Incorporating Clinical Evaluation Requirements Into the Design and Development Process Under MDR

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Focusing on the new European Medical Devices Regulation 2017/745 (MDR), this article reviews a number of regulatory changes and covers several questions important to manufacturers regarding clinical evidence, clinical data, clinical evaluation, clinical safety, clinical performance, clinical outcomes and how they may fit together under new MDR requirements. The author speculates on the impact MDR might have on the design and development process while focusing on the incorporation of the MDR clinical requirements.

Introduction

MDR's Impact on the Design and Development (D&D) Process

The new European Medical Devices Regulation 2017/745 (MDR) poses many new questions and provides a variety of challenges for the medical device industry.[1-3] While there are many regulatory changes, there is little explicit information in the MDR for projecting what the impact MDR may have on the Design and Development (D&D) process. Article 10 makes it clear that MDR must be part of the manufacturer's Quality Management System (QMS), but this raises questions as to whether this is now a "hard" requirement for Class I devices under MDR, which was not under MDD 93/42/EEC.[4] However, in addition to the explicit requirements, there are many implicit changes regarding:

- initiating the Clinical Evaluation Plan (CEP), including Clinical Development Plan (CDP), which is new per MDR earlier in the process than under MDD
- ensuring all of the required processes/procedures for the Strategy for Regulatory Compliance are included in the QMS
- including the General Safety and Performance Requirements (GSPRs),[5] which replace the Essential Requirements from Annex I of the MDR in the design inputs. The GSPRs cover all range of matters including hazardous substances, biocompatibility, sterility, reusable devices, devices for use by lay users, risk management, Instructions for use (IFU) and labeling requirements, packaging, radiation, active devices and more.
- including Applicable Common Specifications and Harmonized Standards in the design inputs
- creating new design outputs, including labeling and IFU (per GSPR 23) and Unique Device Identifier (UDI) carrier, implant card if applicable (Article 18) among many others
- creating new required documentation such as Summary of Safety and Clinical Performance (SSCP) for Class III and implantable devices (per Article 32), PSUR/PMS report (Articles 85 and 86), PMCF plan and PMCF report (Annex XIV)

- updating the new requirements of MDR (in both form and content) for various document outputs, such as Clinical Evaluation Report (CER), Post Market Surveillance (PMS) plan, Technical Documentation (TD) and so forth.

Clinical Data and Evaluation and Definitions

Regarding questions about the terminology used for clinical data and evaluation, it is important to first examine several terms and their definitions included in the MDR and other relevant documents.

In MDR Article 2, the following terms are defined:

(51) Clinical evidence refers to clinical data and clinical evaluation results pertaining to a device of an amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer.

(48) Clinical data is defined as information concerning safety or performance generated from the use of a device and is sourced from the following:

- clinical investigation(s) of the device concerned
- clinical investigation(s) or other studies reported in scientific literature of a device for which equivalence to the device in question can be demonstrated
- reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated
- clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up

(44) Clinical evaluation refers to a systematic and planned process to continuously generate, collect, analyze and assess clinical data pertaining to a device in order to verify the safety and performance as well as clinical benefits of the device when used as intended by the manufacturer.

(52) Clinical performance is defined as the ability of a device, resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for patients, when used as intended by the manufacturer.

(53) Clinical benefit refers to the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis or a positive impact on patient management or public health.

It is also important to consider terms not defined in the MDR.

Clinical safety is not defined in the MDR. However, it is defined in the current MEDDEV 2.7/2 (Revision 2, September 2015), as "freedom from unacceptable clinical risks, when using the device according to the manufacturer's Instructions for Use."[6]

Clinical outcomes are not defined in the MDR, but the term is used in a number of places throughout (including the definition of clinical benefit) in Annex XV:

Annex XV: Methods

All the appropriate technical and functional features of the device, in particular those involving safety and performance, and their expected clinical outcomes shall be appropriately addressed in the investigational design. A list of the technical and functional features of the device and the related expected clinical outcomes shall be provided.

