# RAPS WEBINAR TRANSCRIPT:

## Clinical Evaluations for Unique Product Types Under the EU MDR - Q&A

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## *Q:* Does the PSUR need to be included in the CER?

*A:* No, the PSUR (Periodic Safety Update Report) is a separate document. Of course, it incorporates maybe some data that comes from the CER, but it is not directly linked to the CER because for implantable devices, the notified bodies will review the PSURs on an annual basis. This means you do need to update the full CER. Thus, it will be a separate document - it might be reviewed in combination with the PSUR, but it should not be included within the CER itself.

## *Q:* How do we know if our clinical data will be considered sufficient?

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## *Q:* Does the PSUR need to be included in the CER?

*A:* For legacy devices, MDCG 2020-6 helps to find the answer. Manufacturers always approach their notified bodies to know if there are any guidance documents coming up. They also ask, what sufficient clinical data is? And, how many patients do I need to ask? For which there is not one simple solution. It depends on the risk factor of the device, and market history of your device. In the end, for the MDR, you need to have sufficient data for all indications to demonstrate safety and performance over the expected lifetime.

Let's say if you have an implant that is in the patient's body for the rest of the patient's life, at some point, if you give this to a younger, less than 30-year-old patient, you would need to have 50 years of data for that. So, is this feasible? No, and would it also be feasible to have a premarket clinical study that lasts 10 years? No, of course not. But, let's say you have an implantable device that is in the body for 12 months, of course then you can have sufficient clinical data in this case, which would cover the whole implant lifetime of the device. The basic message here is that it is not that simple. It also depends on the quantity of the indication. If you have an osteoarthritis of the hip, this is a very broad indication, and it is not an easy question to answer, as some other devices only have 40 or 50 devices sold per year. It really depends - look at your indications, look at your proposed lifetime, look at the data sources you might be able to access, especially the PMCF setting, and do not forget the PMCF is

a lifelong requirement for the device. And of course, at some point you will be able to close the gap to get sufficient data.

Just emphasizing those points - the requirement from the GSPR is for the risks to be reduced as far as possible. So, look closely at your risk management and your PMCF activities to determine if you have a PMCF plan that is going to justify and detail an approach, or provide justification on why it is not necessary. It will bear a lot of influence also from the state-of-the-art, because this will be increasingly compared to that of your competitors, so you should be aware of what your competition is doing as well.

## *Q:* For existing devices, how do you structure the Post Market Data analysis so that we do not need to generate new clinical data?

*A:* If you have sufficient data for your device, then you probably would not need it. Post Market surveillance requires that for as long as the device is on the market, and as long as a device is implanted, you have to follow up with the post market surveillance vigilance system. There are some options here for legacy devices to go with the MDCG 2020 – 6, the clinical data for similar devices from the state of the art, then of course, you need to close the gap on your own device. The term clinical data is a very broad term, and again, it depends on the risk of your device. If you have a class 2A instrument that has no direct impact on the patient, at some point you probably will have sufficient clinical data that could be considered. But, for implantable devices, it is nearly impossible to not have any kind of specific PMCF activity to get more clinical data.

Post Market data should be considered as well as part of the spectrum. Aside from cost considerations, this kind of spectrum goes from lower levels of commitment to higher levels of commitment. This can look something like a literature review on product returns, customer surveys, and consumer focus groups. Moving on up, you have retrospective patient reviews and record reviews. Finally, you would go on to registry studies and then finally clinical investigations that may be randomized.

You have a broad variety of different modalities to use. A legal manufacturer needs to determine how comfortable they are with their indications and claims, and with the cost aspects as well to determine how far in that spectrum they are ready to wade, and bear the risk of what they have not committed to. So, you need to find a comfortable place in that spectrum where you can be ready for an MDR audit.

## *Q:* What are the specific requirements for clinical investigations being conducted outside of the EU?

*A:* It depends between pre-market and post-market investigations. Of course, you can always - if you already marketed a device outside of the European Union - conduct a post market study there. You might be able to use this for the initial CE Mark in Europe.

Then if you plan to do a new study, always take into consideration the requirements of ANNEX 15 of the MDR, and every clinical study, regardless of what part of the world it is conducted, should follow the ethical and scientific standards. So ISO 1551 needs to be considered.

