Mapping Your Success - Understanding Clinical Equivalence

2013 BSI Healthcare Roadshow

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Product Expert, General Devices
Understanding Clinical Equivalence

• Review Requirements from Directives on Medical Devices
• Examine Definition of Medical Devices
• Review EU Commission Guidelines on:
  • Clinical Evaluation of Medical Devices (MEDDEV 2.7.1)
  • Post Market Clinical Follow-up (PMCF) Studies (MEDDEV 2.12/2)
EU Directives on Medical Devices
EU Directives on Medical Devices

**MDD & AIMD** modified by Directive 2007/47/EC, effective 21 Mar 2010

- **MDD**: ER 6a – Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X
- **AIMD**: ER 5a - Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex 7
Annex X (MDD) / Annex 7 (AIMD)

- As a general rule, **confirmation of conformity with the requirements concerning the characteristics and performances** ... **must be based on clinical data**.
- **The clinical evaluation:**
  1.1.1 either a **critical evaluation** of the **relevant scientific literature** currently available relating to the safety, performance, the design characteristics and the intended purpose of the device, where:
     - there is demonstration of equivalence of the device with that to which the data relates and,
     - the data adequately demonstrate compliance with the relevant Essential Requirements;
  1.1.2 or a **critical evaluation** of the results of all **clinical investigations** made;
  1.1.3 or a **critical evaluation** of the **combined clinical data** provided in 1.1.1 and 1.1.2 above.
Annex X (MDD) / Annex 7 (AIMD)

Clinical Investigations:

- **MDD**: In the case of implantable devices and devices in Class III clinical investigations shall be performed unless it is duly justified to rely on existing clinical data.

- **AIMD**: Clinical investigations shall be performed unless it is duly justified to rely on existing clinical data.
Clinical Evaluations:

- Many devices developed by incremental innovation, so they are not completely novel.
- Often possible to **draw on the clinical experience and literature reports of the safety and performance of equivalent devices** to establish the clinical evidence.
- Requires comprehensive analysis of pre- and post-market clinical data **relevant to the intended use**:
  - data specific to the device in question
  - data relating to **devices claimed as equivalent**.
CER Updates:

• CER must be **actively updated** with data obtained from the post-market surveillance.

• Where **post-market clinical follow-up (PMCF)** as part of the post-market surveillance (PMS) plan for the device is **not deemed necessary**, this must be duly justified and documented.
Definition of a Medical Device
Definition of “Medical Devices”

MDD/ AI MD - Article 1

• Formal definition

MEDDEV 2.1/ 1

• Medical devices are defined as articles which are intended to be used for a medical purpose.
• Products intended to have a toiletry or cosmetic purpose are not medical devices even though they may be used for prevention of a disease.
• Products with a multiple purpose which may be used occasionally in a medical environment are normally not medical devices, unless a specific medical intended purpose is assigned to them.
EU Commission Guidelines on the Clinical Evaluation of Medical Devices
GUIDELINES ON MEDICAL DEVICES

CLINICAL EVALUATION:
A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES
MEDDEV 2.7.1

• Reflects positions taken in particular by representatives of National Competent Authorities and Commission Services, Notified Bodies, industry and other interested parties in the MEDICAL DEVICES sector

• Guidelines not legally binding . . . alternative approach may be possible or appropriate to comply with requirements

• It is anticipated that the guidelines will be followed within the Member States
MEDDEV 2.7.1 – Key Contents

Sections:
5. General principles of Clinical Evaluation
6. Sources of data / documentation (Stage 1)
7. Appraisal of clinical data (Stage 2)
8. Analysis of clinical data (Stage 3)
9. The CER
10. Role of the Notified Body (NB)

Appendices:
A – E: Sample formats / methodologies
F: NB Clinical Evaluation Checklist
Section 5.1 – Scope of CER:

- Devices should have the same intended use and will need to be compared with respect to their technical and biological characteristics.
  - *Intended use* relates to the clinical condition being treated, the severity and stage of disease, the site of application to/in the body and the patient population.
  - *Technical characteristics* relate to the design, specifications, physiochemical properties including energy intensity, deployment methods, critical performance requirements, principles of operation and conditions of use.
  - *Biological characteristics* relate to biocompatibility of materials in contact with the same body fluids/tissues.
  - Characteristics should be similar to extent that there would be no clinically significant difference in the performance and safety of the device.
MEDDEV 2.7.1 - “Equivalent Devices”

Appx. E, Sec. 4 – Possible format for CER
• Clearly state if the clinical data used in the evaluation are for an equivalent device.
• Identify the equivalent device(s) and provide a justification of the equivalency, cross-referenced to the relevant non-clinical documentation that supports the claim.

