Navigating EU MDR Article 117: EFPIA Industry Experience

Contents

1. About EFPIA

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the biopharmaceutical industry in Europe. With direct membership from 37 national associations, 38 leading pharmaceutical companies, and a growing number of small and medium-sized enterprises (SMEs), EFPIA aims to foster an environment that promotes innovation, discovery, and delivery of new therapies and vaccines for individuals across Europe, while also contributing to the European economy. EFPIA actively collaborates with key stakeholders, including industry representatives, Notified Bodies (NBs), the European Medicines Agency (EMA), and the European Commission, to optimize regulatory processes and improve outcomes for patients.

2. Executive Summary

This article explores the experiences of 14 EFPIA member companies regarding the European Medical Device Regulation (MDR)[1] for integral drug-device combination products (iDDC) over the past three years. It outlines the journey of these companies through the evolving regulatory landscape, highlighting both progress and challenges faced during the submission and assessment of their dossiers.

During this period, NB opinions (NBOps) were obtained for marketing authorizations or variations of iDDCs. Key challenges included the need for clarity regarding General Safety and Performance Requirements (GSPRs) and evidence for conformity of the GSPRs. This article underscores the importance of early engagement and proactive planning to streamline submissions.

Furthermore, it advocates for improved communication between NBs and the EMA to clarify roles and expectations. Enhanced collaboration among the EMA, the Medical Device Coordination Group (MDCG), and NBs is deemed essential for consistent guidance and expedited approval timelines.

Industry stakeholders emphasize also the necessity for a legislative framework that facilitates a joint Scientific Advice process involving NBs and the EMA/National Competent Authorities (NCAs).

This survey is only addressing the challenges within the existing setup in 2024 with no opportunities for scientific advice for iDDC and challenges with variations on existing products – challenging innovation in the EU. EFPIA sees a need for an improved governance with a single, integrated accountable body ensuring an EU harmonized interpretation of requirements for the iDDC.

In conclusion, fostering collaboration among industry stakeholders is crucial for overcoming regulatory challenges, enhancing patient outcomes, and improving the efficiency of the regulatory process for innovative therapies in the European market.

3. Introduction

Before the implementation of MDR, the evaluation of integral iDDCs was only done by the EMA or NCAs without specific guidance in place. Their review covered the drug and device component using the electronic Common Technical Document (eCTD) format, which continues to be the predominant approach by global regulators.

MDR's Article 117 introduced an amendment to the medicinal product Directive 2001/83/EC requiring a separate assessment of the device part of iDDCs to the relevant GSPRs. For the majority of new or modified iDDCs, a NBOp is required, adding another layer of complexity to the approval process.

The unpredictable nature of this process, with its varying timelines, uncertain scope, and lack of firm dates, contrasts starkly with the EMA's predictable timelines and poses a significant challenge for stakeholders. As industry embraces innovative technologies, including connected iDDCs integrated with artificial intelligence, NB capabilities must be available, and acceptable timelines must be met. A collaborative environment among industry stakeholders

[1] Regulation (EU) 2017/745

is crucial for addressing these challenges, improving outcomes for patients, and enhancing the efficiency of the regulatory process for innovative therapies in the European market.

When preparing a new application to the EMA, companies find that referencing the EMA's guidance documents [5], [6] is helpful.

Of all NBOps obtained in the last three years, approximately 39% pertained to prefilled syringes, 39% to prefilled autoinjectors, and 21% to other types of iDDCs.

Of the companies asked 31% had already applied for 1-5 NBOps and 69% more than 5 NBOPs.

3.1 Scope

In scope:

This analysis is based on a survey conducted among the EFPIA members regarding the current function of the NBOp system within the existing framework. The survey aimed to gather insights and experiences from the pharmaceutical industry concerning the operational aspects and challenges of the NBOp process under the MDR Article 117. The key areas of focus included:

The preparation and content of submission dossiers.

- The Notified Body review process.
- Company experiences and training related to NBOp submissions.
- EMA submission procedures.

Out of scope:

This analysis does not address the long-term structural concerns raised by EFPIA regarding combination products, perceived to limit innovation and development within Europe and challenge European competitiveness.

EFPIA is looking forward to the evaluation of the MDR and the subsequent discussions of the regulatory system.

3.2 NBOp process

The methodology employed in this article follows a defined process flow (see Figure 1). To comply with MDR Article 117, manufacturers compile and submit a dossier to a NB for review. After addressing any queries, the resulting NBOp is included in the medicinal product dossier for submission to the NCA or EMA.