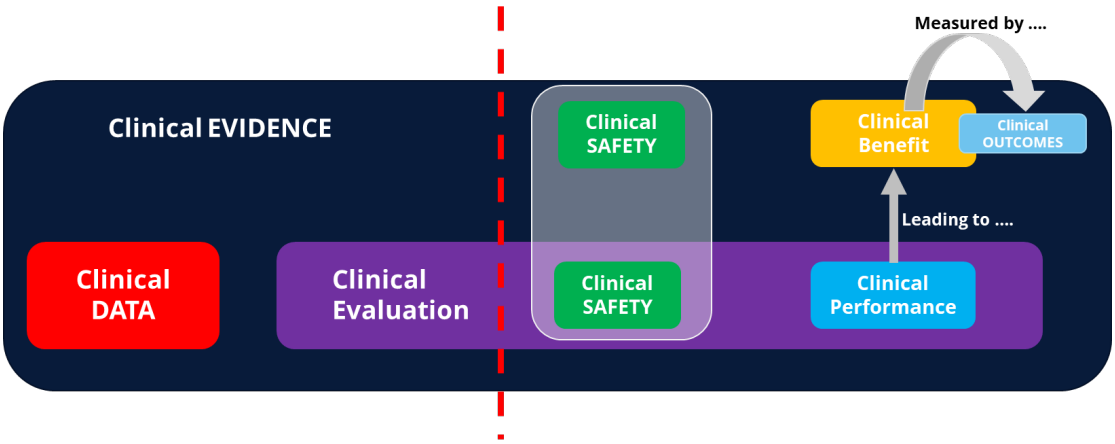
Annex XV: Clinical Investigation Plan (CIP)

Risks and clinical benefits of the device are to be examined, with justification of the corresponding expected clinical outcomes in the clinical investigation plan.

The connection between all these various terms is shown below in **Figure 1.**

- Clinical evidence consists of clinical data and clinical evaluation.
- Clinical evidence is concerned with whether a device is safe (clinical safety) and achieves the clinical benefits.
- Clinical evaluation means the process to assess the clinical data to verify the safety (clinical safety) and clinical performance.
- Clinical performance means the ability of a device to achieve its intended purpose, thereby leading to clinical benefit.
- Clinical benefit is measured in terms of meaningful, patient-centric clinical outcomes.

Figure 1. Connection Between the Various "Clinical" Terminology Used in the MDR.



It is possible to confuse the terms clinical evaluation and clinical investigation. The MDR defines the latter.

(45) In the MDR, clinical investigation means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device.

It is clear that a clinical investigation (or a clinical study or a clinical trial) is one of the data sources which can be part of the clinical data. So, one may think of this as a data source whereas clinical evaluation is a *process* to assess the available clinical data.

Building New Clinical Requirements into Design and Development (D&D)

With terms defined and new terminology understood, how might one incorporate these requirements within the design and development process?

There are many design and development QMS processes, with almost every manufacturer having their own process. Many of the processes share similar traits, such as having various phases defined for the D&D process, several of which end with design reviews, and often prescriptive deliverables defined to be completed per phase (or to be completed before the subsequent deliverables in later phases are begun or finished). For the purposes of this article, assume an example D&D process has five phases:

1. Concept
2. Feasibility
3. Verification and Validation (V&V)
4. Design Transfer to Production (DTP)
5. Postmarket

Figure 2 offers a simplified view of this process, with some deliverables (not an exhaustive list) to be completed per each phase. Those in red are new ones the author suggests the MDR may now require. Those in italics are selected existing deliverables that might be in a generic D&D process today under MDD, ISO 13485:2016 and 21CFR820.[7-9]

Note: this is not an exhaustive list of such deliverables. Risk management and usability, for example, are glaring omissions, among other things, but a simplified view is shown for clarity).

