Changes in EU Clinical Data Requirements and Expectations

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Introduction

Meeting European clinical data requirements in a timely fashion has become a critical factor in the CE marking process and will only increase under the European Medical Device Regulation (MDR).
This discussion will cover

- Key changes related to clinical data under the MDR
- Role of MEDDEV 2.7/1 Rev 4
- Planned EU clinical evaluation guidance for aiding compliance with MDR
- Importance of an effective clinical data strategy / clinical strategy
- Recommendations
Key changes related to clinical data under the MDR
## Modified definitions

<table>
<thead>
<tr>
<th>“Clinical data” in Directives &amp; MEDDEV</th>
<th>“Clinical data” in MDR</th>
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<tr>
<td>Clinical investigation of device concerned</td>
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<td>Clinical investigation of equivalent device in scientific literature</td>
<td>Clinical investigation of equivalent device in scientific literature</td>
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<td>Published and/or unpublished reports on other clinical experience of device concerned or equivalent device</td>
<td>Peer reviewed scientific literature reports on other clinical experience of device in question or equivalent device</td>
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<td>Clinically relevant information coming from PMS, in particular, PMCF</td>
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## Modified definitions

<table>
<thead>
<tr>
<th>“Clinical evaluation”* in MEDDEV 2.7/1</th>
<th>“Clinical evaluation” in MDR</th>
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<tr>
<td>Methodologically sound <strong>ongoing</strong> procedure to collect, appraise and analyse clinical data pertaining to a medical device and to evaluate whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer’s Instructions for Use.</td>
<td>Systematic and planned process to <strong>continuously</strong> generate, collect, analyse and assess the clinical data pertaining to a device in order to <strong>verify</strong> the safety and performance, including <strong>clinical benefits</strong>, of the device when used as intended by the manufacturer.</td>
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*Not defined in Directives*
### Modified definitions

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<th>“Clinical evidence” in MDR</th>
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<td>The clinical data and the clinical evaluation report pertaining to a medical device.</td>
<td>Clinical data and clinical evaluation results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer.</td>
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*Not defined in Directives
Clinical evaluation, investigation, and PMCF

<table>
<thead>
<tr>
<th>MDR Chapters</th>
<th>Articles</th>
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<tr>
<td>CHAPTER VI: Clinical Evaluation and Clinical Investigation</td>
<td>61, Clinical evaluation</td>
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<td>62 – 82, Clinical investigations</td>
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<th>MDR Annexes</th>
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<tr>
<td>ANNEX XIV: Clinical Evaluation and Post-market Clinical Follow-up</td>
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<td>ANNEX XV: Clinical Investigations</td>
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Clinical evaluation: Article 61

Basic requirements on clinical evaluation

• Clinical evaluation must be based on:
  – Critical evaluation of the relevant scientific literature on safety, performance, design characteristics and intended purpose of an equivalent device
  – Results of clinical investigations of the device subject to clinical evaluation, and
  – Consideration of currently available alternative treatment options for that purpose, if any [61(3)]

Note! Directives require that clinical evaluation be based on data in scientific literature, clinical investigations, OR both; last element above is not included.
Clinical evaluation: Article 61

Basic requirements on clinical evaluation

- Class III and class IIb active devices intended to administer and/or remove a medicinal product, **may consult** with an **expert panel** regarding clinical development strategy and proposals for clinical investigation [61(2)].

- For implantable and class III devices, clinical investigation must be performed **except** if: device is designed by **modification** of device already marketed by **same manufacturer**; specified criteria must also be met [61(4)].

- **Exemption** to conduct a clinical investigation on a device from one manufacturer demonstrated to be equivalent to a device already marketed by **another manufacturer** if criteria in 61(4) are met [61(5)].
Clinical evaluation: Article 61

Basic requirements on clinical evaluation – Article 61(5) states:

“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.”
Clinical evaluation: Article 61

Interpretation of need for a contract

• Paragraph 61(5) has been widely interpreted to require a contract any time one manufacturer wishes to use clinical data from an equivalent device from another manufacturer.

• However, the exemption allowed under Article 61(5) refers to criteria in 61(4), which relates only to implantable and class III devices that have been modified.

