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Common regulatory gaps in Clinical Evaluation Reports for medical devices and the pathway towards EU MDR transition

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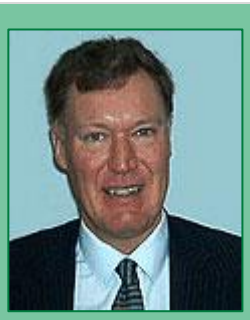

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Common regulatory gaps in Clinical Evaluation Reports for medical devices and the pathway towards EU MDR transition

Introduction

In Europe, medical devices have been regulated centrally since the 1990s when Directive 90/385/EEC (the Active Implantable Medical Device Directive, AIMD Directive[1]) and Directive 93/42/EEC (the Medical Device Directive, MDD[2]) were published. However, even though these Directives underwent a series of amendments in the following years, they remained outdated, especially with respect to the regulation of the growing market of implantable devices and software. The Medical Device Expert Group issued a report in 2002[3] highlighting several of the MDD's weaknesses, including the consistency and reliability of conformity assessments, the lack of transparency in regulatory processes, and poor post-market surveillance (PMS) practices[4]. In addition, a cascade of events in the 2010s, such as the Poly Implant Prothèse breast implant scandal[5], the controversial data on metal-on-metal hip replacements[6], and the deliberate non-disclosure of complications after vaginal mesh implantation[7] revealed serious, chronic vulnerabilities of the fail-safe mechanisms in force. Ultimately, immense pressure was placed on the European Commission to propose a legal text that would eventually lead to safer and more efficiently monitored devices marketed in Europe. The European Commission published the text of the new Regulation (EU) 2017/745 on medical devices (MDR) in May 2017[8], aiming to restore the credibility and reputation of the system via the introduction of dynamic and continuous PMS[9].

The purpose of the MDR is to facilitate regulatory surveillance, to ensure continued user and patient safety, product traceability, quality assurance and transparency, as well as to provide fair market access to manufacturers, boosting innovation and development through centralised and simplified administrative procedures. To enable this, increased safety and performance requirements have been introduced for all medical devices, regardless of how long they have been on the market. Both legacy and new medical devices must now provide sufficient clinical evidence to confirm their intended performance and safe use, as well as their clinical claims throughout their lifetime. The requirement for clinical evidence has become proportional to the device's inherent risks and high-risk devices must provide evidence establishing a concrete clinical benefit.

Reclassification of many medical devices puts additional emphasis on PMS and Post-Market Clinical Follow-up (PMCF) requirements. The obligation of issuing Periodic Safety Update Reports (PSURs) and the requirement to keep in place a procedure to collect and identify adverse events in

clinical practice is intended to strengthen the safety profile of medical devices. Further to this, alignment of risk management activities with PMS findings and proactive collection of clinical data via PMCF is set to ensure that possible systematic misuse or off-label use of a device will be identified with a view to verifying that the intended purpose is correct, while previously unidentified and/or emergent risks will be addressed on time.

Another important update relates to the improvement of transparency. Previously, it was difficult, if not impossible, to access the information submitted by a manufacturer applying for a Certificate of Conformity. Under the MDR, the manufacturer is obliged to issue Summaries of Safety and Clinical Performance (SSCPs) for high-risk devices on an annual basis, which will be publicly available on the European Union's database of medical devices (EUDAMED). Additionally, in terms of traceability, each medical device will be identifiable through a Unique Device Identification (UDI) system.

Compliance with the new regulatory framework is a multi-step, stringent process involving the cooperation of various departments within a corporation[10]. Preparation of a Clinical Evaluation Report (CER) is often the starting point and also serves as a rough gap analysis. The purpose of this article is to identify, classify and discuss the major gaps in documentation and their resulting regulatory impact. The consolidated information aims to provide a meaningful and actionable understanding of systemic gaps, and through that, understanding of the rationale of the MDR's requirements.

Methodology

This meta-analysis considers 121 CERs that were completed between August 2018 and October 2020. Six of these were excluded from the analysis because it was impossible at the time this article was prepared to access the full folder of the project(s). One CER was not included in the study because the clinical evaluation was under revision during the time of preparation of the manuscript. With respect to the regulatory basis of the 114 CER projects assessed, the manufacturer requested a CER under the MDR requirements in 63% of cases (n=72), whereas almost 37% (n=42) of the projects were requests for a CER under the MDD (n=23) or a 'hybrid' CER (n=19). One manufacturer initially requested an MDR CER, which was later converted into an MDD/MDR hybrid CER. Figure 1 illustrates the regulatory basis for the CERs (the compliance statement that was written) plus the types of services requested.

