Regulatorische Änderungen bei den klinischen Datenanforderungen in Europa:
Ist die Literaturroute noch möglich?

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Content

1. Current Clinical Data Requirements
2. Clinical Evaluation - MEDDEV 2.7.1
3. Examples
4. Pre- & Post-Market Clinical Investigation
5. New Medical Device Regulation

http://www.clearswift.com/sites/default/files/images/blog/EU-Regulations-blog.png
http://libertyunyielding.com/wp-content/uploads/2015/05/regulations.jpg
Requirements for Clinical Data

- Dir. 2007/47/EC
- MEDDEV 2.7.1 Rev. 3: Clinical evaluation
- MEDDEV 2.7/4: Guidelines on Clinical Investigation
- EN ISO 14155:2011: Clinical investigations on medical devices for human subjects
- MEDDEV 2.12-2 Rev. 2: Guidelines on Post Market Clinical Follow-Up Studies
Current Requirements for Clinical Data

Dir. 2007/47/EC

Which medical devices require a clinical evaluation?

- ALL Medical Devices regardless of Classification
- Annex I: Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X
Clinical Evaluation

The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer.
Clinical Evaluation according to current MEDDEV 2.7.1 Rev. 3

Which route should you follow for the device under consideration?

Equivalence Route

Clinical Investigation Route
Current Clinical Investigation Route Requirements

MEDDEV 2.7/4 – When should a clinical investigation be undertaken?

- The Conformity Assessment process for active implantable medical devices as well as for class III and implantable medical devices requires that a clinical investigation is undertaken unless it is duly justified to rely on existing data.

Section 1.2 of Annex 7 of directive 90/385/EEC
Section I.1a of Annex X of directive 93/42/EEC

Risk

Innovation
MEDDEV 2.7/4 – When should a clinical investigation be undertaken?

- Depending on clinical claims, risk management outcome and on the results of the clinical evaluation, clinical investigations may also have to be performed for non-implantable medical devices of classes I, IIa and IIb.

- Additional clinical investigations may be feasible to corroborate the existing clinical evidence with regard to aspects of clinical performance, safety, benefit/risk-ratio or to determine relative effectiveness and safety with suitable comparators.
State of the Art

A documented and systematic literature review

A detailed discussion covering the benefit/risk ratio of the device when comparing to:

1. All current available therapeutic alternatives for the same indication
2. Conventional Therapy, Medical Devices and Medicinal Products
3. Similar products from for example competitors for the same indication
Clinical Evaluation – RISK MANAGEMENT PROCESS

Which route should you follow for the device under consideration?

IDEA

RISK IDENTIFICATION METHODS

RISK MITIGATION METHODS

RESIDUAL RISKS ACCEPTABILITY
Clinical Evaluation according to MEDDEV 2.7.1 Rev. 3

- Determination of Scope
- Identification of Clinical Data
- Appraisal
- Analysis of relevant Data
- Clinical Evaluation Report
Equivalence Approach based on current available literature

Same intended use
(Clinical condition/Disease, Severity, Application Site, Patient Population, Critical Performance Parameter)

+ Technical and biological equivalence

+ No clinically significant difference regarding safety and performance

≈
Clinical Evaluation – Example 1

Which route should you follow for the device under consideration?

New Device

Example of available competitors
Which route should you follow for the device under consideration?
Clinical Evaluation – Example 3

Which route should you follow for the device under consideration?
### Equivalence Approach based on current available literature

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Example 1</th>
<th>Example 2</th>
</tr>
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<tbody>
<tr>
<td>Same intended use</td>
<td>YES</td>
<td>YES but possibly different population</td>
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<tr>
<td>Technical Equivalence</td>
<td>YES</td>
<td>YES (B) – NO (A) – A is a short stem with significant different biomech. properties</td>
</tr>
<tr>
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<td>YES (B) – NO (A)</td>
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### Equivalence Approach based on current available literature

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Clinical Evaluation – Example 3

It is normally based on a combination of critical evaluation of the relevant scientific literature and testing according to IEC 60601-2-24.
Clinical Evaluation – Example 3

Infusion pumps

The main function of the device is to pump fluid. Functional safety considers potential hazards related to this function:

- Wrong flow rate
- Wrong volume infused
- Unintended start or stop of infusion
- Buildup of excessive pressure
- Air infusion
- Reverse flow direction

„To develop the device in such a way, that it can not cause any harm in case of a breakdown“
Good Clinical Practice

Scope

The ISO 14155:2011 addressess good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes.
Good Clinical Practice

How to plan a clinical investigation correctly?

