A practical approach to clinical evaluation that fulfills the future EU regulation expectations: principles and examples

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A practical approach to clinical evaluation that fulfills the future EU regulation expectations → what are they?

Principles of a Clinical Evaluation

→ What are we talking about?
→ How to perform a CE – as a manufacturer
→ How to review a CER – as a NB

Examples

The law – the method – the report
What will be new compared to current directives?

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<th>DIRECTIVES 93/42 (2007/47)</th>
<th>NEW REGULATION</th>
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No major changes!

Objectives of the new regulation

Enhanced *legal certainty* and coordination in the field of *clinical evaluation* and investigations

Chapter VI : Article 49 : Clinical evaluation :

Clinical evaluation needed to demonstrate the safety and performance of manufacturers’ devices.

The law – the method – the report
Principles

- Manufacturers shall conduct a clinical evaluation whatever the class of the device
- Clinical evaluation means the assessment and analysis of clinical data pertaining to a device in order to verify the safety and performance of the device

How?

The law – the method – the report
To conduct a clinical evaluation...

- Identify the general safety and performance requirements that require support from relevant clinical data

M ➔ What is the intended use of my device? What do I have to be compliant with? What do I need to prove?

NB ➔ Are these questions clearly defined, with corresponding answers?
Hypertonic nasal spray with sea water

Intended use: Nasal washing in case of allergic rhinitis

PERFORMANCE

- Is the device useful?
  - Is sea water useful for nasal washing?
  - Allergic rhinitis → patients with allergic rhinitis

SAFETY

- Is the device safe?

What are the risks associated with:
  - Nasal washing?
  - Hypertonicity of the sea water?
To conduct a clinical evaluation...

– identify available clinical data relevant to the device and its intended use generated through scientific literature search, clinical experience and/or clinical investigations;

➔ Where will I find relevant information (device and intended use) ?

Scientific literature : PubMed, Cochrane

Keywords ? Filters ? Time limits ? …
NB:

→ What are the sources of clinical data?
→ Are the keywords for literature research appropriate?
→ What about the filters that could have been selected?
→ ....
To conduct a clinical evaluation, ...

– appraise the clinical data sets by evaluating their suitability for establishing the safety and performance of the device;

How will I appraise the data?

Tools for data appraisal:
NHMC,
Oxford,
Evidence Based Medicine,
MEDDEV

NB: Is there a described and relevant method for data appraisal?
To conduct a clinical evaluation, ...

–generate any new or additional clinical data needed to address outstanding issues;

What are the issues?
Do I have enough clinical data?
Are all the questions answered?

–analyze all relevant clinical data to reach conclusions about the safety and performance of the device.
A clinical evaluation shall follow a defined and methodologically sound procedure....

Methodology = presumption of conformity with general requirements.

→ Finding equivalent devices to collect clinical evidence

→ Demonstration of Equivalence
Demonstration of equivalence (Class I, IIa, IIb medical devices)

Clinical data relating to another device may be relevant where equivalence is demonstrated …

…. 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.

→ Performance equivalence has to be proven (comparative testings ?)
→ Security equivalence has to be proven (biocompatibility testings results ?)
Demonstration of equivalence

Differences exist between the device of interest and its competitors

• What are the **clinical impacts** of these differences ?
• What **proves** that these impacts are **negligible** regarding performance and safety ?

Technical equivalence : design, raw material, …
Biological equivalence : tissue in contact with, conditions of use…
• Proofs are expected: benchtesting comparison (absorption for a dress, tensile strength for sutures…)

• Intrauterine devices with copper: length, copper surface?
• Isotonic sea water spray / saline nasal spray?
Demonstration of equivalence
Class III medical devices

In the case of implantable devices and devices falling within class III, clinical investigations shall be performed unless it is duly justified to rely on existing clinical data alone.

Demonstration of equivalence in accordance with Section 4 shall generally not be considered as sufficient justification within the meaning of the first sentence of this paragraph.

Yes, how?

What does generally mean?

To demonstrate what?

So what will be sufficient?
Clinical evaluation report

The clinical evaluation shall be thorough and **objective**, considering both **favourable and unfavourable** data.

- How to demonstrate **objectivity**?
  - Keywords and articles selection:
    (MEDDEV guidelines – presumption of objectivity)

- **Who has written the CER?** (Who will review it?)
  - Expertise justification…
- **Are the unfavourable data mentioned?** If they are none of them, did they have been searched?
Adequacy of claims and clinical data results

- A device intended to reduce pain should have been clinically demonstrated to reduce pain (VAS…)

- A device intended to treat a cerebral aneurism to avoid patient death should not increase the risk of patients’ death
Normal conditions of use
→ Scope of the clinical data

**Performance**

Undesirable side effect
→ Identification / Risk analysis

**Safety**

Benefit / risk ratio acceptability

Confirmation of conformity with the requirements concerning the characteristics and performances ... under the normal conditions of use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit/risk ratio ..., shall be based on clinical data.

The law – the method – the report
Final objective of the CER:
Assessment of conformity with Essential Requirements

The results of the clinical evaluation and the clinical data on which it is based shall be documented in the clinical evaluation report which shall support the assessment of the conformity of the device.

→ All the documentation (articles, test reports) should be available (not only abstract of the articles)
→ The CER conclusion should state that the device is compliant and conform to the general requirements (the risk/benefit balance should be defined).

• Does the safety of the device outweigh the risk?
• Is the device useful?
• Does the device fulfill its intended use?
The law – the method – the report
Always a clinical evaluation report?

What clinical data will be available for
- Syringes?
- Wheelchair or medical bed?

Where demonstration of conformity with general safety and performance requirements based on clinical data is not deemed appropriate, adequate justification for any such exception shall be given based on the results of the manufacturer's risk management and on consideration of the specifics of the interaction between the device and the human body, the clinical performances intended and the claims of the manufacturer.

Safety and performance requirements could also be assessed by non-clinical data.

The law – the method – the report
Tools for safety and performance assessments

- Clinical data
- Pre-clinical evaluation (Non-clinical data)
- Performance evaluation
- Bench testing
- Discussion based on:
  - Risk analysis
  - Intended Clinical Performance
  - Interaction device / human body
The clinical evaluation and its documentation shall be updated throughout the life cycle of the device concerned with data obtained from the implementation of the manufacturer's post-market surveillance plan ... 

For high-risk medical devices, manufacturers should summarize the main safety and performance aspects of the device and the outcome of the clinical evaluation in a document that should be publicly available.
What could not be acceptable:

→ Free articles only for literature selection
→ Summary of articles, compilation of abstracts without any critical analysis
→ Restrictive key words
→ Too short inclusion periods for publication researches
→ …
Upcoming regulation and clinical evaluation: Keep home messages

- No major changes
- Safety and performance assessment → compliance with Essential Requirements
- Clinical data according to claims
- Risk/benefit balance assessment
Thank you for your attention