• A draft CIE guidance has interpreted 61(5) to apply to any implantable or class III device where the new device is manufactured by one manufacturer wishing to use the clinical data from a device CE marked by another manufacturer; however, CIE is seeking an official opinion.
**Clinical evaluation: Article 61**

**Basic requirements on clinical evaluation**

- Specified exceptions to the need to perform clinical investigations for implantable devices and class III devices (e.g., devices placed on the market under MDD or AIMDD, specific devices such as sutures, staples, etc.) [61(6)]

- Clinical evaluation must be updated throughout device life cycle with clinical data from implementation of PMCF plan and PMS plan [61(11)].

For implantable devices and class III devices, PMCF evaluation report and, if indicated, summary of safety and clinical performance, must be updated at least annually with clinical data from implementation of PMCF plan and PMS plan [61(11)].
Clinical evaluation: Article 61

Basic requirements on clinical evaluation: Clinical evaluation report

The clinical evaluation, its results and the clinical evidence derived from it shall be documented in a **clinical evaluation report** as referred to in Section 4 of Annex XIV, which, except for custom-made devices, shall be part of the technical documentation referred to in Annex II relating to the device concerned [61(12)]
Specifies requirements on how to conduct clinical evaluation, including documentation requirements [Any revised MEDDEV 2.7/1 will need to be consistent with Annex XIV]

- Must establish and update a **clinical evaluation plan** that includes minimum contents and a **clinical development plan** [Sec 1]
- Identify clinical data relevant to device and its intended purpose and any gaps in clinical evidence via scientific literature review [Sec 1]
- Appraise clinical data for suitability for establishing safety and performance of device; generate any necessary clinical data, and analyze clinical data to reach conclusions about safety and performance of device including clinical benefits [Sec 1]
Clinical evaluation: Annex XIV, Part A

- Identification of GSPRs that require support from relevant clinical data
- Intended purpose of device
- Intended target groups with indications and contra-indications
- Intended clinical benefits with relevant and specified clinical outcome parameters
- Methods to be used for examination of qualitative and quantitative aspects of clinical safety with reference to determination of residual risks and side-effects
Clinical evaluation: Annex XIV, Part A

- Indicative list and specification of parameters for determining acceptability of benefit-risk ratio for various indications and for intended purpose of device
- How benefit-risk issues relating to specific components such as use of pharmaceutical, non-viable animal or human tissues, are to be addressed, and
- Clinical development plan indicating progression from exploratory investigations (e.g., FIM studies, feasibility and pilot studies), to confirmatory investigations (e.g., pivotal clinical investigations), and a PMCF with an indication of milestones and a description of potential acceptance criteria
Clinical evaluation: Annex XIV, Part A

Specifies requirements on how to conduct clinical evaluation, including documentation requirements

- Clinical evaluation may be based on clinical data of an equivalent device, considering technical, biological and clinical characteristics [Sec 3]

- Technical, biological and clinical characteristics must be similar to extent that there would be no clinically significant difference in the safety and clinical performance of the device [Sec 3]

- Manufacturers must have sufficient levels of access to data relating to devices with which they are claiming equivalence to justify claims of equivalence

- Both favorable and unfavorable data considered in the clinical evaluation must be included in the technical documentation [Sec 4]
Clinical evaluation plan & clinical investigations

Clinical investigation: Annex XV

• Clinical investigations must be in line with the clinical evaluation plan [Chapter I, Sec 2.4]

• Clinical investigation application must include, among other information, details and/or reference to clinical evaluation plan [Chapter II, Sec 1.5]

• Clinical investigation plan must include, among other detailed information, type of investigation with rationale for choosing it, for its endpoints and for its variables as set out in the clinical evaluation plan [Chapter II, Sec 3.6.1]
Clinical evaluation consultation procedure

Article 54, Clinical evaluation consultation procedure for certain class III and class IIb devices

• Applies to:
  – class III implantable devices, and
  – class IIb active devices intended to administer and/or remove a medicinal product (Classification Rule 12)

• Notified Body must follow procedure in Section 5.1 of Annex IX or Section 6 of Annex X

• Exemptions include, e.g. renewal of certificate under MDR, clinical evaluation has been addressed by a CS and compliance of clinical evaluation has been confirmed
Scrutiny procedure

Article 55, Mechanism for scrutiny of conformity assessments of certain class III and class IIb devices

- Notified Body must notify the competent authorities, via EUDAMED, of certificates granted to devices for which a clinical evaluation consultation (Article 54) has been performed, including the summary of safety and clinical performance, the assessment report by the Notified Body, the instructions for use and, where applicable, the scientific opinion of the expert panel.

