Clinical Evaluation Requirements under European Medical Device Regulation, Impact on Businesses, and Brussels Update

MassMEDIC Webinar

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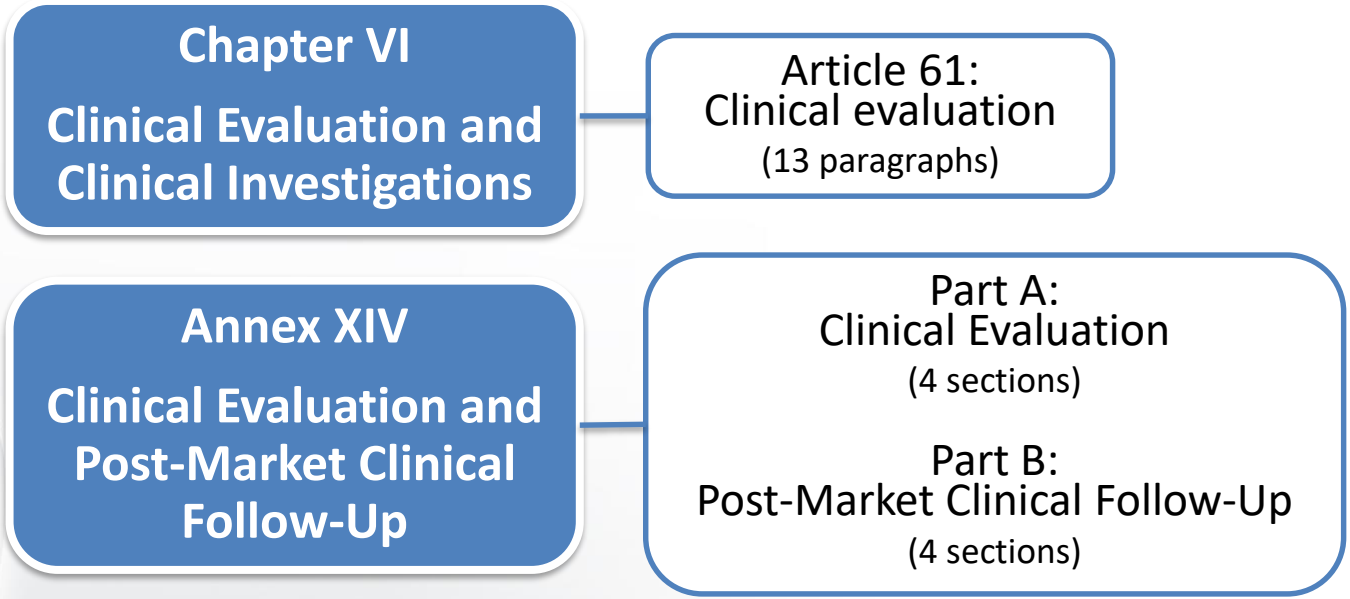
TOPICS

- New clinical evaluation requirements under Medical Device Regulation (MDR)
- EU Guidelines on Clinical Evaluation (MEDDEV 2.7/1 Rev 4) vs MDR
- Impact on small, medium, and large companies
- Recommendations
- Brussels Update

Clinical evaluation requirements under MDR

Clinical evaluation requirements



Clinical evaluation requirements

Clinical evaluation in MDR, excluding Art 61 and Annex XIV (1 of 2)		
MDR Location		No.
Recitals	("Whereas" statements) in 13 different recitals	16 X
Articles 1, 2, 5, 8,9,10	Scope, **definitions**, placing on market, harmonized standards, CS, general obligations of manufacturers	9 X
Article 32	Summary of safety and clinical performance	1 X
Articles 44, 45 and Annex VII	**Requirements related to NBs**	**40 X**
Article 54	**Clinical evaluation consultation procedure for certain class III and class IIb devices**	**6 X**
Article 62 and Annex XV	Requirements related to clinical investigations	4 X

Clinical evaluation requirements

Clinical evaluation in MDR, excluding Art 61 and Annex XIV (2 of 2)		
MDR Location		No.
Article 83	Post-market surveillance system of the manufacturer	1 X
Article 105	Tasks of the MDCG	1 X
Article 106	Provision of scientific, technical and clinical opinions and advice	8 X
Annex II	Technical Documentation	2 X
Annex IX	Conformity Assessment Based on a Quality Management System and on Assessment of Technical Documentation – Chapter I, Quality Management System	3 X
Annex IX	**Chapter II, Assessment of the Technical Documentation**	**11 X**
Annex X	Conformity Assessment Based on Type-examination	2 X

Clinical evaluation requirements

Clinical evaluation – Article 61 (1 of 5)