Figure 2. D&D Process Deliverable Updates Under MDR.

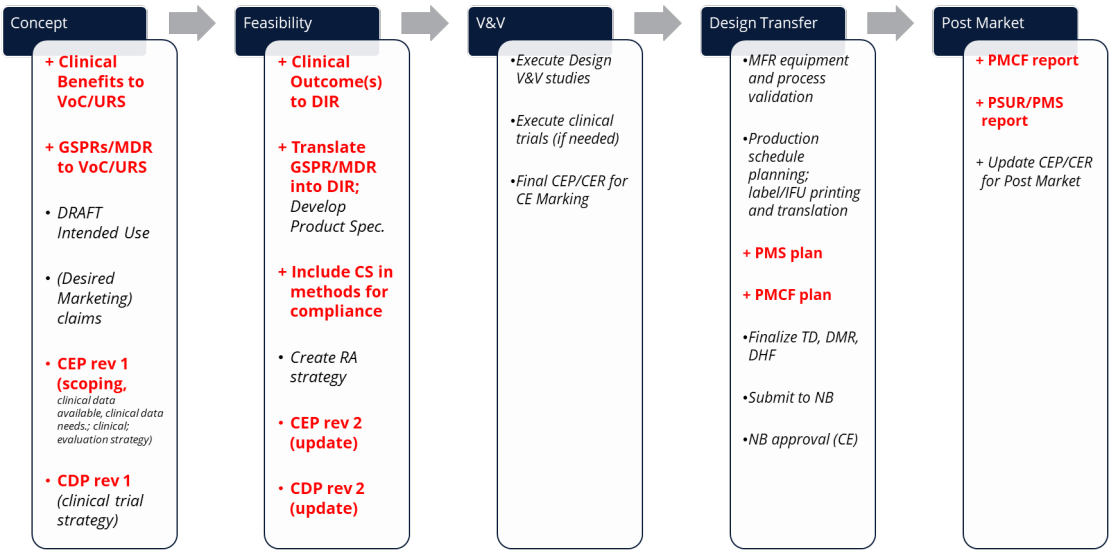


Figure 2 Notes: Voice of the Customer (VoC), User Requirements Specification (URS), Design Input Document (DIR), Common Specification (CS), Regulatory Affairs (RA)

Clinical Benefits, Clinical Outcomes, Clinical Safety, Clinical Performance and Clinical Development Plan (CDP)

Annex XIV of the MDR makes it clear that the intended clinical benefits should be in the CEP, as well as the clinical outcome parameters. Clinical benefit also needs to be in the IFU per GSPR 23.4. Thus, it seems reasonable that intended clinical benefit be added to the Voice of the Customer (VoC), User Requirements Specification (URS) or similar document. One might argue if this is a "hard requirement" or not; it appears to be a best practice since by adding such elements to the URS or similar document they will naturally flow through the process, and related inputs will make it into the Design Input Requirements (DIR) (engineering document), outputs into the product specification (and so forth) just as for any other user requirement. In the case of clinical benefit, the analogue to engineering inputs in the DIR might be the clinical outcomes since, per definition, clinical benefits are "expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health."

Examples of clinical benefits include:

- positive impact on clinical outcome (such as reduced probability of adverse outcomes, e.g., mortality, morbidity or improvement of impaired body function)
- the patient's quality of life (significant improvements, including by simplifying care or improving the clinical management of patients, improving body functions, providing relief from symptoms)

- outcomes related to diagnosis (such as allowing a correct diagnosis to be made, provide earlier diagnosis of diseases or specifics of diseases, or identify patients more likely to respond to a given therapy)
- positive impact from diagnostic devices on clinical outcomes
- public health impact (such as to the ability of a diagnostic medical device to identify a specific disease and therefore prevent its spread, to identify phases, stages, location, severity or variants of disease, predict future disease onset) (from MEDDEV 2.7/1 Revision 4).[10]

With focus on the Clinical Development Plan (CDP), again Annex XIV of the MDR requires this new plan as part of the CEP to indicate "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 as referred to in Part B of this Annex with an indication of milestones and a description of potential acceptance criteria." In essence, this CDP is a strategy for the clinical investigation(s) the manufacturer believes necessary to obtain needed clinical data for the device in question.

