination with RM team

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

Summary and Outlook

- The new MDR poses formidable challenges for all stakeholders
- 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)

Thank You!

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