Appx. F, Sec. 3.2.3 – NB Checklist
• If differences are identified, an assessment must be done to demonstrate potential significance of differences on safety & performance
MEDDEV 2.7.1 – “Equivalent Devices”

Appx. F, Sec. 3.2.3 (Footnote) – Meaning of Equivalence

• **Clinical:**
  • C1 - same clinical condition or purpose
  • C2 - same site in the body
  • C3 - similar population (including age, anatomy, physiology)
  • C4 - similar relevant critical performance for specific intended use

• **Technical:**
  • T1 - similar conditions of use
  • T2 - similar specifications and properties
  • T3 - similar design
  • T4 - similar principles of operation

• **Biological:**
  • S1 - same materials in contact with the same tissues or body fluids
FDA – “Predicate Devices”

FDA Predicate Device ≠ MEDDEV 2.7.1 equivalent device

Substantially equivalent predicate device (per FDA):
• Device has the same intended use as the predicate; and
• Device has the same technological characteristics as the predicate;

OR

• Device has the same intended use as the predicate; and
• Device has different technological characteristics and the information submitted to FDA;
• does not raise new questions of safety and effectiveness; and
• demonstrates that the device is at least as safe and effective as the legally marketed device.
MEDDEV 2.7.1 – “Equivalent Devices”

• Equivalence should be substantiated based on a detailed assessment.
• Focus should be on discussing the DIFFERENCES rather than highlighting the SIMILARITIES.
• Some devices have very narrow clinical purposes (such as hip replacements) but others have multiple purposes (such as meshes or dressings or fillers). In these cases, equivalent devices should have the same purposes.
**Stage 1**

**Identify** clinical data from:
- Literature searching & / or
- Clinical experience & / or
- Clinical Investigation

**Stage 2**

**Appraisal** of individual data sets:
- Suitability
- Contribution of results to demonstration of performance and safety

**Stage 3**

**Analysis** of relevant data:
- Strength of overall evidence
- Conclusion about performance and safety

* Conformity to harmonized performance standard may be sufficient to demonstrate compliance to ERs

Figure 1:

MEDDEV 2.7.1 - “Equivalent Devices”

Stepwise Approach

• Identify potential “equivalent devices” for search strategy

Example:

- A
- B
- C
- D
- E
- F
- G

- Identify data (CER Stage 1) – Discover clinical data on A, B, C, F, and unknown device G
- Appraise data (CER Stage 2) – Determine device C is not equivalent and data for F is weak (small sample size)
- Analyze data (CER Stage 3) – Data from A, B, & G supports safety & performance but gap identified
- Repeat as warranted – Search again on device G
- Write CER
  • Justify Equivalence on Devices A, B, and G
  • Write PMS Plan (to include PMCF for subject device)
Demonstration of equivalence

Example:
• For devices cited in literature

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Subject Device</th>
<th>Comparative Devices</th>
<th>Potential Clinical Impact of Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contraindications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sizes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lifetime</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Etc.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on expert analysis

Source of data should be cited

EQUIVALENT?
Equivalent Devices – Watch-Outs

- Equivalent devices not identified
- Equivalent devices not EU medical devices
- Improper equivalent devices identified – not equivalent for clinical, technical, and biological
- Piecing equivalent features out of multiple devices
- Gaps in demonstration of equivalence – insufficient data / information
  - Not all information in public domain
  - Preclinical data can be used to fill in gaps
- Equivalence argument does not cover key parameters that may impact safety or performance
- Differences from subject device not characterized
- Potential clinical impact of differences not discussed
- Citations do not identify devices used or other key information
  - Manufacturer must demonstrate (i.e. justify) equivalence with the device
BSI Examples Where Equivalence Argument Has Been Rejected

• Devices are judged to be alternate treatments
  • Composed of different materials in contact with tissues resulting in different biological response (e.g. biologic vs. synthetic)
  • Dissimilar material form (e.g. sheets vs. granules vs. foam)
  • Dissimilar principles of operation (e.g. stop bleeding by pressure vs. natural hemostasis vs. included medicinal agent)
  • Vastly different absorption profiles (e.g. non-absorbable devices claimed to be equivalent to absorbable ones)
  • Different clinical uses (e.g. hemostasis vs. aid to wound healing)
• Only clinical data available for equivalent device is for off-label use
CER Stage 2: Data Appraisal – Merits/Limitations