The requirement from the MDR for a CDP "dovetails" well with the recommendation from MEDDEV 2.7/1 Revision 4 Section 6.2 for a clinical evaluation in the development phase, as well as just before CE marking and in the PMS phase.[11] It reminds us clinical evaluation is an ongoing process and initiating it early in the development phase is beneficial as it helps manufacturers identify data needed for market access (i.e., CE marking). During this first clinical evaluation, shown in **Figure 2** as CER Revision 1, the manufacturer can:

- Explore if equivalence to another device is possible and can be adequately proven. If not, it may leave a "gap" in the clinical data which will need to be filled in some other way, such as with investigation data, literature data or PMS data for the device under evaluation.
- Determine what clinical data are already available (e.g., in the case of a line extension or a device for which equivalence can be demonstrated) versus what data are needed. Establish what clinical data still need to be gathered.
- Define what clinical safety and clinical performance mean for the device in question.

As explained by the MEDDEV, defining clinical safety for the device under evaluation aligns well with the MDR requirement in Annex XIV for the "specification of methods to be used for examination of qualitative and quantitative aspects of clinical safety with clear reference to the determination of residual risks and side-effects" that must be part of the CEP. This might take the form of identifying adverse events and harm resulting from the use of the device as well as the related rates of those experience by comparator devices and/or the clinical state-of-the-art. For example:

- For device X, clinical safety will be defined by Major Adverse Cardiovascular Events (MACE) X months post-op.
- For device Y, clinical safety will be determined by the Serious Adverse Events (SAE) rate compared to that for the clinical state of the art.

- The Adverse Events (AEs) for the device in question assessed by determining how the nature and frequency (rates) of these AEs compare to the clinical state of the art."

These elements must now be in the CEP per Annex XIV of the MDR, but also will connect to the criteria for risk acceptability and risk management.

Similarly, we might define clinical performance end-points, which may take the form of clinical outcomes (recall these are "meaningful, measurable, patient-relevant") or may not be.

For example, coronary stents for the treatment of Coronary Artery Disease (CAD) have gone through changes in the past few decades. Originally, there was Plain Old Balloon Angioplasty (POBA) for the treatment of CAD, which was replaced by Bare Metal Stents (BMS), and eventually by Drug Eluting Stents (DES). Crosby, et al, nicely describe the various endpoints which might be used.[12]

- In the past, "restenosis" (re-narrowing of the coronary vessel) was measured by "binary stenosis," defined as a 50% or more Diameter Stenosis (DS) at follow-up. It can be measured either visually or by Quantitative Coronary Angiography (QCA). These patients may or may not present with symptoms.
- More recently, Target Lesion Revascularization (TLR) has been used as an alternative measure. This is s defined as the need for a repeat intervention, such as Previous Percutaneous Transluminal Coronary Angioplasty (PTCA) or coronary artery bypass grafting CABG at the site of the lesion due to the recurrence of symptoms. It is a clinical way to measure restenosis, although it can occur for reasons other than restenosis, such as disease progression or a new lesion adjacent to the original treated area. The Target Lesion Recurrence (TLR) rate will typically be approximately half that of the binary restenosis rate, meaning that binary restenosis can be asymptomatic. Often, an approximate 70% diameter vessel stenosis is needed for a patient to have ischemic symptoms. Since binary restenosis is defined as at least a 50% diameter stenosis, there are patients who have binary restenosis but do not need a repeat intervention since they are still asymptomatic. TLR continues to be one of the strongest endpoints for understanding restenosis clinically.
- The ability of drug-eluting stents to inhibit neointimal hyperplasia calls for the use of a more sensitive measure of vessel patency. Late Lumen Loss (LLL), the angiographic representation of neointimal hyperplasia, is a precise and effective method of measurement. Not a new concept, late loss has been utilized for several years as a representation of the extent of neointimal hyperplasia. Clinical trials have demonstrated that late loss is independent of vessel size. Calculation of late loss allows the level of restenosis to be accounted for in all vessels, regardless of size. Unlike binary restenosis, late loss does not allow a narrowed vessel of any magnitude to go undetected. Late loss is measured in millimeters. The following is the equation in the QCA lab for this process:

Late Loss = (Minimum Lumen Diameter (MLD) Post Procedure) – (MLD at time of Follow-up.)

This example illustrates the following points:

1. How relevant clinical outcomes can change over time, with the clinical state of the art (binary stenosis replaced by TLR).
2. TLR is clearly a clinical outcome which can be used to measure clinical benefit (e.g., absence of symptoms of vessel narrowing).
3. LLL is a measure of clinical performance but may not be a clinical outcome.

Several additional examples for various type and class of device are given in **Table 1**. These are all fictious examples and are shown for illustrative purposes only.

Table 1. Example of Clinical Benefits, Clinical Outcomes and Clinical Performance for Various Medical Devices.

Device (Class)	**Intended Use Recall, clinical performance is the ability to achieve this, leading to a clinical benefit.**	**Clinical Benefit**	**Clinical Outcomes** **Major Adverse Event (MAE)**	**Clinical Performance**
Embolic Protection Device (III)	<DEVICE> is intended to endovascularly obstruct or occlude blood flow in vascular abnormalities of the neurovascular vessels. <DEVICE> is indicated for endovascular embolization of: • Intracranial aneurysms • Other neurovascular abnormalities such as arteriovenous malformations and arteriovenous fistulae	Reduces embolic stroke rate in <describe patient population and clinical conditions>	1. MAE ≤ X% 2. Acute Stroke Rate (within 30 days) ≤ X% 3. others	1. Acute success (ability to navigate through anatomy) to target 2. others

Drug Eluting Stent (III)	The DES is indicated for improving coronary luminal diameter in patients with symptomatic ischemic heart disease due to discrete *de novo*coronary artery lesions.	Absence of symptoms of vessel narrowing	1. Mortality/MAE ≤ X% at X months 2. TLR 3. others	1. LLL as measured by (describe) 2. Descriptive analysis of morphometric, lesion composition and stent strut data by OCT at X months 3. others
Radiotherapy System (IIb)	Linear accelerators (linacs) are intended to provide stereotactic radiosurgery and precision radiotherapy for lesions, tumors, and conditions anywhere in the body under the direction of a licensed medical practitioner.	The clinical benefits of the use of linacs (and accessories) is control of tumor growth.	1. Absence of tumors/lesion X days post treatment 2. Median survival time (some measure of treatment toxicity) 3. others	1. Delivery of X amount of radiation to Y type of tumor 2. others
Dental Cement (IIa)	(Cement) is used for adhesive luting of the following: • Metal crowns, bridges, inlays and onlays • Resin crowns, bridges, inlays and onlays • Metal (prefabricated or cast) and non-metal/fiber endodontic posts • Porcelain crowns, inlays and onlays	• Retention of the restorations • Favorable aesthetic qualities • Low post-op sensitivity (for self-adhesive cements)	1. Restoration survival rate 2. Median restoration survival time; 3. Pulp irritation; 4. Sensitivity /Pain to percussion; 5. others	1. Adhesion strength to enamel and/or dentin *in situ* 2. others
Hammer used in orthopedic surgery (Ir)	Assisting in bone preparation for orthopedic surgery.	None (!) (Such a device might be a candidate for a CER using Art 61(10) of	None (!)	1. Measure of usability of the hammer 2. others

		the MDR, based on pre-clinical data)		

According to MEDDEV, “As the initial clinical evaluation identifies the questions to be answered by a clinical investigation, the clinical evaluation process should generally commence in advance of any clinical investigation.” Perhaps “CER Revision 1” as shown in **Figure 2** could be in the feasibility phase. It is not intended that this “sketch” be precise; rather, it is a general sequence and flow of events.

