RAPS WEBINAR TRANSCRIPT:

Clinical Evaluations for Unique Product Types Under the EU MDR with Dr. Pratibha Mishra's

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Clinical Evaluation and the Product Life Cycle

Clinical evaluations are addressed in Article 61-part A, and it has several mentions throughout the regulation. It is well understood to be an important process in the device life cycle. It is very closely related to other pre and post market activities that take place during the life cycle of a medical device. Findings from a CER, for example, will feed into the ISO 14971 risk management process. Clinical evaluation will also inform the decision of whether post-market clinical follow up (PMCF) activities are required for your device, what type of activities can be planned, or if one is planned already, it will serve as an input for the CER.

The MDCG 2027 guidance provides templates for the PMCF plan and report, and it states quite clearly that the impact of the PMCF on the CER needs to be considered. The Post Market Surveillance Plan also will have to consider the findings of the CER, and the CER will in turn evaluate the findings from the PMS report in terms of device safety.

Furthermore, the MDR also requires creation and maintenance of additional documentation like the Summary of Safety & Clinical Performance (SSCP) and the Periodic Safety & Update Report (PSUR), which along with the vigilance reports, have to be uploaded to the EUDAMED database. The SSCP and PSUR - these new documents are also interlinked with the CER in terms of information that is captured in these documents.

Clinical Evaluation - Stakeholders

Clinical evaluation requires inputs from several cross-functional experts: the marketing team for example, will provide information on similar devices, the clinical research team for planned, ongoing, or completed clinical investigations, regulatory experts for the guidelines and standards that are applicable for the device under evaluation, and the risk teams for potential and residual risks associated with the device. All these stakeholders need to be involved in the planning, creation, and maintenance of a CER.

Clinical Evaluation – Process and Procedure

Clinical Evaluation Planning (CEP) Stage 0: Before clinical evaluation is undertaken, a plan is created, which is stage 0 of the process. The plan is intended to outline the scope and the pathway for the clinical evaluation to be followed, and it serves as a basis for subsequent steps. The MEDDEV Rev 4.0 guideline provides the checklist with considerations for a CEP, which is a very useful document to refer to in the planning stage.

Clinical Evaluation Process Stage 1 – 3: The next three stages - stage 1, 2, and 3, involve identifying the relevant sources of data, appraising the quality and suitability of the data with respect to safety and performance of the device under evaluation, and the analysis of evidence gathered from these data sources.

Clinical Evaluation Report (CER) Stage 4: Stage 4 will involve the creation of the final report by deriving conclusions from the data that has been analyzed so far, and demonstrating compliance to the General Safety and Performance Requirements (GSPR) from Annex. 1 of the MDR related to device safety, performance, and the benefit risk profile when used as intended.

This is not the end of the process though, after submission of the CER to the notified body, there may be observations from the reviewers, which need to be addressed. The CER also is a live document that needs periodic updates. The frequency of these updates will be dictated by the risk category of the device and the post-market experience. For example, identification of a new risk from the PMS data may instigate an update of a CER.

Clinical Evaluation – Data Sources

The content that goes into a CER is heterogeneous, the sources of input data may be internal - that is data the manufacturer generates during the life cycle of the product, or data from external sources. The internal data may include verification and validation testing, other performance and safety-related preclinical studies that have been conducted by the compatibility evaluation, and external sources of data can be from a clinical trial registry. Additionally, this includes published literature that can be found from literature databases, or adverse event databases that are maintained by regulatory authorities of different countries. Depending upon the region where the device is marketed, these databases can serve as a source of information on safety alerts, recalls, or other information that is reported for the device or similar devices.

Clinical Evaluation Report – Essential Aspects

Essential aspects to be included in every CER for compliance with MDR requirements:

State-of-the-Art (SoTA): The CER is required to include a review of current technical capabilities, or accepted clinical factors, with respect to the device, the procedure, or patient management. In our experience here at Celegence, we have found that quantitative, or at least a comprehensive qualitative assessment of the benefits and risks of the device in comparison to other alternatives, is focused on during the notified body reviews of a CER.

Clinical Data: For clinical data, the extent of clinical data that needs to be presented depends on the novelty and the complexity of a device. Once again, MEDDEV Rev 4.0 is a helpful guide to know what kind of data can serve as evidence, and how to appraise this data. The approach that we follow is to critically analyze the evidence in terms of how it links to the state-of-the-art (SoTA) and to meet specific predetermined safety and performance objectives. We have seen that the clinical evidence the notified body expects in a CER, is expected to support each indication of a device, or each indication of all the devices, if there is more than one device under evaluation.

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Non-Clinical/Pre-Clinical Data: Non-Clinical/Pre-Clinical Data - like the usability and human factor evaluation studies are also important sources of information to substantiate performance, and can also be leveraged. Once again, validation to standards or other performance bench testing needs to be linked to the actual clinical performance or the State of the Art (SoTA) requirements from the particular device, or device family, when the data is being analyzed. This is something that notified body observations tend to highlight, which is the gap between information presented and its meaning, in terms of demonstrating safety and performance.

Post Market Surveillance: We know that reliance on the active post market data is no longer sufficient. Post market data needs to be proactively collected and that is very important under MDR. PMCF activities are indicated when more clinical evidence is required and as mentioned before, data collected from the PMCF will feed into the CER and the conformity assessment that is done as part of the CER.