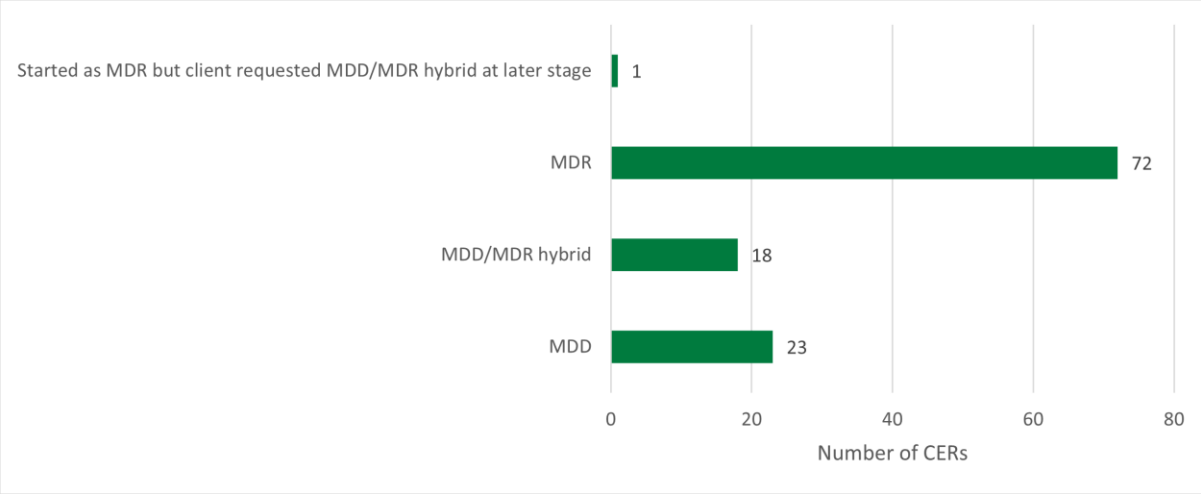

Figure 1a. Regulatory basis for the CERs (based on the compliance statement)

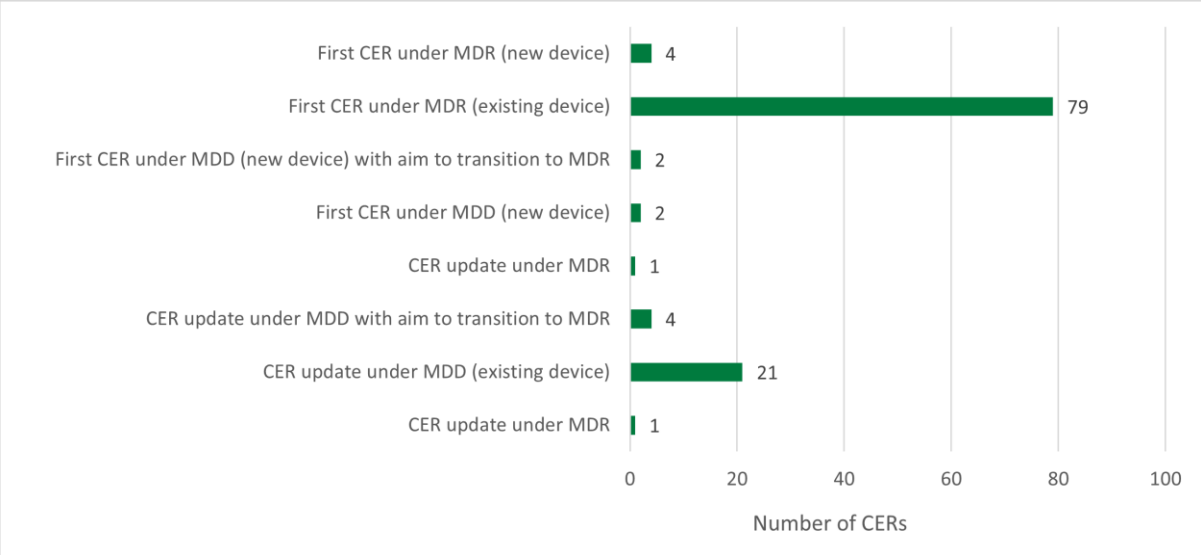

Figure 1b. Types of services requested for the included CER projects

Medical devices of all classes were included in the analysis (*see* Table 1).