Basic requirements on clinical evaluation

- Conformity with **relevant** general safety and performance requirements (GSPRs) must be based on clinical data providing sufficient clinical evidence [Article 61(1)]
  ["sufficient clinical evidence" not defined]

NEW

- Must specify and justify level of clinical evidence [Article 61(1)]
- Expert panel can be consulted on clinical development strategy and proposals for clinical investigation for class III devices and class IIb active devices intended to administer and/or remove a medicinal product [Article 61(2)]

Clinical evaluation requirements

Clinical evaluation – Article 61(3) (2 of 5)

Basic requirements on clinical evaluation

- Must follow a defined and methodologically sound procedure [Article 61(3)] *[process and contents are in MDR instead of guidance document]*
- Clinical evaluation must be based on:
  - Data in the scientific literature related to an equivalent device; data must adequately demonstrate compliance with relevant General Safety and Performance Requirements (GSPRs)
  - Results of clinical investigations, and
  - NEW Consideration of currently available alternative treatment options for that purpose, if any *[state of the art in medicine]*

[Article 61(3)]

Clinical evaluation requirements

Clinical evaluation – Article 61 (3 of 5)

Basic requirements on clinical evaluation

- Three different sets of criteria for not needing to conduct a clinical investigation in Articles 61(4), 61(5), and 61(6); multiple interpretations of Article 61(5)

NEW

  - **Implantable devices and class III devices** designed by modification of device already marketed by same manufacturer; other criteria must be met [Article 61(4)]
  - **Non-CE marked device demonstrated to be equivalent** to a CE marked device from a different manufacturer; manufacturer of non-CE marked device can rely on paragraph 4 in order not to perform a clinical investigation [Article 61(5)]
  - **Implantable devices and class III devices** placed on the market under AIMDD or MDD or that are sutures, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips or connectors [Article 61(6)]

Clinical evaluation requirements

Clinical evaluation – Article 61 (4 of 5)

Basic requirements on clinical evaluation

- Requirements related to products without a medical purpose (these products are listed in Annex XVI) [Article 61(9)]
- Must update clinical evaluation with clinical data from implementation of PMCF Plan (Part B, Annex XIV) and PMS Plan (Article 84) [Article 61(11)]
  [more detailed vs Directives]
- Clinical evaluation must be documented in a clinical evaluation report [Article 61(12])

Clinical evaluation requirements

Clinical evaluation – Article 61(11) (5 of 5)

Basic requirements on clinical evaluation

NEW

- **Implantable devices and class III devices**
  - PMCF evaluation report and,
  - Summary of safety and clinical performance, if indicated,

must be updated at least annually with clinical data from implementation of PMCF plan and PMS plan

[Article 61(11)]

Clinical evaluation requirements

Clinical Evaluation – Annex XIV, Part A (1 of 3)

Specifies requirements on process and documentation of clinical evaluation

- Must establish and update:
  - **Clinical Evaluation Plan** that includes minimum contents, and
  - **Clinical Development Plan**

NEW

- Under AIMDD and MDD, these aspects are covered in MEDDEV 2.7/1 Rev. 4
- Any future revision of MEDDEV 2.7/1 Rev. 4 will need to be consistent with MDR Annex XIV

Clinical evaluation requirements

Clinical Evaluation Plan

(1 of 2)

- GSPRs that require support from relevant clinical data
- Intended purpose of device
- Intended target groups with **indications and contraindications**
- 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 requirements

Clinical Evaluation Plan (2 of 2)

List and specification of parameters to be used to determine, based on state of the art in medicine, 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 pharmaceuticals, non-viable animal or human tissues, are to be addressed, and

Clinical development plan indicating progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations, and a PMCF, with an indication of milestones and a description of potential acceptance criteria.

Clinical evaluation requirements

Clinical Evaluation – Annex XIV, Part A (2 of 3)

Specifies requirements on process and documentation of clinical evaluation

- Steps in clinical evaluation process:
  - **Identify** clinical data, and any gaps via scientific literature review
  - **Appraise** clinical data for suitability for establishing safety and performance of device
  - **Generate** any necessary clinical data
  - **Analyze** clinical data to reach conclusions about safety and performance of device including clinical benefits

Clinical evaluation requirements

Clinical Evaluation – Annex XIV, Part A (3 of 3)

Specifies requirements on process and documentation of clinical evaluation

- Threshold for equivalence:
  - Based on technical, biological and clinical characteristics
  - Characteristics must be similar so that there is no clinically significant difference in the safety and clinical performance of the device
  - Manufacturers must demonstrate that they have sufficient levels of access to data relating to equivalent devices to justify claims of equivalence

Clinical evaluation requirements

Post-Market Clinical Follow-Up – Annex XIV, Part B (1 of 1)

