GMED LNE GROUP Newsletter

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Version Française

CLINICAL EVALUATION IN THE ERA OF THE REGULATION (EU) 2017/745

In few months, the European Directives 93/42/EEC concerning medical devices and 90/385/EEC concerning active implantable medical devices will be repealed by Regulation (EU) 2017/745, of which the date of application have been postponed to 26 May 2021.
The goal of the Regulation is clear, to establish a robust, transparent, predictable and sustainable regulatory framework for medical devices, which ensures a high level of safety and health protection whilst supporting innovation.
In particular, in order to ensure a high level of safety and health protection, regulatory requirements relating to clinical investigations, clinical evaluation, vigilance, market surveillance, transparency and traceability of medical devices have been considerably strengthened.

A WHAT'S NEW?

Even if the main lines of clinical evaluation remain the same and the Regulation (UE) 2017/745 remains in the continuity of the Directives 93/42/EEC and 90/385/EEC and keeps the same approach, however the Regulation provides stronger clinical evaluation requirements, more precise details and is much stricter on certain points in particular the demonstration of equivalence. Also, it brings many novelties particularly concerning the post-market clinical follow-up and the traceability of the devices notably by means of a Unique Device Identification system (UDI system) and EUDAMED database.
It is clear that a new vision of clinical evaluation is being put forward.

Indeed, an entire annex is dedicated to clinical evaluation (Annex XIV, Part A) and post-market clinical follow-up (Annex XIV, Part B), and a second annex is dedicated to clinical investigations (Annex XV).
As stated in Article 10 of the Regulation, manufacturers carry out a clinical evaluation based on clinical data providing sufficient clinical evidence, in accordance with the requirements set out in Article 61 and Annex XIV of the Regulation (EU) 2017/745.
The Regulation concerning medical devices introduces the concept of "sufficient clinical evidence" and addresses the clinical investigation, that already existed in the Directives, in another way.
These changes reflect the need to place the clinical investigation at the heart of clinical evaluation, as well as the need to strengthen the demonstration of the clinical performance and safety of medical devices on the European market.

These new provisions will lead to a significant increase in the number of clinical studies.

But how define this notion of "sufficient clinical evidence" which is not defined in the MDR?

The MDCG guidance 2020-6 about sufficient clinical data gives indications about clinical data providing sufficient clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements, as per Article 61(1) of the Regulation (EU) 2017/745, for legacy devices and link with the MEDDEV 2.7/1 rev.4 sections which are still relevant under the Regulation (EU) 2017/745 that can be helpful for the gap analysis.
We can retain that the estimate of the character "Sufficient" is based on the relevance of the data in quantitative and especially qualitative terms based on methodologically robust scientific criteria and clinically relevant.
In summary, the Regulation (EU) 2017/745 is more developed which makes it self-supporting, with a clear tendency to harden to ensure greater transparency and security.

As with the Directives, a clinical assessment follows a defined, methodologically sound procedure and there are still several ways to obtain these clinical data (Article 61 of the Regulation (EU) 2017/745):

- analyze the data from the literature on the device itself or a device with which equivalence has been demonstrated, we will return more specifically on this point;
- compile data specific to the device itself resulting from clinical investigations or post-marketing monitoring data;
- added to this is the need to consider the currently available treatment alternatives, if they exist.

For implantable or class III medical devices, clinical investigations are necessary unless the manufacturer of the device under study justifies, under certain conditions that we will detail later, an equivalence with a competing product already marketed.
If the clinical investigation remains mandatory for all class III and implantable devices, some exceptions have been described in sections 4 and 6 of Article 61 of the Regulation (EU) 2017/745 (already certified medical device according to the directives, modification of an EC device, some implantable medical devices as staples or orthodontic appliances, dental crowns, screws, wedges, and as described above if equivalence with another device can be demonstrated in accordance with the new regulations).
The publication of Regulation (EU) 2017/745 introduces the creation of expert panels, competent in the field of medical devices. These groups may have several missions in the life cycle of a medical device (Article 106 of the Regulation (EU) 2017/745). The European Commission Implementing Decision 2019/1396 of 10 September 2019 laying down detailed rules for the application of the Regulation (EU) 2017/745 expert panels in the medical devices field laying down modalities of application of the Regulation (EU) 2017/745 expert panels in the field of the medical devices. This list of expert panels is available on the European Commission website.