- Risk Analysis
- Clinical evaluation

Study Plan

Endpoints
- Scientific validity

Suitability
- Clinical relevance

All relevant legal and regulatory requirements
Clinical Investigation Route

Study design

- Type
- Measures to avoid bias
- Primary and secondary endpoints with rationale for selection and measurement
- Methods and timing for assessing, recording, and analyzing variables
- Justification for choice of comparator(s)
- Subjects (inclusion, exclusion criteria, number, duration)
- Study related procedures incl. post-study medical care
- Monitoring plan
Clinical Investigation Route

Statistical Methods

- design, method and analytical procedures
- sample size
- level of significance
- expected dropout rates
- pass/fail criteria
- provisions for an interim analysis
- criteria for termination on statistical grounds

What is most important statistical or clinical significance?
### Approval in the European Union

The first involved NCA provides a EUDAMED No. This number must be used for all further submissions in EU, some NCA provide an additional registration number.

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Clinical Investigation Route

Documents evaluated by EU Notified Bodies

- CIP
- Letter of No Objection – Approval of Competent Authority
- Ethics Committee opinion
- Signed and dated final report
PMCF Requirements according to current MEDDEV 2.12/2 Rev. 2

Why PMCF?

Rare complications or problems become apparent after wide-spread or long term use of the device.

An appropriate PMS Plan is key to identifying and investigating residual risks associated with the use of medical devices placed on the market.

To confirm the safety and performance throughout the expected lifetime of the device, the continued acceptability of identified risks and to detect emerging risks on the basis of factual evidence.
Why PMCF?

There may be limitations to the clinical data available in the pre-market phase:

- Duration
- Number of subjects
- Investigators involved (Heterogenicity?)
- Subjects (Heterogenicity?)
- The controlled setting of a clinical investigation vs. the full range of clinical conditions encountered in general medical practice
PMCF required

**PMCF is mandatory for:**

- Innovative Products
- Significant changes
- High product related risks
- High risk anatomical locations/target populations
- Emergence of new information on safety or performance
- Where CE marking was based on equivalence
- Unanswered questions of long-term safety and performance
Responsibilities of a EU Notified Body

The Notified Body shall

- Review the appropriateness of the manufacturer’s general PMS procedures and plans
- Verify that PMCF is conducted by or on behalf of the manufacturer by appropriately competent assessors
- Verify that Clinical Investigations were conducted in accordance with relevant provisions of the directive(s), related guidance and standards
- Verify the need for PMCF and/or appropriateness of any justification
- Assess the appropriateness of the proposed PMCF plan
Responsibilities of a EU Notified Body

The Notified Body shall

• Verify if the gathered PMCF Data were used to update the clinical evaluation report
• Consider whether based on the specific device assessment, data obtained from PMCF should be transmitted between scheduled assessment activities
• Consider an appropriate period for certification of the product in order to set a particular time point at which PMCF data will be assessed
• Set conditions to submit interim reports between certification reviews
Clinical Evaluation Report (CER)

The appropriate CER shall be prepared as a stand-alone document to facilitate the assessment of a third independent party.

The stand-alone document must comprise:

- Product description
- Background regarding device technology
- Intended Use, Indications and Contraindications
- Claims regarding performance and safety
- Relevant bench- and preclinical data
- Nature and extent of clinical data
- Suitability of the referenced information
- Acceptability of the risk/benefit ratio
- PMCF Plan

The appropriate CER must be: Signed and dated by the evaluator(s)

The appropriate CER must include: A justification for the choice of evaluator(s)
Where are we heading to?