Equivalence: This is a very important topic - the MDCG 2025 guidance should serve as a basis for clinical evaluation if the equivalence pathway is to be followed. Dr. Fink will talk about equivalence under MDR in his presentation later on. So I would just like to say that based on our experience with notified body observations, it is very important to select the right device as the equivalent device if this pathway is chosen. All of this data ultimately is required for the analysis and substantiation of the benefit risk ratio in the favor of the device.

Benefit-Risk Analysis: All the data that we have collated needs to be analyzed to highlight the type, magnitude, and duration of benefits that are offered to the patient or the user. What is the medical necessity that the device serves, and whether the benefit risk ratio is substantiated by evidence that is precise and falsifiable.

Classification of Medical Device Software

It is now critical to evaluate the benefit risk profile of the software in its own right. The classification of the software as a device or accessory, is independent of its location, or how it is interconnected with the hardware. It depends on the risk associated with its involvement in the medical decision-making process. It is a factor of the significance of information that is provided by the software, and its role in the diagnosis or therapy, as well as the seriousness or criticality of the medical condition.

When conducting clinical evaluation for medical device software, in addition to traditional evidence that is gathered from literature, it is also a useful approach to include survey based studies for substantiating performance. Also, demonstration of equivalence where possible, as per MEDDEV REV 4.0 and MDCG 2025 guidance, can be considered with similar products in the market.

Medical Device Software – Clinical Evaluation

The clinical evidence to be presented in the CER - will depend on the intended use of the software. The software could have an independent intended use and clinical benefits. It could also have an intended use and clinical benefits that drives or influences another medical device that serves a medical purpose, or the software may have no intended purpose of its own and it may just be an accessory or a component of another medical device. For example, when establishing state-of-the-art (SoTA) in the CER for a software, it can be based on the review of literature for establishing clinical validation, a competitive assessment with other devices with the same intended use, or other software that works on the same base algorithm. For technical validation, it can be demonstrated by validation studies that are conducted for software architecture design for IEC 62304, and the main operating function, which is IEC 62366. This is data that the manufacturer will already have from the pre-market activities that were performed for the particular software. This can be leveraged into the clinical evaluation for these kinds of devices.

The risk evaluation, among other things, should include a review of cyber security vulnerability databases of different agencies such as the European Union Agency for Cyber Security (ENISA). There are several databases similar to ENISA that can be a good source of information for risks related to cybersecurity, and the assessment of the benefits offered by the device software is irrespective of its categorization. This is different from the risks that are involved based on its involvement in the medical decision-making, which is what needs to be highlighted in a clinical evaluation report.

Combination Products and Novel Technologies with Medicinal Products

A combination product will consist of a pharmaceutical product and a medical device. These products may be integral or non-integral among other types. MDR has introduced new requirements for notified body involvement in the regulatory approval process for integral medical devices under Article 117. The market authorization dossier for such products, which is submitted to the competent authorities, is now expected to include an assessment of the conformity to GSPRs for the device component of such products.

A cliical evaluation report can be a document that demonstrates conformity to GSPRs to fulfil the requirement that article 117 has raised for such products. The demonstration of clinical evidence for these products has become much more significant under MDR than previous directives. The CER - it should be noted - is a separate process. It cannot replace the investigational studies that are conducted for the drug entity. However, often they do not consider evaluation of the safety or performance of the medical device component as its key endpoint.

For a new device under development, this is an important consideration to be made now under the new regulations in the clinical development plan stage, one can include such studies or include key device measures to focus on the device component when a clinical investigation is being planned. For cases where the device is already on the market, PMCF studies can be useful. The PMCF is focused on the safety and performance aspect of the device component which can help gather technical evidence for a DDC product.

Combination Products - Clinical Evidence

When talking about clinical evaluations for drug device combination products, the state-of-the-art (SoTA) in the CER can be based on a description of the technical platform or device families that these devices work on. And once again, provide a competitive assessment from literature with other alternative delivery systems and their benefits and risks to the patient or users. In addition, it has

to be highlighted in the CER - what the direct benefits are from such devices, from its intended use, as well as indirect benefits such as the ease of use, or quality of life that is offered by using such products as compared to alternatives. These benefits need to be weighed against risks such as those arising from, among other things, interactions of the drug and device components.

It must be kept in mind though that the final decision of the safety and performance of these kinds of devices still rests with the competent authority. If there are safety concerns, for example, the stability of the drug component or the integration of the two components, if that is under the question, then the notified body opinion report that has been provided under Article 117 may be overruled by the competent authorities decision.

Conclusion

A well-planned regulatory strategy needs to be in place for medical device software and drug device combination products just like any other medical device. It should be in place as early as possible in the life cycle of the clinical evaluation plan. Beginning early in the life cycle will help to ascertain the amount of clinical evidence that's available, and if there is a need for PMCF activity. The CER that will follow this plan will serve as an important document to demonstrate safety and performance, and for a favorable benefit risk ratio of the device when used in the field, which is critical, and is what the notified bodies are looking for in their review.

Thank You!!

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Celegence has a wealth of knowledge to help you navigate through the complex regulatory challenges that the new EU MDR bring.

We can assist you throughout the entire process to ensure that you and your business are compliant with all of the EU MDR requirements.

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