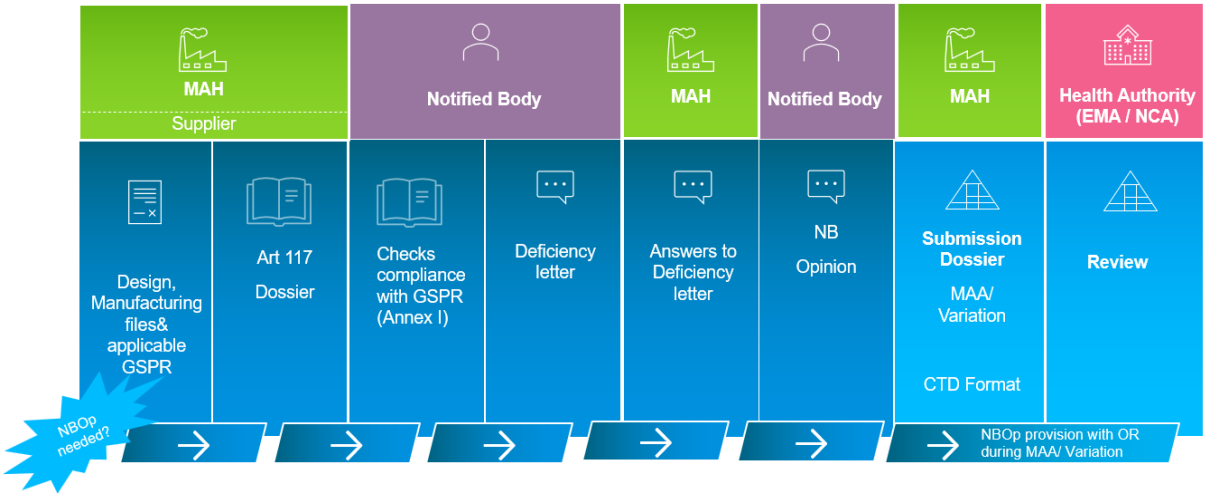

Figure 1 Process flow diagram

Initially, the company must evaluate if a NBOp is needed in case of a new iDDC or a change to an existing product. The latter depending on whether the change impacts the device component's safety and performance and/or significantly impacts the delivery or the quality, safety or efficacy of the medicinal product.

While EMA guidance [6] clarifies that modifications like indication extensions, new strengths, or pharmaceutical forms may not require a new NBOp if justifiable, confirming this strategy with the EMA, either informally or through a pre-submission meeting, is crucial for preventing timeline delays.

Notably, seeking feedback from the NB on this matter is not possible, as they tend to defer to the EMA or NCAs, cite Article 54 of the MDR or the Team Notified Body[2] (Team NB) Code of Conduct, which restricts their ability to consult.

If a NBOp is necessary, selecting an accredited NB is the next step. While New Approach Notified and Designated Organisations (NANDO) Information System lists 50 NBs accredited under MDR. However, not all of them provide Article 117 services EFPIA members typically select from a group of 4 commonly used NBs. This preference may come from having an established relationship, or business considerations such as the NB expertise, dedicated resources for review, and/or offering expedited review options.

Companies usually initiate contact with their selected NB approximately nine months before their planned NBOp submission. Most of these assessments relate to initial Marketing Authorization (MA) Applications (MAAs), with 92% of companies agreeing on a submission slot and established review timelines with the NBs. This ensures alignment with the EMA MA timelines, in which EMA has strongly recommended submitting the NBOp at time of submission, especially for short variations procedures. However, some companies prefer and have been successful with parallel reviews in which the NBOp is provided during the MAA review procedure. Misalignment of these timelines can lead to delays in the approval process, highlighting the need for proactive communication with the EMA.

To streamline the process, early discussions (e.g. project introduction; structured dialogue) with the NB is highly advantageous. These discussions facilitate collaboration and provide

[2] European Association for Medical Devices of Notified Bodies

early regulatory guidance, issue identification, improved submission quality, and efficient resource planning. Early planning is crucial for selecting the right NB, establishing contractual agreements, securing a submission slot for timely EMA submission, and involving suppliers early to support the creation of GSPR-compliant deliverables.

In cases of change variations, it is understood that a NB review may generate a complete new NBOp covering the full device.

4. Preparation and Content of Submission Dossier

The preparation of the NBOp submission package typically takes between six (61% of companies) to nine months (31% of companies), with only 8% planning more than 12 months for preparation. Companies report a good understanding of NBOp requirements and have allocated sufficient resources to adapt to the NBOp requirement. However, adopting a standardized format or developing specific recommendations for content for iDDC NBOp submissions would improve efficiency. This could be achieved by balancing technical documentation recommendations and aligning NBs practices specifically for iDDCs.

To clarify NB assessment requirements for combination products, EFPIA and Team NB held a collaborative meeting in January 2024. The meeting focused on addressing challenges faced by EFPIA members when preparing submission dossiers, specifically regarding engagement, process validation, GSPR applicability, labeling, and clinical evaluation reports. Further details are provided in the following sections.

Based on the feedback from NBs, summary reports alone are inadequate. The NBs request original device verification reports containing actual data for the review.

4.1 Relevant GSPR and NB consistency

Annex I of MDR provides a comprehensive list of GSPRs. Under the previous directives, this was known as Essential Requirements which were historically turned into a checklist or form, of which similar list exists globally for standalone medical devices. Manufacturers would then note which requirements apply and the method of conformity, often pointing to the document or section of the technical documentation.