- **Suitability** – appraise quality and relevance
  - characterize merits / limitations
  - document reasons for exclusions
- **Contribution** – weigh value by considering confounding influences
  - underlying medical conditions
  - concomitant treatment(s)
  - bias
## MEDDEV 2.7.1 – “Equivalent Devices”

Appx D Example:

- **CER Stage 2: Data Appraisal – Suitability**

**Table D1** Sample Appraisal Criteria for Suitability

<table>
<thead>
<tr>
<th>Suitability Criteria</th>
<th>Description</th>
<th>Grading System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate device</td>
<td>Were the data generated from the device in question?</td>
<td>D1 Actual device</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D2 Equivalent device</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D3 Other device</td>
</tr>
<tr>
<td>Appropriate device application</td>
<td>Was the device used for the same intended use (e.g., methods of deployment, application, etc.)?</td>
<td>A1 Same use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A2 Minor deviation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A3 Major deviation</td>
</tr>
<tr>
<td>Appropriate patient group</td>
<td>Where the data generated from a patient group that is representative of the intended treatment population e.g., age, sex, etc.) and clinical condition (i.e., disease, including state and severity)?</td>
<td>P1 Applicable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P2 Limited</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P3 Different population</td>
</tr>
<tr>
<td>Acceptable report/data collation</td>
<td>Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?</td>
<td>R1 High quality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R2 Minor deficiencies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R3 Insufficient information</td>
</tr>
</tbody>
</table>

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CER Stage 3: Data Analysis – Sufficiency

- If clinical literature is presented for equivalent devices,
  - is this clinical data when taken together with the available preclinical data sufficient to demonstrate conformity with ERs covering safety and performance of the device in question under normal conditions of use?
  - are there gaps in either the demonstration of compliance with each relevant essential requirement or in the demonstration of equivalence that needs addressing through the means of a specifically designed clinical investigation(s)?
  - is the data sufficient to address the clinical hazards identified in the risk analysis?
- If no, a clinical investigation(s) will be needed. The objectives of the clinical investigation(s) should focus on those aspects not sufficiently addressed by the available data.
EU Commission Guidelines on Post-Market Clinical Follow-up (PMCF) Studies
EUROPEAN COMMISSION
DIRECTORATE GENERAL for HEALTH and CONSUMERS
Consumer Affairs
Health technology and Cosmetics

MEDDEV 2.12/2 rev2
January 2012

GUIDELINES ON MEDICAL DEVICES

POST MARKET CLINICAL FOLLOW-UP STUDIES
A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES
Circumstances that may justify PMCF studies include:

- Innovation, unanswered questions on long-term safety and performance, emergence of new information on safety and performance
- High risk design, materials, components, invasiveness, clinical procedures, anatomical locations, target populations
- Severity of disease, unstudied subpopulations, interaction with other medical products or treatments
- Generalizability of pre-market clinical data
- Verification of safety and performance when exposed to a larger and more varied population of users
- Risks identified from literature, adverse events, clinical investigations or PMS
- Where CE marking was based on equivalence.

Focus of PMCF ➔ Subject Device
MEDDEV 2.12/2 - PMCF Studies

Clinical data from PMCF Studies:

- Not intended to replace the pre-market data necessary to demonstrate conformity with the provisions of the legislation.
- Critical to update the clinical evaluation throughout the life-cycle of the medical device and to ensure the long term safety and performance of devices after their placing on the market.
- The objective is to confirm clinical performance and safety, the acceptability of identified risks, and to detect emerging risks on the basis of factual evidence.
- Provides real world experience obtained in larger, heterogeneous and more complex populations, with a broader (and potentially less experienced) range of end-users than is usually the case with clinical investigations.
Clinical data from PMCF Studies:

- Most useful for identifying less common but serious device-related adverse events; providing long term information about safety and performance, including durability data and information about failure modes; and elucidating the end-user “learning curve”.

- Particularly useful source of clinical data for low risk devices that are based on long standing, well-characterised technology and, therefore, unlikely to be the subject of either reporting in the scientific literature or clinical investigation.
Questions