- A competent authority and, where applicable, the Commission may, post-market, apply further procedures and, where deemed necessary, take appropriate measures relating to Notified Body competence / designation or device compliance or non-compliance.
Requirement for summary of clinical evaluation

Article 32, Summary of safety and clinical performance

- Required for *implantable devices* and for *class III devices*, other than custom-made or investigational devices
- Must be clear to intended user or if relevant, the patient
- NB must validate the summary and upload it to Eudamed
- Manufacturer must mention on label or IFU where summary is available
- Eight elements are required including:
  (f) the summary of *clinical evaluation* and relevant information on PMCF
Review by Notified Body of equivalent device data

Annex IX, Conformity Assessment Based on a Quality Management System and on Assessment of Technical Documentation – Section 4

• 10 subsections that apply to class III devices and certain class IIb implantable devices (except sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips and connectors)

• Section 4.5: If clinical evidence is based partly or totally on data from an equivalent device, the Notified Body must:
  – assess the suitability of using such data, taking into account factors such as new indications and innovation
  – clearly document its conclusions on claimed equivalence, and on relevance and adequacy of data for demonstrating conformity, and
  – for any characteristic of the device claimed as innovative or for new indications, assess to what extent specific claims are supported by specific pre-clinical and clinical data and risk analysis.
# Clinical evaluation requirements

Excluding Art 61 and Annex XIV, no. of times "clinical evaluation" appears in MDR

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<tr>
<th>No.</th>
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<tr>
<td>16 X</td>
<td>Recitals (&quot;Whereas&quot; statements), in 13 different recitals</td>
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<tr>
<td>9 X</td>
<td>Articles 1, 2, 5, 8 Scope, definitions, placing on market, harmonized standards, CS, general obligations of manufacturers</td>
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<tr>
<td>1 X</td>
<td>Article 32 Summary of safety and clinical performance</td>
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<td>40 X</td>
<td>Articles 44 &amp; 45, and Annex VII Requirements related to NBs</td>
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<td>6 X</td>
<td>Article 54 Clinical evaluation consultation procedure for certain class III and class IIb devices</td>
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<td>4 X</td>
<td>Article 62 and Annex XV Requirements related to clinical investigations</td>
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<tr>
<td>1 X</td>
<td>Article 83 Post-market surveillance system of the manufacturer</td>
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<td>1 X</td>
<td>Article 105 Tasks of the MDCG</td>
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<td>8 X</td>
<td>Article 106 Provision of scientific, technical and clinical opinions and advice</td>
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<td>2 X</td>
<td>Annex II Technical Documentation</td>
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<td>3 X</td>
<td>Annex IX Conformity Assessment Based on a Quality Management System and on Assessment of Technical Documentation – Chapter I, Quality Management System</td>
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<td>11 X</td>
<td>Annex IX Chapter II, Assessment of the Technical Documentation</td>
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<td>2 X</td>
<td>Annex X Conformity Assessment Based on Type-examination</td>
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Other clinical data-related changes

- Requirements for Notified Body personnel with clinical expertise [36(1)]
- Technical documentation requirements for clinical data [Annex II, Section 6 and Annex III]
- QMS and clinical data-related documentation [Section 2 of Annex IX]
- Clinical evaluation requirements for devices without a medical purpose (listed in Annex XVI of MDR, such as, dermal fillers) [61(9)]
- Clinical investigation required for products without a medical purpose unless existing data from an analogous device is duly justified [61(9)]
- Other changes, e.g., manner in which Notified Bodies are required to evaluate clinical evidence, clinical evaluation, and PMCF
Post-market clinical follow-up (PMCF)

Annex XIV, Part B, Post-Market Clinical Follow-Up

- Sec 5: PMCF is a continuous process that updates clinical evaluation, which must be addressed in PMS plan
  - When conducting PMCF, clinical data from a CE marked device must be proactively collected and evaluated with aim of:
    - confirming safety and performance throughout expected lifetime of device
    - ensuring continued acceptability of identified risks, and
    - detecting emerging risks on basis of factual evidence
Post-market clinical follow-up (PMCF)

Annex XIV Part B overview

- PMCF shall be performed pursuant to a documented method laid down in a PMCF plan [Sec 6].