For all class III devices and class IIb active devices intended to administer and/or remove a medicinal product from the body, the manufacturer may, prior to its clinical evaluation and/or investigation, consult an expert panel with the aim of reviewing the manufacturer's intended clinical development strategy and proposals for clinical investigation (Article 61(2) of the Regulation (EU) 2017/745).

One of the other notable novelties provided by the Regulation is the Scrutiny: Clinical evaluation consultation procedure (Article 54 of the Regulation (EU) 2017/745).

This procedure applies to:

- class III implantable devices and;
- class IIb active devices intended to administer and/or remove a medicinal product.

The notified body shall notify its competent authorities and the Commission through the electronic system (Article 57 of the Regulation (EU) 2017/745) whether or not the procedure is to be applied.
That notification shall be accompanied by the clinical evaluation assessment report.
This procedure is not required in case of:

- renewal of a certificate issued under this Regulation;
- device designed by modifying a device already marketed by the same manufacturer for the same intended purpose, provided that the manufacturer has demonstrated to the satisfaction of the notified body that the modifications do not adversely affect the benefit-risk ratio of the device or;
- the clinical evaluation has been addressed by a common specifications and compliance of clinical evaluation has been confirmed by the Notified Body.

However, an important clarification guidance (MDCG 2019-3 rev.1: Interpretation of article 54(2)b of the Regulation (EU) 2017/745) was issued in April 2020 about the point (b) (Device designed by modifying a device already marketed by the same manufacturer) as there was no indication of whether a “device already marketed” refers to devices already marketed under the Directives or the Regulations.
This point, then, concerns devices already certified under the directives, but even if, the nuance is important, it has to be noted that, in respect to devices that have been marketed already under the relevant Directives, the word “modification” shall be meant as limited only to those modifications needed in order to comply with the new legal requirements introduced by the Regulation (EU) 2017/745.
Also, the MDCG indicates in this guidance that clarifications in respect to the applicability of Art. 54(2)b of the Regulation (EU) 2017/745 with regard to devices already marketed under the Regulation (EU) 2017/745 are to be provided in a separate guidance.

B NOVALTIES ON EQUIVALANCE

A significant change has been implemented regarding the use of equivalence with a competing product that requires stricter supervision.
Indeed, in addition to the need to demonstrate equivalence on the three clinical, biological and technical aspects, the criteria of which have been reinforced by the new regulation (Annex XIV of the Regulation (EU) 2017/745), the manufacturer wishing to use the clinical data of an equivalent device of a competitor must satisfy the following conditions:

- the two manufacturers have concluded a contract which explicitly grants the manufacturer of the second device full and permanent access to the technical documentation and;
- the original clinical evaluation was performed in accordance with the requirements of the Regulation (EU) 2017/745 and;
- the manufacturer of the second device provides clear evidence to the notified body.

The Medical Device Coordination Group issued the MDCG 2020-5: Guidance on Clinical Evaluation - Equivalence, on April 2020, available to the manufacturers and notified bodies.
This guide is very interesting since, Article 61 section 5 of the Regulation (EU) 2017/745, could be interpreted to always require a contract when a manufacturer wishes to use clinical data from an equivalent device from another manufacturer. However, the exemption allowed under this Article 61 section 5 of the Regulation (EU) 2017/745 refers to criteria in Article 61 section 4 of the Regulation (EU) 2017/745, which only concerns implantable devices and class III devices. This exception was retained, this guidance specify that the contract will be required only for classes III and implantable devices.
Nevertheless, the manufacturer still has to have a sufficient level of access to data relating to the claimed equivalent device even for the class of devices which do not require a contract.
It is obvious that the demonstration of equivalence may be difficult or impossible in the case of limited access to the technical documentation of the equivalent device.