Breast implant scandal: What went wrong?

Rec. 2013/473
MEDDEV 2.7.1
Rev. 4

2007/47EG

MDD
AIMD
IVDD

„To establish a robust, transparent, predictable and sustainable regulatory framework for medical devices which ensures a high level of safety and health whilst supporting Innovation“
EU Regulations Proposal – Scrutiny Procedure

Medical Device Coordination Group

A new expert group to:
- Made up of members appointed by the Member States and chaired by the Commission
- Achieve harmonized implementation of this regulation
- Establish an additional „scrutiny mechanism“

Manufacturer Submission → Notified Body → Notified Body Review → Notified Body Pre-report → Notified Body Approval Board → CE

Commission → Medical Devices Coordination Group MDCG → Scrutiny? → Scrutiny Start → MDCG Scrutiny

T= 28 Days

MDCG final comment → T= 60 Days
EU Regulations Proposal – Scrutiny Procedure

Proposal Parliament

Manufacturer Submission → SNB → SNB Evaluation → SNB Approval Board → CE

- Commission
- Scrutiny?
- MDCG → T= 20 Days
- If scrutiny
  - Evaluation of CER, PMCF and other relevant doc
  - T= 30 Days*

Opinion°

°Appeal procedure

*Clock Stop System
EU Regulations Proposal – Scrutiny Procedure

Council of the European Union

Manufacturer Submission → NB → Notification to the authorities Art 42(2a) → EUDAMED

Expert Panel* → NB

60 Days

1. Summary of safety and performance
2. NB Assessment Report
3. Instructions for Use
4. Expert Panel Decision
5. Justification of NB in case of divergent views

- Competent authority or Commission may apply appropriate measures
- Monitoring and assessment of NB
- Review NB Assessment
- Changes to designations and notifications
- Challenge to the competence of NB
- Evaluation regarding devices suspected to presenting an unacceptable risk or non-compliance

*For New Products: New technology and not line extension
Clinical Evaluation according to MEDDEV 2.7.1 Rev 3

Which route should you follow for the device under consideration?
Article 49: Clinical Evaluation

Manufacturers shall conduct a clinical evaluation in accordance with the principles set out in this Article and Part A of Annex XIII.

A clinical evaluation shall follow a defined and methodologically sound procedure based on either of the following:

- A critical evaluation of the relevant scientific literature
- A critical evaluation of the results of all clinical investigations
- A critical evaluation of the combined clinical data
EU Regulations Proposal – Clinical Investigations Requirements

- For Class III medical devices and Implantable medical devices clinical investigations shall be performed unless it is duly justified to rely on existing clinical data alone.

- Demonstration of equivalence shall generally not be considered as sufficient justification within the meaning of this sentence.

- Equivalence can only be demonstrated when the device has the same intended purpose and when the technical and biological characteristics of the devices and the medical procedures applied are similar to such an extent that there would be not a clinically significant difference in the safety and performance of the devices.

Preamble (47) in the proposed regulation
- Clinical investigations in line with major international guidance in this field, such as the international standard ISO 14155:2011.
Council

- In the case of implantable devices and devices falling within class III, clinical investigations shall be performed except if the device has been **designed by modifications** of a device already marketed by the same manufacturer if the modifications have been scientifically demonstrated by the manufacturer and accepted by the Notified Body as being equivalent.

- In this case the Notified Body shall check that the **PMCF plan** is appropriate and includes post market studies to **demonstrate the safety and performance** of the device.

*Clear contract between different device manufacturer*
A PMCF Study

To be performed according to a PMCF Plan with the aim of:

- confirming the safety and performance of the device throughout its expected lifetime
- identifying previously unknown side-effects and monitoring the identified side-effects/contra-indications
- identifying and analyzing emergent risks on the basis of factual evidence
- assuring the continued acceptability of the benefit/risk ratio
- identifying possible systematic misuse or off-label use of the device
For devices classified as class III and implantable devices, the PMCF report, and if indicated, the summary of safety and clinical performance referred to in Article 26(1) shall be updated at least annually with these data.
Questions?

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