- Must analyze findings of PMCF and document the results in a PMCF Evaluation Report that must be part of the CER and technical documentation [Sec 7].

- Conclusions of PMCF Evaluation Report must be taken into account for clinical evaluation and in risk management [Sec 8].
For implantable devices and class III devices, as part of the process to be exempted from having to conduct a clinical investigation
   – NB must check that PMCF plan of the marketed device is appropriate [61(4)]

Products without a medical purpose
   – Clinical evaluations must be based on safety data including data from PMS, PMCF and, where applicable clinical investigation [61(9)]

Clinical evaluation must be updated
   – With clinical data from implementation of PMCF plan and PMS plan, and for class III devices and implantable devices, PMCF evaluation report must be updated annually with such data [61(11)]
## Post-market clinical follow-up (PMCF)

Excluding Art 61 and Annex XIV, no. of times "Post market clinical follow up" or "PMCF" appears in MDR

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<td>Summary of safety and clinical performance</td>
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<td>1 x</td>
<td>Article 56</td>
<td>Certificates of conformity</td>
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<tr>
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<td>Article 74</td>
<td>Clinical investigations regarding devices bearing the CE marking</td>
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<td>1 x</td>
<td>Article 80</td>
<td>Recording and reporting of adverse events that occur during clinical investigations</td>
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<td>1 x</td>
<td>Article 81</td>
<td>Implementing acts</td>
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### Post-market clinical follow-up (PMCF)

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<tr>
<td>1 x</td>
<td>Article 86 Periodic safety update report</td>
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<tr>
<td>1 x</td>
<td>Article 106 Provision of scientific, technical and clinical opinions and advice</td>
</tr>
<tr>
<td>3 x</td>
<td>Annex II Technical Documentation</td>
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<tr>
<td>2 x</td>
<td>Annex III Technical Documentation on Post-Market Surveillance</td>
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<tr>
<td>9 x</td>
<td>Annex VII Requirements To Be Met by Notified Bodies</td>
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<tr>
<td>10 x</td>
<td>Annex IX QMS and Assessment of the Technical Documentation</td>
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<td>Annex XI Conformity Assessment Based on Product Conformity Verification</td>
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<td>1 x</td>
<td>Annex XIII Procedure for Custom-Made Devices</td>
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MDR clinical investigation requirements

**Articles 62 – 82 and Annex XV**

- Adapted from EU clinical study-related guidance documents
- Similar to requirements in EN ISO 14155:2011 (yes, overlap, e.g. informed consent, others)
  - Gap analysis performed (by presenter and another ISO TC 194, WG 4 member)
  - Efforts made to address differences and still maintain international relevance

**Important to address differences when adapting your procedures to MDR!**
Current Clinical Investigation Guidance
MDR clinical investigation requirements

• Many MDR clinical investigation requirements are the same or very similar to requirements in AIMDD and MDD, guidance in MEDDEV 2.7/2 revision 2, MEDDEV 2.7/3 rev 3, MEDDEV 2.7/4 and procedures specified by EN ISO 14155:2011, however there are new requirements

• The following are examples of the new requirements
MDR clinical investigation requirements

Clinical investigation-related definitions

• Currently clinical investigation definitions are from:
  – EU guidance documents and EN ISO 14155:2011 (over 40 clinical investigation-related definitions)

• Under MDR:
  – Eleven (11) related to clinical investigations, some differing slightly from those in EN ISO 14155:2011
  – Future revised ISO 14155 addresses these differences

Important to check definitions in company procedures to ensure compliance with MDR and other regulations
MDR clinical investigation requirements