C TRACEABILITY AND TRANSPARENCY

Among the other noticeable changes, a new post-market surveillance system will be implemented to identify each medical device according to its own code called UDI (Unique Device Identification Article 27 of the Regulation (EU) 2017/745). All these data will be listed in the European Medical Device Database called EUDAMED (Article 33 of the Regulation (EU) 2017/745). This UDI code, specific to each medical device, will allow very precise traceability.
The UDI system should apply to all devices, except custom-made and performance study/investigational devices.
The obligation for UDI assignment applies as from the date of general application of the new Medical Devices Regulation (26 May 2021).
The obligation for submission of UDI in the EUDAMED database applies mandatorily as from 18 months of its application provided that registration of devices in EUDAMED is fully functional before the date of application (Article 123 of the Regulation (EU) 2017/745), otherwise 24 months after the availability of EUDAMED functionality (Article 34 of the Regulation (EU) 2017/745). In the case of implantable devices and Class III devices, the manufacturer shall also produce a summary of safety and clinical performance (Article 32 of the Regulation (EU) 2017/745). This summary shall be made available to the public via EUDAMED.
The draft of this summary shall be submitted to the notified body and shall be validated by that body. After validation the notified body shall upload this summary report to EUDAMED.
The European Commission made available the MDCG 2019-9: Summary of safety and clinical performance guide for manufacturers and notified bodies on September 26, 2019.
The new regulation also introduces the obligation to provide to patient with an implantable device an implant card (Article 18 of the Regulation (EU) 2017/745). The MDCG 2019-8: Guidance document implant card on the application of Article 18 Regulation (EU) 2017/745 on medical devices provides information, among others on mentions to be made on this card.

D PMS AND PMCF

This codification of the post-marketing surveillance rules introduced in the new Regulation therefore requires the need for each device to have a Post-Market Surveillance System (PMS) according to the risk class and the type of device (Chapter VII Section 1 and Annex III of the Regulation (EU) 2017/745).
The Post-Market Clinical Follow-up (PMCF) is part of this Post-Market Surveillance System (PMS) and the clinical evaluation must be updated throughout the life cycle of the device concerned using the clinical data obtained by the manufacturer as a result of implementation of its PMCF plan.
A certain number of documents are thus expected with novelties here again including the PSUR (Article 86 of the Regulation (EU) 2017/745):

- **Post-Market Surveillance plan (PMS)**: methods and procedures for carrying out surveillance;
- **Post-Market Surveillance report**: summary of the results and conclusions of the analysis of the data obtained, explanation of the reasons for corrective and dpreventive actions;
- **PMCF plan**: methods and procedures to update post market clinical assessment, identify side effects, contraindications, update benefit / risk assessment ...
- **PMCF Evaluation Report**: analysis of the relevance of the PMCF results;

- **PSUR**: Periodic Safety Update Report:
  - requires for medical devices class IIa, IIb and III;
  - contains the conclusions used for the benefit / risk assessment, the synthesis of the results and conclusions of the monitoring data analysis (PMCF), the volume of sales of the device and an estimate of the size and other characteristics of the population using the device and, if possible, the frequency of use of the device;
  - requires a regular update:
    - IIa: as needed, at least every 2 years;
    - IIb: at least once a year;
    - III: at least once a year.
  - for class III devices or implantable devices, manufacturers shall communicate PSURs to its notified body via the electronic vigilance and post-marketing surveillance system referred to in Article 92 of the Regulation (EU) 2017/745. The notified body shall examine the reports and record its assessment, together with any measure taken, in the same electronic system at the disposal of the authorities.

Two guidance's MDCG 2020-7: Guidance on PMCF Plan Template and MDCG 2020-8: Post-Market Clinical Follow-up (PMCF) Evaluation Report Template deal with this new requirement.

Also, with this objective of the new regulation to ensure more transparency and exchange of information, the notification of reporting of serious incidents and field safety corrective actions have also new documentary requirements always via the electronic system relating to the vigilance and the post-marketing surveillance:

- serious incident report: circumstances, consequences, ...
- security corrective measures: information sent to users, reasons, risks, actions, ...
- summary report: instead of incident reports when the context is known / mastered. With the agreement of the competent authority;
- evolution report: non-serious incident, but increase of frequency and / or gravity;
- corrective action report: implementation, evidence of effectiveness.

Conclusion

If we were to retain some of the most important changes about the clinical evaluation it would be:

- The reinforcement of the criteria and conditions of demonstration of the equivalence with this big novelty of the regulation which requires the total access to the data of the concurrent equivalent device;
- Implementation of a Unique Device Identification system (UDI) to ensure better traceability;
- The requirement to submit an SSCP (Summary of Safety and Clinical Performance) for implantable and class III medical devices accessible to the public via EUDAMED;
- The obligation to regularly transmit the PSUR (Periodic Safety Activity Report) to its Notified Body;
- The procedure regarding clinical evaluation consultation for class III implants and class IIb active devices intended to administer and/or remove a medicinal product (Article 54);
- The possibility for the manufacturers of consulting a European designed experts' panel for all class III devices and class IIb active devices intended to administer and/or remove a medicinal product for reviewing the manufacturer's intended clinical development strategy and proposals for clinical investigation (Article 61(2)).

