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Future Challenges for Clinical Evaluation of Medical Devices

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Also in the new European Medical Device Regulation (MDR) the clinical evaluation is a key component of the concept for safe and secure medical devices. However, so far several of the manufacturer's obligations such as clinical evaluation were set out only in the annexes of the EU directives 90/385/EEC and 93/42/EEC, which have been transposed into national law within each member state. In order to significantly reinforce the existing regulatory approach the EU legislator incorporated the clinical evaluation and further obligations into the "enacting provisions of this regulation to facilitate its application" (Recital 29 MDR). Indeed, the clinical evaluation of medical devices became part of the general obligations of manufacturers (Art. 10) and Art. 61 as well as Annex XIV part A determine the central requirements for clinical evaluations in the MDR.

Clinical evaluation is based on the establishment of processes by the manufacturer covering the entire product life cycle (inclusive regular updates) and requires careful alignment with the risk management process (Recital 33 MDR). With the beginning of first exploratory studies / product ideas the life cycle usually starts (Annex XIV section 1a), whereas the end of the life cycle is product-specific and thus very individual. As an approximate rule the end of the life cycle can be equated with the end of the documentation storage as specified in the MDR annexes.

With the clinical evaluation "the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer" are verified (Art. 2 (44) MDR). Therefore, the specification of the intended purpose for the medical device serves as the starting point.
In the following paragraphs, future challenges for clinical evaluation arising from new and partially less concrete requirements are discussed.

Challenge 1: Higher Risk Classes

An important preparative step of the clinical evaluation is the risk classification (low > high risk: I, IIa, IIb, and III), since for higher risk classes special requirements are existing, e. g.

- The manufacturer may consult an expert panel (Art. 106 MDR) for class III and class IIb active devices intended to administer and/or remove a medicinal product regarding the clinical evaluation (Art. 61 (2) MDR). The expert panels are in general expected to give advice in product development and assist the EU Commission in the preparation of guidelines and common specifications.
- With exemptions clinical investigations are mandatory for class III devices and implantable devices (Art. 61 (4) MDR).

It should be noted that for certain products as stand-alone software (rule 11 of Annex VIII) usually higher risk classes will apply. For example, software that generates information relevant to therapy or diagnosis-related decisions generally falls into Class IIa. However, depending on the potential consequences of the therapy decision, Class IIb or III may also be relevant. Since for medical devices higher than class I the involvement of a Notified Body is mandatory, the clinical evaluation and conformity assessment of many more products will be externally evaluated and performed in the future (see also challenge 6).

Challenge 2: Sufficient Clinical Data

Clinical investigations need not to be performed for implantable and class III devices, if the clinical evaluation of a marketed device in accordance with Directives 90/385/EEC or 93/42/EEC is based on sufficient clinical data (Art. 61 (6) MDR). Currently, there is no general definition existing for „sufficient clinical data"

"Clinical evaluation is affected by some the most significant regulatory changes of the MDR."

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because this is very much dependent on the product. In the future there will probably be EU-wide product-specific assessment criteria in form of guidelines or common specifications.

Challenge 3: Equivalence to Marketed Devices

Clinical evaluation may be based on literature of equivalent products (Art. 61 (3) MDR). The equivalence has to be demonstrated according to the three characteristics described in section 3 of Annex XIV. All three characteristics need to be fulfilled and there may not be clinically significant difference in the performance and safety of the devices. How this practically shall be done for certain product groups as software is currently unclear. The manufacturer may rely on the clinical evaluation of equivalent products from other manufacturers. However, depending on the risk class of a device or its purpose to be implanted the requirements regarding the contracts differ. For non-implantable devices of risk classes I - IIb it shall "be clearly demonstrated that manufacturers have sufficient levels of access to the data of the device they are claiming equivalence with" (Annex XIV section 3). In opposite, for implantable devices or devices of risk class III the two manufacturers need a contract in place that "explicitly allows the manufacturer of the second device full access to the technical documentation on ongoing basis" (Art. 61 (5) MDR). How to deal with the difference between „sufficient levels of access" and „full access to the technical documentation" in practice is not clear yet. The clinical evaluation of the equivalent product must have been performed in compliance with MDR requirements. Aspects that are not covered by the clinical evaluation may be addressed in a clinical investigation limited to those aspects or the clinical investigation may be designed to demonstrate the comparability of the clinical safety and performance of the own product with the equivalent product.