Table 1. Classification of included devices

Classification of devices	Number of devices
For CERs under the MDD	
Class I	10
Class I, IIa	1
Class I, IIa, IIb	1
Class IIa	5
Class IIb	6

Classification of devices	Number of devices
Class III	1
For CERs under the MDR	
Class I	18
Class I, IIa	4
Class I, Ir, IIa	3
Class I, Ir, IIa, IIb	5
Class Ir	7
Class Is	2
Class IIa	13
Class IIb	17
Class III	2
Notes *19 CERs were written as 'hybrids' therefore classification of the devices was described under both the MDR and the MDD. The scope of some CERs, usually surgical instrumentation used in combination with implantable devices, included medical devices of various classes.*	

A 'hybrid' CER combines requirements from both the MDR and the MDD. In most cases, the decision for this type of clinical evaluation was dictated by the manufacturer's intention to ensure the uninterrupted marketing of the medical device during the transition to MDR requirements.

The medical devices relating to the 114 CER projects assessed herein were grouped in generic categories to allow anonymity of manufacturers and brand names (*see* Table 2). Surgical instrumentation, which is the most prevalent group, includes both independent surgical instruments and system-specific instruments. The former are used to perform distinct tasks during surgical processes, whereas the latter are used in combination with implantable systems, such as long bone implants. Medical devices of all classes were included.

Table 2. Classification of medical devices by generic category

Type of medical device	Number of devices
Surgical instrumentation	33
Miscellaneous (do not fit in any of the other categories)	21
Monitoring/diagnostic devices	17

Type of medical device	Number of devices
Implantable devices	12
Cardiovascular devices	6
Ophthalmic devices	6
Endoscopic devices	5
Hospital beds	4
Transport devices	4
Surgical lights	3
Wound drainage	3

The 114 CER projects were prepared for 14 different manufacturers. Of these, 48 were prepared for different affiliates/business units of the same manufacturer and 17 were prepared for a manufacturer that had previously merged with another company.

The first step of the analysis involved the collection of information with respect to the documentation provided by the manufacturer for the preparation of the CER, and the identification of the main gaps at the start of each project (i.e. the identification of documents missing or partially available at the time when the CER author started writing the report).

The main focus was on the availability of the following, which were ranked in order of severity (1 = greatest severity, 9 = lowest severity):

1. Updated risk management data, where full risk management data are defined as delivery of all the following: risk analysis report + Failure Mode and Effects Analysis (FMEA) + Process Failure Mode and Effects Analysis (PFMEA) + risk management report.
2. Biocompatibility reports.
3. Verification and validation (V&V) testing reports.
4. Full PMS data as an indication of an active PMS programme, where full PMS data are defined as delivery of all the following: sales + complaints + trend reporting + Corrective and Preventative Actions (CAPAs) (if issued) + Field Safety Corrective Actions (FSCAs) (if applicable) + PMCF data + data from registries.
5. Technical documentation as per Annexes II and III to the MDR.
6. Copies of the instructions for use (IFU) and other applicable labelling documents.
7. Essential Requirement (ER)/General Safety and Performance Requirement (GSPR) checklists.
8. Compliance with applicable standards.

9. Previously released CER, regardless of its compliance statement.

The proposed severity ranking is risk-based and considers the data that are most likely to trigger non-conformities for a manufacturer with respect to the new and/or increased requirements. The greater the severity, the less likely it is that definitive conclusions regarding the requirements of safety, performance and acceptability of the risk/benefit ratio for a given medical device can be drawn. The ranking was determined based on the enhanced safety and performance requirements established by the MDR with respect to risk management and PMS. Risk management was deemed to be the most severe gap as the new Regulation significantly increases requirements in comparison to the MDD, mandating that all manufacturers generate and keep up-to-date risk management plans, identify and analyse all known and foreseeable hazards, estimate and evaluate all use-associated risks, and mitigate those risks as far as possible throughout the lifecycle of the medical device starting as early as the design phase. The combination of Article 10(2)'s obligation to establish a risk management system with the explicit GSPRs of Annex I to the MDR emphasise the dynamic nature of the process, which aims to ensure that risk mitigation strategies and changes to control measures proceed as far as possible without adversely affecting the risk/benefit ratio. Biocompatibility and PMS continuously feed into risk management updates contributing to the lifecycle management of medical device monitoring. On the one hand, PMS is now a holistic, cross-functional, systematic and proactive process ensuring adequate medical input into the risk management process during product development and enabling manufacturers to identify and manage possible product safety issues proportionally to device-associated risks based on its intended use. On the other hand, biological safety, defined as 'freedom from unacceptable biological risk in the context of the intended use' in ISO 10993, is an integral part of the risk management process, receiving additional attention in the MDR. The need to generate a Biological Evaluation Plan and address all risks relating to the composition of a medical device, which comes into contact with a patient's and/or user's body, adds a significant gap in remediation processes. For this reason, it was considered a more severe gap in this analysis as manufacturers need to implement elaborate activities to comply with the new requirements. V&V also receive additional attention within the MDR as they relate to potential design changes, which are under greater scrutiny in the MDR and must be reported in a timely manner and substantiated.