Article 2(49), Introduction of “sponsor”

- ‘Sponsor’ means any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation

Under Directives, manufacturer is responsible for clinical studies; investigator-initiated studies not specified, leading to MS variations in regulation of investigator-initiated studies

Under MDR, investigators initiating clinical studies will be responsible for meeting MDR clinical study-related requirements; does not preclude agreements on study conduct between investigators and manufacturers
**MDR clinical investigation requirements**

**Legal representative must be appointed (Art 62)**

- Designated by sponsors not in the EU
- Responsible for ensuring compliance with sponsor’s obligations
- Member State option not to apply rule if study is conducted only in their territory

**New restrictions regarding appointment of monitor (Annex XV)**

- Sponsor must appoint monitor who is independent from investigational site

Note! Monitor restriction not in Directives nor in EN ISO 14155:2011
MDR clinical investigation requirements

SAE reporting to Member States (Art 80)

• SAEs, which have a causal relationship with an investigational device, comparator or investigation procedure, or where such causal relationship is reasonably possible, must be reported to Member State without delay

Prohibition of waivers (Annex XV)

• Policy regarding follow-up and management of any deviations from the CIP at the investigational site and clear prohibition of use of waivers from the CIP
MDR clinical investigation requirements

Article 78, Coordinated assessment procedure for clinical investigations

- New process for submitting clinical investigation application
- Sponsor of study to be conducted in more than one Member State (MS) can submit single application electronically to all MSs
- Sponsor must propose a coordinating MS

[continued next slide]
New Clinical Investigation Requirements

Coordinated assessment procedure for clinical investigations

• MS must agree within 6 days, which is to be coordinating MS
• If no agreement, MS proposed by sponsor must assume role
• Detailed requirements are specified on process
• Applied only by MSs agreeing to apply procedure until 27 May 2027, when it becomes mandatory....

...HOWEVER, this could change if alternative recommendations made after Commission review required by 26 May 2026!
Role of MEDDEV 2.7/1 Rev 4
MEDDEV 2.7/1 REV 4

- Revision 4 published in June 2016
- Complete re-write of Revision 3
• Applies to AIMDD and MDD and not MDR

• However, considered “gold standard” re clinical evaluation!

• Section 2, Scope, states that due to changes in European medical device legislation: “Parts or all of this document are likely to be revised.”

• Commission and CIE Working Group: MEDDEV 2.7/1 Rev 4 will not be immediately revised; instead, guidance documents helping to bridge gap between MEDDEV and MDR will be developed.
Article 61(3) of MDR requires that a clinical evaluation must follow a defined and methodologically sound procedure and be based upon certain types of clinical data.

- MEDDEV and Directives specify that a clinical evaluation must be based on clinical data from: scientific literature related to the safety and performance of an equivalent device, the results of clinical investigations made, or both these sources.

- MDR requires that clinical evaluation must be based on scientific literature related to the safety and performance of an equivalent device, the results of clinical investigations made, and a third source not included in the Directives or the MEDDEV, which is: a consideration of currently available alternative treatment options for that purpose, if any.
MDR VS MEDDEV 2.7/1 REV 4

• MEDDEV 2.7/1 Rev 4 will continue to be extremely important in complying with clinical evaluation requirements under MDR

• However, when MEDDEV is used for the purpose of complying with the MDR, differences between the MEDDEV and MDR must be addressed and the MDR requirements must take precedence
Planned EU clinical evaluation guidance for aiding in compliance with MDR
CIE Working Group

• Working Group on Clinical Investigation and Evaluation (CIE)
  – Member States, EFTA countries, Turkey and Industry and Notified Body associations; presenter is a member of European Association of Authorized Representatives (EAAR), which is a member of this group
  – Directorate General, Internal Market, Industry, Entrepreneurship and SMEs (GROW)
    • European Commission department responsible for EU policy on the single market, industry, entrepreneurship and small businesses
  – Website last updated 4 Nov 2016 (Agenda only)
  – Meetings are in Brussels
Register of Commission expert groups and other similar entities

Commission Expert Group

**Name:** Working Group on Clinical Investigation and Evaluation (E01576)

**(Active - Group which operates on a permanent basis)**

**Abbreviation:** CIE

**Policy Area:** Public Health

**Lead DG:** GROW - DG Internal Market, Industry, Entrepreneurship and SMEs

**Type:** Informal, Permanent

**Scope:** Limited

**Mission:** To support the strategic development of the clinical investigations’ sector. Act as a platform for exchange of information on clinical investigations.