Special Case: Devices With no Medical Purpose (Annex XVI Devices)

Under the MDR, certain groups of devices without an intended medical purpose are now included within the scope and, as such, are regulated like medical devices. The list includes intense pulse light devices for hair removal, aesthetic contact lenses, dermal fillers, breast implants for augmentation and devices used for liposuction, lipolysis or lipoplasty. The question may arise, if they have “no medical purpose, what is the clinical benefit?” The MDR addresses this in Article 61(9):

“In the case of the products without an intended medical purpose listed in Annex XVI, the requirement to demonstrate a clinical benefit in accordance with this Chapter and Annexes XIV and XV shall be understood as a requirement to demonstrate the performance of the device. Clinical evaluations of those products shall be based on relevant data concerning safety, including data from post-market surveillance, PMCF, and, where applicable, specific clinical investigation. Clinical investigations shall be performed for those products unless reliance on existing clinical data from an analogous medical device is duly justified.”

For such devices, demonstration of clinical performance is sufficient.

An “analogous device” means “the same device with intended medical purpose.” So, for the aesthetic contact lenses that would be contact lenses to improve vision, for breast implants for augmentation the analogous device would be breast implants for reconstruction.

Scoping the Clinical Evaluation

One weak aspect of CEP/CERs is “scoping.” Today, many CERs have a scope such as “to demonstrate device X meets the requirements of the MDD” or “to show device X meets ERs 1, 3 and 6” or “the scope of this clinical evaluation is device X.” These definitions are all quite vague and do not define the actual research question(s) to be addressed by the clinical evaluation. Defining what safe means for the device in question (ER 1, GSPR 1 and 8), as well as performance (ER 3, GSPR 1 and 8) as well as identifying and minimizing all undesirable side-effects (ER 6, GSPR 1 and 8) can help give some specificity to the research questions, which in turn can drive more directed literature searches, for example. It is recommended the guidance in Section 7 of MEDDEV 2.7/1 Revision 4 is used (since there is not yet any more detailed guidance with respect to MDR) when developing the research questions and “scoping” for the CEP/CER.

Regulatory Affairs (RA) Plan vs Strategy for Regulatory Compliance

In many D&D processes, a variety of plans are created early in the development process. These include marketing plans, clinical plans and often a regulatory plan or RA Plan. These plans often lay out the regulatory strategy for bringing the device to market and may cover many regions, such as US, Canada, Asia, South America and Europe. In the past, manufacturers often launched in the EU first, as that was the "easier" option and launched later in the US. This paradigm seems to have shifted or be shifting in recent years due to the 5th amendment to the MDD, MEDDEV 2.7/1 Revision 4, MDR and other requirements. It is important to distinguish the RA Plan from the strategy for regulatory compliance, as required by the MDR. The latter includes a number of procedures within the QMS to address identification of relevant legal requirements, qualification, classification, handling of equivalence, choice of and compliance with conformity assessment procedures, including product changes, as described in Article 10(9a) and Annex 2.2c. As such, the traditional RA Plan and this strategy for regulatory compliance may be related but are not the same. The former is a discrete plan; the latter is an assemblage of procedures covering various aspects for compliance.