The key point of available device-specific clinical data was not included in the above ranking. According to Article 61(1) of the MDR, '[c]onfirmation of conformity with relevant general safety and performance requirements … under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit-risk- ratio … shall be

based on clinical data providing sufficient clinical evidence'. Device-specific clinical data is therefore considered an essential element of a clinical evaluation that is outside the scope of this analysis.

The manufacturer response rate was also evaluated as, based on the authors' experience, low response rates are highly associated with lack of data and subsequently with delays in the writing process and the certification/recertification of a medical device. Three levels of manufacturer response were assigned: Low, Moderate and Good, according to the readiness of the manufacturer to provide requested data. For 48 of the CERs, the manufacturers were rated as Good, they were rated as Moderate for 28 CERs and Low for 21 CERs. For 17 CERs, the rating was not applicable, primarily because the CERs were being written in parallel with the remediation of the technical documentation.

Requests to develop CERs under the MDD were not excluded from the study because the grace period offered by the European Commission on May 2020 and the revised CER guidance (MEDDEV 2.7/1 rev 4)[11] resulted in a shift towards renewal of MDD certificates to prolong the preparation time for full MDR transition.

Statistical methods

Frequencies and percentages were used to describe the data. To test for the association between the variables, the Chi square and the Fisher exact test were applied. To calculate the statistical power of the test, the G*Power software was used. The level of significance was set at 5% ($P<0.05$).

Results

Gaps on essential documents at the start of the 114 CER projects are summarised in Table 3. These gaps were ranked according to severity on a scale of 1–9 (as described above) and each CER was given a severity rank according to the essential documents that were missing (if multiple documents were missing, the severity rank corresponded to the greatest severity rank).

Table 3. Overview of the availability of essential documents at the start of the 114 CER projects

Essential document	Number of projects where document was available at the start	Number of projects where document was not available at the start	Not applicable
Risk management data	62 (54%)	49 (43%)	3 (3%)
Biocompatibility reports	38 (33%)	73 (64%)	3 (3%)
V&V testing reports	45 (39%)	66 (58%)	3 (3%)
PMS data	41 (36%)	68 (60%)	5 (4%)

Essential document	Number of projects where document was available at the start	Number of projects where document was not available at the start	Not applicable
Technical documentation	42 (37%)	72 (63%)	–
IFU & labelling documents	71 (62%)	40 (35%)	3 (3%)
ER/GSPR checklists	43 (38%)	69 (60%)	2 (2%)
Compliance with harmonised standards	81 (71%)	27 (24%)	6 (5%)
Previously released CER	100 (88%)	9 (8%)	5 (4%)

Figure 2 shows the greatest severity ranking for each of the CER projects.