Specifies requirements for PMCF as process for updating clinical evaluation

- Continuous process that updates clinical evaluation
- Must be addressed in PMS Plan
- Proactive collection and evaluation of clinical data
- Must develop a **PMCF Plan** that specifies methods and procedures for collecting and evaluating clinical data; MDR specifies contents of PMCF plan

Details of requirements are new

NEW

- Must document results in a **PMCF Evaluation Report** that must be part of the CER and technical documentation
- Conclusions of PMCF Evaluation Report must be taken into account for clinical evaluation and in risk management

MEDDEV REV. 4 vs MDR

MEDDEV REV. 4 vs MDR

Developed to assist in complying with the Directives, not the MDR

- MEDDEV 2.7/1 Rev. 4 is a guidance document, which is being treated as if it were a regulation by some Competent Authorities (CAs) and NBs
  - Some NBs are issuing nonconformities based on contents of the MEDDEV; however, nonconformities should be issued against Directives
  - Principal author of MEDDEV 2.7/1 Rev. 4, who is from a CA, has stated in open meetings that the MEDDEV is a guidance document only; however, other CAs are requiring their NBs to ensure that companies follow the MEDDEV
- NBs have varied significantly regarding when MEDDEV 2.7/1 Rev. 4 should be followed
- At European level, thinking is that a complete revision will take several years, so specific guidance on issues such as, equivalence, may be developed earlier

Not exhaustive!

MEDDEV REV. 4 vs MDR

Subject	MDR	MEDDEV 2.7/1 Rev 4
GSPRs not based on clinical data	Art 61(10): must substantiate reasons in technical documentation	10.3. Evidence-based justification should be presented in a CER!
Updating clinical evaluation	Art 61(11): updating throughout device lifecycle & for class III devices and implantable devices, annual update of PMCF evaluation report & SSCP	6.2.3 When no new information, annually for devices w significant risks or every 2 to 5 years for devices not expected to have significant risks
Clinical evaluation plan	Annex XIV, Sec 1 Requires a plan and lists specific minimum contents	7. Calls for a plan; however, lists elements to consider and not specific contents; some differences with MDR
Clinical development plan	Annex XIV, Sec 1 requires this plan be included in clinical evaluation plan	No mention of clinical development plan
Equivalence	Annex XIV, Sec 3, similar to MEDDEV, but not limited to only a single device; sufficient level of access to data relating to equivalent device	A1. Equivalence can only be based on a single device. A12. Level of access to equivalent device in guidance on NB assessment of clinical evaluation in a design dossier or type examination dossier

MEDDEV REV. 4 vs MDR

MEDDEV 2.7/1 Rev 4 on Clinical Evaluation

- Some companies may wish to consider developing clinical evaluation based on MDR now or at next update (i.e., before operating under the MDR); however, advisable to agree approach with NB, where applicable

- If this approach is taken, recommend that you:
  - Develop an SOP and template based on MDR
  - Meet MDR requirements and follow MEDDEV guidance where applicable
  - Address definitions that differ between Directives, MEDDEV and MDR to ensure compliance with Directives until operating under MDR
  - When operating under MDR, make any needed revisions to ensure compliance with MDR

Impact on small, medium, and large companies

Impact on companies

Insufficient clinical data / evaluation under MDR may delay or prevent EU device launch

Start-ups, early phase
Executive management and investors may not appreciate stringent requirements for clinical data and clinical evaluation
Pressure is to meet milestones and design and manufacture device(s) with small number of staff; may pay insufficient attention to clinical data / clinical evaluation need
Often one person is responsible for multiple tasks, including clinical evaluation, and thus difficulty in dedicating sufficient time to this issue
May be difficult to have person(s) who meet clinical evaluator qualifications as described in MEDDEV 2.7/1 Rev. 4
Challenge in contracting with a NB and one which can agree on clinical data / clinical evaluation approach

Impact on companies

Insufficient clinical data / evaluation under MDR may delay CE marking or lead to withdrawal of CE mark

Small / medium companies
Executive management may not appreciate stringent requirements for clinical data and clinical evaluation
Devices may be at different points in their lifecycle (design and development, CE marking, maintenance of CE mark), with some requiring initial clinical evaluation and others clinical evaluation update
May be difficult to have person(s) who meet clinical evaluator qualifications as described in MEDDEV 2.7/1 Rev. 4
Pressure on available personnel to comply with MDR, its more detailed requirements, and where relevant, MEDDEV 2.7/1 Rev. 4
Pressure on possibly needing to defend weaker than desirable clinical data and clinical evaluation

Impact on companies

Inability to properly organize activities and / or assign sufficient resources may lead to delay in CE marking or withdrawal of CE mark for some devices