General Safety and Performance Requirements (GSPR) Inputs

Just as with the Essential Requirements (ER) from the MDD today, the GSPRs must be incorporated into the design inputs for devices to be placed on the EU market. These requirements cover a whole range of key requirements, such as biocompatibility, shelf life, sterilization, suitability of packaging, devices for lay users, hazardous materials, requirements for labeling and IFU, including UDI and many other aspects, which are not within the scope of this article. Additional information can be found in various sources.[13]

Common Specifications and Harmonized Standards

Common Specifications (CS) are a new item introduced by the MDR and are described in Article 9. They can be thought of as "more important harmonized standards" in the sense that "Manufacturers shall comply with the CS referred to in Paragraph 1 unless they can duly justify that they have adopted solutions that ensure a level of safety and performance that is at least equivalent thereto…" In the hierarchy of regulations and standards, they sit just below regulations and just above harmonized EU standards.

Therefore, it seems evident that were one or more cs apply to the device in question, the requirements within it must be added to the design inputs, just as those for EU harmonized standards are today.

With regard to EU harmonized standards, there has been discussion of when the approximately 200 standards harmonized under the MDD will be updated and/or harmonized with the MDR. With the publication of the draft standardization request[14] to CEN and Cenelec by the European Commission in June 2019, it seems that five will be in place by May 2020. These cover QMS, product risk, clinical investigations and symbols for labeling. Many other horizontal standards (such as those covering biocompatibility and sterilization, for example) may not be ready until after this time. This also applies for product-specific, vertical standards. As such, it is not yet clear how notified bodies will interpret the use of standards not harmonized to the MDR (e.g., standards harmonized to the MDD), and how much

pragmatism will be brought to bear when performing product assessments.

However, the key point from the perspective of this article is that EU harmonized standards for MDR should have their requirements included in the engineering design input documents.

PMS Plan/Report

Another very clear aspect is that each device should have a Postmarket Surveillance (PMS) plan as described in Article 84 and Annex III of the MDR. In addition, that PMS plan should be part of the technical documentation. As shown in **Figure 2,** a PMS plan should be created before entering the PMS phase and during the completion of the TD ahead of submission to the NB. There are many details one could cover regarding the creation of the PMS plan, including what it should look like, the PMS process itself and how that should integrate with the rest of the QMS. But, again, that is not the focus of this article. The key point here is that a deliverable to generate a PMS plan should be added to the D&D process to ensure compliance with the MDR requirement.

This plan will lead to a PMS report or PSUR per Articles 85 or 86 of the MDR. These also need to be created/updated on a frequency specified in the MDR based on the class of the device. These also must be part of the TD. Again, adding suitable deliverables in the D&D process would seem to be a prudent way to manage the generation of compliant documentation to meet the MDR within a QMS.

Postmarket Clinical Follow-up (PMCF) Plan/Report

Similar to a PMS, a PMCF plan will need to be available and part of the TD, as described in Annex III and Annex XIV of the MDR. There is debate as to whether a PMCF plan is always required, as Annex XIV seems to imply in the author's view, since it describes PMCF as a continuous process, for which it seems there will always be a plan, which may or may not include a PMCF study/specific methods as part of that plan, which may or may not include a PMCF investigation (per Article 74) as all or part of that study. Annex III makes it clear that one can justify not doing PMCF, in which case, it is suggested, one simply ignores the requirements in Annex XIV Part B if it has been justified that PMCF is not required as part of the PMS plan.

Given that PMCF plan is generated for any given device, it too shall be part of the TD (since it is part of the PMS plan per Annex III).

In analogy with the PMS report/PSUR, Annex XIV of the MDR requires a PMCF report (whenever we have PMCF), which also must be part of the TD. So a D&D process deliverable for this seems obvious.

Conclusion

This article aimed at providing an overview of the impact on the design and development process under MDR with a focus on the incorporation of the clinical requirements within MDR. Because many of these requirements are implicit rather than explicit this summary offered possible new D&D deliverables and approximately where in the process they might be added. The connection between intended use, clinical

benefits, clinical outcomes and clinical performance has been outlined with some practical examples given.

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