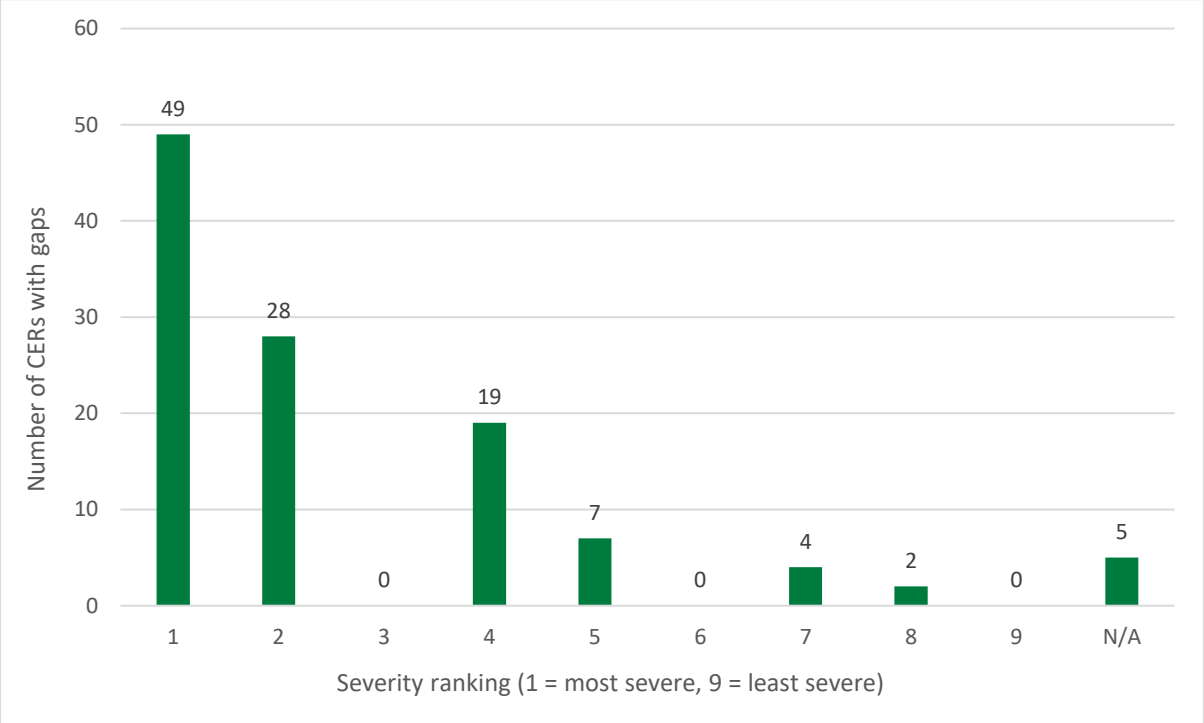

Figure 2. Greatest severity ranking of gaps for each of the 114 CER projects, where N/A shows the number of CER projects that had no missing essential documents

The majority of projects (n=49) had the greatest severity ranking due to missing essential risk management documents, followed by rank 2 (biocompatibility reports).

Unavailability of biocompatibility reports was the most common gap across the pool of data assessed in the present study (*see* Table 3), which accounted for 64% of the projects (n=73). Lack of technical documentation and ER/GSPR checklists followed closely in gap prevalence (n=72 and n=69, respectively). In comparison, lack of IFUs remained relatively low; only 35% of projects were unable to provide them at the start (n=40). Deficiencies in V&V testing and PMS data were also notable, with

the quality and accuracy of PMS data being suboptimal in practically 60% (n=68) of the projects. Even with MDD updates, about 30% (n=9) of projects were started without proper PMS data. Out of the 114 CER projects, 66 (almost 58%) of all projects were started without sufficient information on bench testing and pre-clinical data (*see* Table 3, V&V testing reports), which is consistent with the failure of manufacturers to provide technical documentation in 63% of the projects in this study (n=72).

Chi square tests for the association of major gaps in documentation among all medical device categories (*see* Table 4) showed that, as expected, there was no statistically significant difference in the number of major gaps across the device categories (P value of Fisher exact test=0.120, which is greater than the level of significance set, P<0.05). Almost all medical device categories had multiple gaps among the three critical categories, in other words they were lacking documentation in at least two categories of risk management data, biocompatibility reports or V&V testing reports.

Table 4. Chi square tests for the association of critical gaps in documentation among all medical device categories

Medical device category	**Critical gaps in at least one of the following: risk management data, biocompatibility reports, V&V testing reports**		
	No gaps	**≥1 gap**	**TOTAL**
Cardiovascular devices	1 (17%)	5 (83%)	6 (100%)
Endoscopic devices	2 (40%)	3 (60%)	5 (100%)
Hospital beds	1 (25%)	3 (75%)	4 (100%)
Implantable devices	1 (8%)	11 (92%)	12 (100%)
Monitoring/diagnostic devices	8 (47%)	9 (53%)	17 (100%)
Ophthalmic devices*	3 (100%)	0	3 (100%)
Surgical instrumentation	10 (30%)	23 (70%)	33 (100%)
Surgical lights	0	3 (100%)	3 (100%)
Transport devices	0	4 (100%)	4 (100%)
Miscellaneous medical devices	7 (33%)	14 (67%)	21 (100%)
Wound drainage	1 (33%)	2 (67%)	3 (100%)
TOTAL	**34 (31%)**	**77 (69%)**	**111 (100%)**