When it comes to the transferability of the data that MEDDEV 2.7.1 Rev 4 talked about, is the transferability of clinical data outside of the European Union to the European population. The MDR does not really require this, but your notified body might challenge you on it. If you have the same device being used for a completely different patient population, maybe a younger patient population, then you can try to conduct a study in a second world country. If you are trying to transfer that kind of data into the European Union for a completely different patient population, the notified bodies could challenge you on that - saying that you have a lot of data on the patient population with an average age of 40 years old, but now you are applying with a different indication for the European Union, even if it is the same device. So, if the data is transferable, it is no problem to use for European Union data, but as I said, talk to your study investigator to determine if it is transferable from a clinical perspective.

## *Q:* Should the EUDRA vigilance administered by the EMA be one of the databases to consider for the clinical evaluations of DDCs?

*A:* The straight answer is no, because EUDRA vigilance is talking about the drug entity of the medicinal product. Technically, from a device point of view, considering the risks which have been arising from medicinal products, it can be considered as a part of the clinical evaluation. With that said, EUDRA vigilance is not a viable source because notified body opinion reports are completely based on devices, and the device interactions with the medicinal product. You are supposed to be taking into account the device and its interactions in the drug-device combination. The straight answer is no, please do not take any of the information from EUDRA vigilance.

## *Q:* Does PSUR in this context mean pharmacovigilance of the combination products submitted to the EMA?

*A:* No. Periodic safety update reports are completely based on the risk classification. Class 3 devices and implants require an annual submission of the PSUR reports. Class 2B requires annual submissions, and 2A requires submission once every two years. This is the summary of information that you are drawing from risk management, clinical evaluation, and post market surveillance. But in case you are trying to work out the risk classification, implants will have a direct implication from PSUR to article 18 with the implant card and article 32 with the SSCP (summary safety clinical performance). Technically, the PSUR is a summary of the information from the clinical evaluation from post market surveillance or any of the other product performance studies. So, this should not include pharmacovigilance or any of the medicinal products, but for any of the intricate risks that are associated with the device, the drug interactions should be proactively considered.

## *Q:* For DDCs using platform technologies, there could be a large volume of clinical trial data. How do we decide which trials to include in the CER?

*A:* I would suggest that the clinical investigation section of the CER be organized by clinical indication, and that the evidence supporting the clinical indication be presented together. In addition, some clinical indications do not support a specific indicated use, which you may be worried about. There are two ways to go then, in the event that you have strong evidence from the remaining clinical investigations, you may just decide that you can drop the study, and only list the pivotal studies. On the other hand, if you have a limited number of studies and you need the evidence to show support for the overall clinical safety and efficacy, put it in a general section, which may precede your specific indication. Whether that is an approach that your notified body approves, remains to be seen, and that will depend entirely upon your notified body and your relationship with them.

## *Q:* If you have conducted several clinical investigations for an integral device, does it still require a PMCF study?

*A:* The PMCF is a scaled down version of a clinical investigation. A clinical investigation, otherwise referred to as a clinical trial, is a segment within the clinical evaluation. So technically, if we have some problems that can not be answered in a holistic approach, a clinical investigation has to be addressed in a single PMCF study. This is particularly in terms of high-risk products. It is not possible to answer all of the questions that are related to the bar compatibility, shelf life, the performance, and the efficacy. In those areas, if there is a question, it is always advisable that the notified body will be looking for objective evidence - what is the proactive approach the manufacturer is taking, identifying CAPA investigations, and singling out a PMCF study. So, it is not possible to conclude if either one study is enough, or if 10 studies are required. If there is a substantial number of clinical investigations conducted on a product, we still will be forgetting some of the other corners. So, when the product is performing in the market, you will come across some live information, like issues with the device failure, device incompatibility side effects, or any other areas which have to be considered as a single study in the Post Market Clinical Follow-up. If the MDR does not say a PMCF has to be conducted once every 5 years, or once every 10 years, there should be a proactive approach for manufacturers to conduct. Otherwise, PMCF sources the information for clinical evaluation and post market surveillance. Which are taken once again in PSUR & SSCP segments. Please make sure the PMCF is a tradition of your product trend analysis.

## *Q:* Which GSPRs are relevant to include in the clinical evaluation for a DDC?

*A:* In a direct sense, if you can segregate or categorize the entire general safety performance requirements, you have three essential chapters. Chapter one is the general requirements, which is GSPR one all the way to nine, and they are mandatory. All of the manufacturers have to comply. So, if you go to chapter 2, it talks about the design and manufacturer. Then chapter 3 includes information that has been provided along with the device.

We need to categorically understand that from one, all the way to nine, in most of the situations, you need to talk about the risk-benefit analysis. So, for a drug device combination, we need to understand which of these segments can be demonstrated from the risk management point of view. Straight to the point here - GSPR 12.1, and 12.2 focus on medicinal product directives 2001 / 83 EC. For

those medicinal products and the devices, how are they integrated? Are the DDCs integral DDCs? Or non-integral DDCs?