Finally, It should be borne in mind that guidances don't constitute a legal obligation and the requirements of the regulations are mandatory and take precedence.

Furthermore, although the guide MEDDEV 2.7 / 1 rev.4, was inspired in part by the new regulation and still represents the state of the art, it's important to highlight that its requirements do not go as far as the requirements of the regulation, a gap analysis is essential.

Sources:

- *MDCG 2020-5: Guidance on Clinical Evaluation - Equivalence, April 2020*
- *MDCG 2020-6: Guidance on Sufficient Clinical Evidence for Legacy Devices, April 2020*
- *MDCG 2019-3 rev.1: Interpretation of article 54(2)b April 2020*
- *MDCG 2020-13: Clinical evaluation assessment report template, July 2020*
- *MDCG 2020-7: Guidance on PMCF Plan Template, April 2020*
- *MDCG 2020-8: Post-Market Clinical Follow-up (PMCF) Evaluation Report Template, April 2020*
- *Regulation (EU) 2017/745 Of the European Parliament and of the Council of 5 April 2017 on medical devices*
- *MDCG 2019-4: Timelines for registration of device data elements in EUDAMED April 2019*
- *MDCG 2019-8: Guidance document implant card on the application of Article 18 Regulation (EU) 2017/745 on medical devices*
- *MDCG 2019-9: Summary of safety and clinical performance - A guide for manufacturers and notified bodies*
- *IMDRF/UDI WG/N48 FINAL: 2019 Unique Device Identification system (UDI system) Application Guide*
- *MDCG 2018-3 rev.1: Guidance on UDI for systems and procedure packs, June 2020*
- *European Commission: Factsheet for Manufacturers of Medical Devices 12/08/2019*
- *European Commission Implementing Decision 2019/1396 of 10 September 2019 laying down detailed rules for the application of Regulation 2017/ 745_ groups of experts in the field of medical devices*
- *Guide MEDDEV 2.7/1 rev.4: Guidelines on medical devices: Clinical Evaluation - A guide for manufacturers and notified bodies under Directives 93/42/EEC and 90/385/EEC*

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To go further

TRAINING FOR NORTH AMERICA REGION

The Clinical Evaluation Requirements (CER) under the EU MDR 2017/745
1-day training session | May 26 | November 3

- Identify the key changes for Clinical data under the Regulation (EU) 2017/745 (MDR)
- Determine what is considered "sufficient" clinical data for clinical evaluations
- Understand the Clinical Investigation Requirements
- Identify he Post-Market Surveillance Requirements (PMS), the Post-Market Clinical Follow-Up (PMCF), and the Periodic Safety Update Report (PSUR)

→ CHECK OUT THE PROGRAM

TRAINING FOR EUROPE AND OTHER PART OF THE WORLD (EXCL. US)

Understand the regulatory requirements of the clinical evaluation and post-market clinical follow-up under Regulation (EU) 2017/745
SA65 | 1-day training session | On demand

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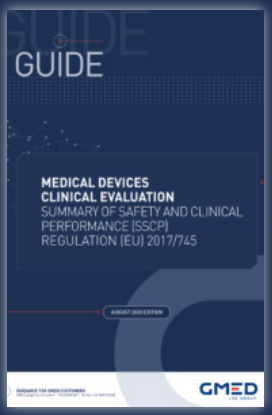
GUIDE

Medical Devices Clinical Evaluation – Summary of Safety and Clinical Performance (SSCP) – Regulation (EU) 2017/745



It is the manufacturer's responsibility to specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements under Regulation (EU) 2017/745.

This guide recalls the principles of clinical evaluation and describes the different elements to be included in:

- The clinical evaluation plan
- The clinical evaluation report
- The post-market surveillance plan including the post-market clinical follow-up (PMCF) plan
- The PMCF evaluation report

All these documents are part of the technical documentation, within the framework of CE marking procedures for medical devices, regardless of the medical device class

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