Challenge 4: (Alternative) Sources

What if literature data are not sufficient for clinical evaluation? Observations from post-market surveillance (such as vigilance data) as well as results from PMCF studies may be used as additional sources. This is the reason, why some manufacturers started already to collect post market surveillance (PMS) data for their devices from other markets such as the USA, including data from Investigator Initiated Studies (IIS). Whether these data are sufficient to demonstrate the performance, clinical safety and clinical benefit of each product depends on their quality and informative value. This is independent from the time in the market. In the event of insufficient clinical data, clinical investigations (e.g. PMCF studies) must be carried out in order to close the gaps.

Challenge 5: Clinical Evaluation Reporting

The overall reporting of the clinical evaluation is getting more complex and will require the following documents with the application of the MDR:

- Clinical Evaluation Plan (CEP, Annex XIV, Part A, section 1)
- Clinical Evaluation Report (CER, Art 61 (12) MDR)
- Post-market surveillance plan (PMS plan, Art. 84, Annex III) covering proactive and passive activities to collect and analyse market-related experience including disclosure of methods and protocols to manage those post-market activities
- Post-market clinical follow-up plan (PMCF plan, Annex XIV, Part B) or a justification as to why a PMCF is not applicable (outlined in the PMS plan)
- PMS report for class I products which summarises the results and conclusions of the post-market surveillance data.
- Periodic Safety Update Report for class IIa, IIb and class III devices (PSUR, Art. 86 MDR)
- Clinical Evaluation Assessment Report (CEAR, Annex VII section 4.6; to be compiled by the notified body)

The CER contains the conclusions of the clinical evaluation and was already mandatory before, but the content and acceptability is changing. In addition,

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the manufacturer has to provide for certain high-risk devices a publicly available "Summary of safety and clinical performance" (Art. 32 MDR). The Notified Body in turn documents the results of the clinical evaluation assessment in the CEAR, which is shared with the expert panel, the competent authorities, the authority responsible for notified bodies and the EU Commission in the case of certain high-risk devices. Post-market surveillance data, to the collection of which the manufacturer commits himself in the PMS plan, are summarised in the PSUR and contain among others also the main findings of the post market clinical follow-up (PMCF).
Notably, provisions regarding the frequency of clinical evaluation updates are missing in the MDR whereas the MEDDEV document 2.7/1 rev. 4 contains such information.

Challenge 6: Evaluation by Notified Bodies

Obligations of notified bodies are significantly reinforced in the MDR. That also applies to the requirement to examine the clinical evaluation of the manufacturer more accurately. Beside that the notified bodies are themselves subject to assessment by the respective competent authority in relation to the examination of the clinical evaluation report. For certain high-risk products, they are obliged to consult the expert panels set up by the European Commission in terms of clinical evaluation (Clinical evaluation consultation procedure acc. to Art. 54 MDR). Since notified bodies already have to invest strong efforts in the re-accreditation the before mentioned aspects will additionally shorten their capacities.

Challenge 7: Previous Guidance Documents

Although not legally binding, guidance documents released from the legislator were considered already previously by manufacturers and notified bodies for the interpretation of the law text. The European Commission published in the past a series of Medical Devices Guidelines (MEDDEV). Although the in 2016 published MEDDEV 2.7/1 rev. 4 on clinical evaluation refers in principal to the requirements laid down in the Directives 93/42/EEC and 90/385/EEC, it has partially been taken up in the MDR. Manufacturers should therefore consider the MEDDEV 2.7/1 rev. 4 as further guidance for the implementation and documentation of the clinical evaluation and investigation after the date of application of the MDR.
Moreover, the Medical Device Regulators Forum (IMDRF) has published in 2017 a more specific document concerning the clinical evaluation of software as a medical device that requires essentially three components: proof of a valid clinical association, analytical validation and clinical validation. Worthy of note, however, is that the IMDRF guideline does not, other than the MEDDEV documents, refer to any binding law text (e.g. Directive 93/42/EEC) and represents more of a consensus between different worldwide regulatory stakeholders.
In summary, manufacturers should review their existing processes for clinical evaluation early enough, reconsider their staff capacities and monitor the future guidance documents or even technical specifications by the European Commission.

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