You need to make a decision about how the drug is interacting with the device. Also, the interaction of the device with any of the other components, which may be medicinal products or others, needs to be defined in the terms of risk management. Please focus on GSPR 12.1, and 12.2 towards labeling, ten, four, and five. The labeling of the device component will be overruled by the medicinal product regulations, so technically, even if you are going to mention single-use, or any other kind of labeling, they only pertain to the device. So, you need to be cautious about assessing the risk. Take a proactive approach towards labeling as per ten, four, and five. Going across, the other mandatory information you are providing in your IFU is from GSPR 23, which are the essential bits. Focus on GSPR 1 to 9, 12.1, 12.2, 10.4.5, and towards 23.

## *Q:* For software that is an accessory to a medical device, what kind of clinical evidence is required?

*A:* It depends on what the software is doing. If the software has its own intended purpose, or if the software is playing a relevant part, or, if the software is making a relevant decision, then you need to have clinical data specifically for that intended use. So, depending on the risk class of the software, that would decide the amount and quality of clinical data you would need, but again, it really depends on what the manufacturer's definition is for what the software is doing. of the device with any of the other components, which may be medicinal products or others, needs to be defined in the terms of risk management. Please focus on GSPR 12.1, and 12.2 towards labeling, ten, four, and five. The labeling of the device component will be overruled by the medicinal product regulations, so technically, even if you are going to mention single-use, or any other kind of labeling, they only pertain to the device. So, you need to be cautious about assessing the risk. Take a proactive approach towards labeling as per ten, four, and five. Going across, the other mandatory information you are providing in your IFU is from GSPR 23, which are the essential bits. Focus on GSPR 1 to 9, 12.1, 12.2, 10.4.5, and towards 23.

## *Q:* How do we know what type of PMCF study we need to conduct?

*A:* Starting from the end of the spectrum - that is the least commitment to the greatest - it goes literature reviews, proactive product returns, surveys, consumer focus groups, retrospective patient

record reviews, registry studies, and finally clinical study. You have to get a feeling for the amount of risk the legal manufacturer is willing to carry into the future to balance that with the costs of the time and money to collect this data. While some manufacturers will have deep pockets, they will be able to proceed further into the spectrum, while others will understand that they have relatively little resources, high costs, and little time before their certifications expire. They might have to even delay their MDR audits until they are able to complete one or more of these investigations, so you need to get a feel for your resources, the levels of risk that you deal with, and the clinical indications that you are addressing.

## *Q:* Can you elaborate on how to deal with Legacy devices with a lack of clinical data?

*A:* As a legal manufacturer, you need to consider the list that goes from literature review to clinical investigation. You must take into consideration the risk level of the device, and then develop a sense for the cost in terms of time and expenses, and then balance that with the available resources for the manufacturer. Then, to address the clinical gaps, there is a MDCG guidance on this - 2020.6. It is not unreasonable to suggest to your notified body that an investigation may be a considerable expense, requiring the legal manufacturer to complete it over several years. I believe the most important thing a notified body wants to see - is that you have a plan to address the gaps, and a defined approach as you proceed through the negotiations.

## *Q:* In many instances, indications for use remains silent on patient groups that are regarded as sensitive populations by MEDDEV 2.12 / 2. Will these practices be allowed after the date of effectivity for the MDR?

*A:* This is one area that falls into the area of best practices. I cannot really say how the regulation will be enforced and in what way, but my sense is that this is an area long ignored by regulatory obligation. There are two relevant risk trajectories to be considered - first, the legal manufacturers remain silent on use in Paediatric and elderly patients, and they decline to prepare themselves accordingly. In such cases, it would be difficult for the person in the audit to bear the risk to be asked this at any time. If it does not occur during the first audit, this could occur during subsequent audits. So, this is not really a safe trajectory. The alternative is for a manufacturer that remains silent on the indications for sensitive populations to prepare for the post market clinical follow up plan. As

we document investigations that would have been done in a paediatric and elderly population, such documents would provide the basis for claiming that the legal manufacturer that is addressing what has been this area of regulatory obligation. I mean with sensitive populations, it really depends on what the device is doing, what is the type of the device. So, at some point, the manufacturer needs to address this in their PMCF study, and do not forget with MDR manufacturers, they now clearly need to find a target population. If the manufacturer defines the target population with no age limitations, the notified bodies will challenge manufacturers on if they are able to confirm safety and performance for all the different age populations from your claim on the label.

## Helping You With
## The New EU MDR Challenges

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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