Large multinational companies
Executive management may not appreciate threats to maintaining CE mark related to insufficient clinical data
Pressure to address clinical evaluation for hundreds or thousands of devices, including legacy devices, and possibly different risk categories or different therapeutic areas
Need to organize staff across various departments and/or subsidiaries
Even with clinical evaluation teams, may face difficulty in meeting deadlines for achieving CE mark within desirable timelines or maintaining CE mark for all devices
May have multiple NBs with varying clinical evaluation expectations

Recommendations

Recommendations

Executive management

- Need to be made aware of importance of meeting increasingly stringent clinical evaluation requirements or risk either not achieving or losing CE mark

Multi-departmental resources (clinical, regulatory, quality management system, risk management)

- Need to be assessed, including available clinical expertise, for addressing new MDR clinical evaluation requirements
- Qualified personnel need to be identified for managing and implementing clinical evaluation process

Implementation plan

- Develop a formal plan for complying with MDR with device priorities, including clinical evaluation as a specific component

Recommendations

MDR transitional provisions in Article 120

- Review them now to determine effect on existing and planned devices; where possible, consider compliance with MDR where requirements do not conflict with AIMDD or MDD; develop a clear understanding of the extension of transition period for devices, based on NB certificate expiry dates, applicable to your devices

Legacy devices

- Develop policy and agree approach with NB, especially for devices being up-classified

MEDDEV 2.7/1 Rev. 4

- Develop policy and timetable on using this guidance in agreement with NB; consider complying only with parts of MEDDEV that are consistent with MDR, if agreeable with NB

Definitions

- For compliance with MDR, address differences in definitions in Directives and guidance documents (e.g., MEDDEVs) during review of existing procedures and documents

Recommendations

Develop SOP for the clinical evaluation process

Use either MDR or MEDDEV 2.7/1 Rev. 4 to identify the information needed to develop the clinical evaluation plan and clinical evaluation report before starting the process

Ensure that Risk Management Reports facilitate identification of clinical risks

- Avoid pointing to clinical evaluation or clinical investigation as risk control measures. Why? "Risk control" is defined as: "a process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels." [EN ISO 14971:2012]
- Instead, clinical evaluation and clinical investigation are generally used to verify whether or not risk control measures have been effective or if additional measures should be taken.

Recommendations

Pay attention to concept of **"state of the art"**, which is important in MDR and MEDDEV 2.7/1 Rev. 4

- Phrase, "taking account of the generally acknowledged state of the art", is throughout MDR
- MDR requires that the Clinical Evaluation Plan include a list and specification of parameters to be used to determine acceptability of benefit-risk ratio for various indications and intended purpose of the device, based on the state of the art in medicine [Annex XIV, Part A, 1(a)]
- MEDDEV 2.7/1 Rev. 4 emphasizes that review of current knowledge/state of the art is needed to conduct the appraisal and analysis of clinical data of the device

Brussels Update

Brussels Update

- Competent Authorities for Medical Devices (CAMD) (www.camd-europe.eu/)
  - National competent authorities; established to enhance collaborative working, communication and surveillance of medical devices
  - Led by **CAMD Executive Group** (CEG)(www.camd-europe.eu/aims/camd-executive-group)
  - Produced a roadmap: "*Medical Devices Regulation/In-vitro Diagnostics Regulation (MDR/IVDR) Roadmap*" – can download from homepage
  - What is #1 priority for implementation of MDR & IVDR? Clinical Evaluation & Clinical Investigation (MD); Performance Evaluation & Performance Studies (IVD)

Brussels Update

- New information on Brexit policy, “Notice to stakeholders – Withdrawal of the UK and EU rules in the field of industrial products” (https://ec.europa.eu/docsroom/documents/27241?locale=en)
- Commission requested stakeholders to provide notes on text inaccuracies by 30 Nov 2017. Revised MDR / IVDR versions expected to be available in Q1 2018.
- Notified Body designation formally started on 26 Nov 2017. Team NB (www.team-nb.org/) (24 NBs) state that majority of their members have already applied.
- All NBs must be re-designated. Re-designation process expected to take 9 to 18 months. Thus, for devices requiring NB involvement, the transition period is effectively halved for MDR.

Brussels Update

- Eudamed: still doubts about whether it will be functioning by 26 May 2020; however, MDR provides derogation measures in Article 123, Entry into force and date of application – in paragraph (d)

- European stakeholder working groups, e.g., Borderline Products, Clinical Investigation and Evaluation (CIE), Notified Bodies, Eudamed, Vigilance, etc. (https://ec.europa.eu/growth/sectors/medical-devices/dialogues-parties_en) will be reorganized

- Existing guidance documents are being examined for revision to be consistent with MDR / IVDR

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THANK YOU!