** For three CER projects of this category, there were no available data for biocompatibility, risk management documents and V&V testing and therefore those CERs were not included in this table.*

A sub-analysis of the gaps for the top three medical device categories (surgical instrumentation (n=33), miscellaneous medical devices (n=21) and monitoring/diagnostic medical devices (n=17)) confirmed

the findings reported above (*see* Table 5). A gap is defined as a failure to deliver the document on time or the document being unavailable.

Table 5. Major gaps in documentation at the start of the CER process for the top three medical device categories

	Gap	No. of CER projects
Major gaps within surgical instrumentation (n=33)	Updated full PMS data	28 (85%)
	Technical documentation	25 (76%)
	Biocompatibility study report	23 (70%)
Major gaps within miscellaneous medical devices (n=21)	Biocompatibility study report	14 (67%)
	V&V testing reports	13 (62%)
	ER/GSPR checklist	12 (57%)
Major gaps within monitoring/diagnostic medical devices (n=17)	Biocompatibility study report	8 (47%)
	V&V testing reports	8 (47%)
	ER/GSPR checklist	7 (41%)

Surgical instrumentation in this analysis includes standalone surgical instruments, endoscopic instruments and instruments that are part of larger systems (e.g. orthopaedic implants). Therefore, the identified gaps represent a wide spectrum of medical devices. As seen in Table 5, non-updated PMS data was the most common gap within this category.

Chi square tests for the association of major gaps in documentation among the top three medical device categories once again showed that there was no statistically significant difference between the number of major gaps across the three medical device categories (P value of Chi square test=0.490, which is greater than the level of significance set, $P<0.05$). Within the 71 most prevalent medical devices (i.e. surgical instrumentation, miscellaneous and monitoring/diagnostic medical devices), 46 medical devices had at least one major gap in documentation: 28 had gaps in all three critical categories (risk management, biocompatibility, V&V testing), 14 had gaps in two major categories and only four medical devices had gaps in one major category. The power of the test was 0.94, which is greater than the generally accepted level of 0.80, meaning the test power was adequate.

Discussion

The majority of CER projects (n=49) were assigned to the greatest severity ranking because essential risk management documents were missing, and this was followed by rank 2 (n=28) for biocompatibility reports. Only five projects provided all essential documents at the outset, thus confirming that lack of

essential documents is commonplace among manufacturers transitioning to the MDR, with the most crucial documents often coinciding as the unavailable ones. In fact, this analysis has shown that most gaps were associated with a lack of critical documents.

Lack of biocompatibility reports (n=73), either lack of updated or compliant documentation reflecting the current state-of-the-art expectations or actual lack of biocompatibility testing, was the most common gap across the pool of CER projects assessed in the present study (*see* Table 3). Despite the fact that a state-of-the-art standard is available (i.e. ISO 10993-1:2018), the majority of manufacturers could not provide evidence of compliance with it. While compliance with standards is not mandatory, with respect to biocompatibility, compliance with the respective standards is the optimal way to fulfil the requirements. Such evidence includes the necessary information for the safety of the composition of medical devices that come into contact with a patient or user's body. Within the MDR context, biocompatibility studies have been further upgraded and carry greater importance, due to adding input to the risk management process. Therefore, delays in the release of harmonised standards may have an impact on finalisation of the transition towards the MDR. At the time of writing, only EN ISO 10993-23:2021 had been harmonised with respect to biological evaluation.

Lack of technical documentation and ER/GSPR checklists follow closely in gap prevalence (63% and 60%, respectively). Their lack may be justified by the fact that manufacturers remediate on all levels at the same time. Lack of IFUs remained relatively low (62% of projects were able to provide it at the start) in comparison to technical documentation and ER/GSPR checklists. This is consistent with the fact that IFUs are central to the technical documentation that is undergoing major changes within the MDR, and thus are among the first documents to be updated. Despite this, of the 37 projects with an MDR compliance statement that provided an IFU at the start, none had MDR compliant IFUs. This was mainly due to the expectation of a revision of labelling statements after the release of the CER.