**Task:**
- Assist the Commission in relation to the implementation of existing Union legislation, programmes and policies
- Assist the Commission in the preparation of legislative proposals and policy initiatives
- Coordinate with Member States, exchange of views

**Contact:** GROW-COSMETICS-AND-MEDICAL-DEVICES@ec.europa.eu

**Publication in RegExp:** 20 Jan 2006

http://ec.europa.eu/transparency/regexpert/index.cfm?do=groupDetail.groupDetailPDF&groupID=1576
Current CIE guidance

- MEDDEV 2.7/1 rev.4, Clinical evaluation: Guide for manufacturers and notified bodies (June 2016)
- Appendix 1: Clinical evaluation on coronary stents (December 2008)
- MEDDEV 2.7/2 rev. 2, Guidelines for Competent Authorities for making a validation/assessment of a clinical investigation application under directives 90/385/EEC and 93/42/EC (September 2015)
- MEDDEV 2.7/4, Guidelines on Clinical investigations: a guide for manufacturers and notified bodies (December 2010)

CIE work packages and guidance

• Clinical Evaluation Work Package #1
  1. Equivalence and the MDR (led by UK’s MHRA)
  2. Sufficient clinical evidence (actually “sufficient clinical data”) and the MDR (led by Ireland’s HPRA)
  3. Legacy products and the MDR (may be incorporated into item #2) (led by HPRA)

• Summary of Safety and Clinical Performance Work Package #2
  – New type of information for patients and healthcare practitioners regarding implantable devices and class III devices; information should be understandable, reasoned, objective and balance.

• Template Development and Interaction with MDR EUDAMED Work Package #3
CIE draft equivalence guidance

• Intended to provide additional guidance on establishing equivalence; current version is 2.0 of 9 April 2018 – still in active development

• Will attempt to bridge gap between differences in MDR and MEDDEV 2.7/1 Rev 4 regarding equivalence

• Possible topics:
  – Differences between MDR and the MEDDEV on the clinical, technical and biological characteristics that must be considered for establishing equivalence
  – Interpretation of Article 61, paragraphs 4 – 6, concerning exemptions to need to conduct a clinical investigation
  – Guidance on equivalence of medical devices with a medicinal substance acting in an ancillary manner
  – Example of an equivalence table
In meantime, how should you document equivalence?

• Pay close attention to MEDDEV 2.7/1 Rev 4 in Annex A1, Demonstration of equivalence

• Include equivalence table in CER that includes clinical, technical and biological characteristics broken down into specific elements that need to be considered, e.g., clinical condition or purpose, severity and stage of disease, etc., and list corresponding information for at least:
  • Device under evaluation
  • Device to which equivalence is to be claimed
  • Differences (namely concentrate on these)
  • Whether differences lead to clinically significant differences in safety and clinical performance of the device
  • Justification for differences not considered to invalidate equivalence
CIE draft guidance on sufficient clinical data

- Intended to help interpret sufficient clinical data in Article 61(6)(a); current version is 4.0 of 9 April 2018 – still in active development

- Intended to help manufacturers in analyzing clinical data to determine if data represent sufficient clinical data

- Possible topics:
  - General aspects to consider regarding determination of “sufficient clinical data”
  - Relationship with MEDDEV 2.7/1 Rev 4
  - Steps in determining whether available data represent sufficient clinical data
CIE draft guidance on sufficient clinical data

• Article 61, Clinical evaluation, paragraph (6)(a):

6. The requirement to perform clinical investigations pursuant to paragraph 4 shall not apply to implantable devices and class III devices:

(a) which have been lawfully placed on the market or put into service in accordance with Directive 90/385/EEC or Directive 93/42/EEC and for which the clinical evaluation:

— is based on sufficient clinical data, and

— is in compliance with the relevant product-specific CS for the clinical evaluation of that kind of device, where such a CS is available; or

(b) that are sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips or connectors for which the clinical evaluation is based on sufficient clinical data and is in compliance with the relevant product-specific CS, where such a CS is available.
Importance of an effective clinical data strategy
Clinical data strategy

- Clinical data strategy or clinical strategy is often provided to Notified Body to obtain feedback on its acceptability [think Pre-Sub for Europe, but without any guidance]

- However, this process and terms, “clinical data strategy” or “clinical strategy,” are not in the MDR

- MDR term “clinical development strategy” is in the MDR, in Article 54, Clinical evaluation consultation procedure for certain class III and class IIb devices

  - For all class III devices and class IIb devices referred to in point (b) of Article 54(1) [class IIb active devices intended to administer and/or remove a medicinal product], an expert panel may be consulted with aim of reviewing manufacturer's intended clinical development strategy and proposals for clinical investigation.
Why are companies *currently* providing clinical data strategy or clinical strategy (or clinical development strategy) documents to **Notified Bodies**?

- To ensure acceptability of approach under the Directives that the manufacturer wishes to take to provide acceptable level of clinical data, usually for higher risk devices, for example:
  
  - Use of clinical data from an equivalent device
  - Conducting a clinical investigation with a small sample size
  - Intention to conduct a PMCF study, but use of clinical data from an equivalent device for CE marking

- To ensure acceptability of a clinical study design
Clinical data strategy or clinical strategy documents addressing clinical data expectations under the MDR may be useful where:

- Devices are being up-classified and current clinical data may not be sufficient
- Current clinical data are considered weak (legacy devices)
- It is necessary to determine if a clinical evaluation is based on sufficient clinical data to allow exclusion from need to conduct a clinical investigation for an implantable or class III device placed on market under the Directives [Article 61(6)(a)]
Requested review by Notified Body

- Recommended steps for requesting review of clinical data strategy document by Notified Body

  - Advise Notified Body that you wish to do this to understand its willingness to do this, policies for the process, estimated response time, any additional costs,

  - Develop a well-structured document:

    - Title, date (revision) of document; signatures and dates for author, review and approval and perhaps author; page numbers (page x of y); table of contents (preferable linked to text)

    - Depending upon purpose, consider including: Introduction or Purpose, Intended Use, Device Description, Overview of preclinical testing (bench, in-vivo), Risks related to clinical safety and performance, plans for generating clinical data (clinical data from equivalent device in scientific literature, pre-market clinical studies), overview of PMCF plans, other information depending upon device-specific issues
General recommendations
General recommendations

- Inform executive management of importance of meeting increasingly stringent clinical data and clinical evaluation requirements or risk either not achieving or losing CE mark
  - Translated: you need sufficient time and adequate resources

- Determine / identify when company intends to comply with MDR for each device family

- Review MDR provisions on clinical evaluation and PMCF in a thorough manner to ensure clear understanding of all requirements

- Evaluate resources, including available clinical expertise, for addressing clinical data and clinical evaluation requirements
General recommendations

- Identify company procedures and documents that concern clinical data (e.g., clinical evaluation, clinical investigation, PMCF plans, PMCF documents)
- Conduct gap analysis between above procedures and documents and MDR requirements, and implement any improvements needed
- Address differences in definitions in Directives and guidance documents (e.g., MEDDEVs) during review of existing procedures and transition to MDR
- Review MDR transitional provisions in Article 120 to determine effect on existing devices and those in planning phase
- Develop clinical data policy for legacy devices
General recommendations

• Plan now for any new projects for CE marking under the Directives, especially when clinical data are needed (e.g., Notified Body cut-off dates)

• Determine whether clinical data-related procedures, activities and documentation are adequately managed within the quality management system

• For class III implantable devices and class IIb actives devices intended to administer and/or remove a medicinal product, identifying the pros and cons of consulting an expert panel review your company’s clinical development strategy and proposals for clinical investigation(s)

• Review requirements that NBs must meet regarding clinical evaluation to help in determining acceptability of clinical evaluation procedures, practices and documentation
QUESTIONS?

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