With respect to PMS data, it has been the authors' experience that manufacturers are challenged by the new requirements due to the lack of complete PMS data collection, which is often reflected in the lack of sales per geographical region, incomplete internal complaints records, omissions and/or failures to close CAPAs, etc. This observation is consistent with the findings, especially among legacy devices and standard surgical instrumentation whose manufacturers were very often unable to provide sales and complaints data for periods longer than the two to three most recent years. The difficulty for some manufacturers to appreciate the more stringent, emerging regulatory framework, is reflected in the fact that in at least two projects the manufacturer withdrew their request once they were informed that a PMCF study would be required to support the clinical safety/performance of their medical devices. Similarly, manufacturers tend to dedicate significant

time in discussions/negotiations about literature and state-of-the-art search strategies, and tend not to comprehend fully how literature findings, PMS and risk management data all feed into the clinical evaluation. All these processes are important to substantiate the GSPRs, as well as to determine potential required revisions of labelling statements.

Similarly, V&V test reports were often incomplete or failed to reflect the current state of the art. Harmonised standards listed under the Directives cannot be used to provide presumption of conformity with MDR requirements, plus compliance with state-of-the-art standards does not automatically translate into compliance with current legal requirements. This bottleneck forming around the delay of harmonisation and lack of official guidance increases the risk associated with the regulatory strategy towards market access in the European Union.

With respect to gaps per medical device category, non-updated PMS data was the most common gap for surgical instrumentation. This is partially explained by the fact that scope lists are subject to frequent changes, as well as up-classification of accessories to medical device status. As manufacturers are called to remediate for the transition to the MDR, it seems that an internal reordering of product codes is taking place, reflecting their effort to determine which medical devices in their portfolio will remain on the market under the MDR.

For the miscellaneous medical devices and monitoring/diagnostic medical devices categories, the gaps were almost identical and associated with missing V&V, biocompatibility data and lack of ER/GSPR checklists. In the authors' experience, the lack of these checklists is directly related to major gaps in MDD and MDR technical documentation. It is not always clear to manufacturers that ER/GSPR checklists are an essential part of the technical documentation, or that they may be used as gap analysis guides that will trigger a more efficient remediation.

The major limitation of this study is that the 114 CERs evaluated herein come from 14 different manufacturers, which is not a high number and may not reflect the actual real-world situation as both the severity and occurrence of identified gaps may be a manufacturer-specific illustration. However, the variety of medical device types and inclusion of medical devices of all classes helps to counterbalance this limitation, as different device types and classes introduce considerable differences in requirements and therefore allow useful conclusions to be drawn. Additionally, the traits of manufacturers included herein (e.g. wide product portfolio, leading position in the global market, status of regulatory compliance over time) are representative of the average companies that were already in the market while the MDD was in force and are actively pursuing MDR certification. Another limitation lies in the fact that implantable devices included in this analysis have not undergone a sub-analysis because 11/12 projects were from the same manufacturer, who was extensively remediating during the preparation of the CERs.

Conclusions

The MDR introduces significant changes across the technical documentation of medical devices mandating manufacturers to provide sufficient evidence of compliance with the applicable GSPRs. To meet the increased requirements for clinical evidence, manufacturers must generate and collect risk-based PMS data throughout the expected lifetime of a medical device and critically appraise them in combination with literature data for the intended medical field and respective indications, while taking into account design specifications, usability, and V&V reports. Although the first step of the transition to the MDR must always be a holistic gap analysis and the development of a concrete plan for compliance of the Quality Management System, it is often the preparation of CERs that hampers remediation activities due to systemic gaps and lack of appropriate technical documentation. Within this context, the authors of this article evaluated a total of 114 CER projects for medical devices of various types and of all classes to identify, classify and discuss the major documentation gaps and their resulting regulatory impact. Unavailability of biocompatibility reports was found to be the most common gap (64%). Lack of technical documentation and ER/GSPR checklists closely followed (63% and 60%, respectively). Although lack of IFU remained relatively low (35%), lack of supportive evidence for claims included therein was noticeable. Deficiencies in V&V testing and PMS data were significant, with the quality and accuracy of PMS data being suboptimal in 60% of the projects. A total of 43% of the CER projects could not provide an updated risk management file at the outset. Only five projects provided all essential documents at the start, confirming that lack of critical documents is commonplace among manufacturers transitioning to the MDR.

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