For iDDCs, there is a recognized need for enhanced understanding of GSPRs during late-stage development. As Team NB reiterated, manufacturers decide and must justify which GSPRs apply to their products. However, companies face challenges due to inconsistencies in reviewer interpretations, even within the same NB such as:

- the identification and justification of applicability of requirements
- the applicability of GSPRs relating to wear, maintenance and calibration
- the interpretation of what “non-applicable” means in the context of the GSPR checklist
- the review of non-sterile products, where one NB required involvement of a specialized microbiologist
- interpretation of single-fault condition for single-use autoinjectors

4.2 Process Validation

In our discussion with Team NB, companies highlighted challenges in several areas. These included the content, justification and timely availability of device-related process validation data. Specifically, the challenges arise in areas such as process risk assessment (GSPR 1-4), packaging (GSPR 11, if sterile ensuring microbial state), and transportation (GSPR 6-7). For initial MAAs of iDDCs, process validation approaches may be divided between drug product and device parts related data and may not be fully available at the time of the NBOp submission. Acceptance of evidence justifying the "representativeness" of the intended commercial product and process would benefit companies, as supported by Team-NB. In addition, the ability to leverage established quality system processes for control and transfer to manufacturing, as well as some clear delineation of the NBs review versus EMA's, would be beneficial. Establishment of clear criteria and harmonization amongst all stakeholders would be helpful as companies still face challenges.

4.3 Labeling

Team NB confirmed that labeling falls under the medicinal product directive 2001/83/EC and is not within the scope of NB review. However, NBs expect evaluations regarding risk assessment, biocompatibility, sterility and risk assessments for CMR[3] substances like cobalt. Additionally, information about handling instructions included in the patient information leaflet for the product should be provided to NB to evaluate usability engineering/human factors aspects and warnings related to the device part.

4.4 Clinical Evaluation Report

Team NB also confirmed that a clinical evaluation report (CER) for an iDDC is not required unless there is a specific clinical or safety claim related to the device part.

However, still some companies are asked to provide a CER by some NBs.

4.5 Supplier Documentation

Another notable area for enhancement pertains to the provision of supplier information in the NBOp process. To demonstrate compliance with the relevant GSPRs, companies must include supplier documentation, but NBs have required documentation that exceeds typical design and development documentation.

Some suppliers have expressed a desire to establish a generic device file like practices of master files for devices to the US FDA. In addition, some suppliers insisted on direct interaction with the NB to address proprietary information on sterilization procedures, complicating the process. Conversely, other suppliers have proactively shared necessary information, facilitating the NBOp review process.

[3] substances classified as carcinogenic, mutagenic, or toxic for reproduction

The preparation phase has seen positive experiences with suppliers, who demonstrate a clear understanding of NBOp requirements and are responsive throughout the authoring and reviewing process. A robust Quality Assurance agreement between companies and suppliers has ensured timely and accurate information delivery. However, clearer instructions from the NBs regarding required information would enhance the process, especially as suppliers often have concerns sharing proprietary information. A confidentiality agreement is typically not required, as NBs adhere to stringent regulations and oversight concerning impartiality and confidentiality due to their designation (MDR Article 109). However, NB are willing to set-up these agreements, if explicitly request by suppliers.

5. NB Review Process

Companies provided feedback on their experiences with NBs during the review process, including BSI, TÜV SÜD Product Service, DNV GL, and DEKRA. While feedback was mainly positive, some challenges were noted.

Despite different portals and processes for uploading documentation, companies find them user-friendly. Most companies perceive the NBOp process as well-defined, with some helpful instructions on the NBs webpages, but with varying degrees of detail depending on the NB.

5.1 Review Rounds and Timelines

Companies typically undergo one to three review rounds, with overall review times ranging from less than three to up to 12 months, averaging about 5.6 months. Most companies (65%) require two rounds to address queries from the NBs. Some companies receive advance review schedules, aiding in setting expectations. NBs adhere to agreed timelines in 84% of cases, although discrepancies arise when companies use multiple NBs over time.

5.2 Review of Technical Documentation

Most companies find NBs approachable and supportive during the review phase. NBs are willing to clarify information requests and align on required evidence. However, as laid out in section 4.1. inconsistencies between different NBs were observed.

5.3 NBOp Report

Company review of the draft NBOp report before final issuance, as offered by NBs, is appreciated, allowing corrections of inaccuracies. Companies also prefer a concise report format e.g. as laid out in Team NBs position paper [10]. In some instances, with other regulators who recognize or follow EU's approach, a clear and concise determination that the product meets the relevant GSPRs would be sufficient, and not a full lengthy assessment report.

5.4 Company Experience and Trainings

Companies and NBs are on a learning journey regarding MDR Article 117 and the necessity of including an NBOp in the iDDC MAA dossier. Knowledge continues to build, with many companies initiating early engagement with trade associations, NBs, and consultants to achieve successful outcomes. While the development expectations and general deliverables have not changed dramatically, internal company training and awareness of this process have improved the understanding of GSPRs and related evidence, facilitating development and faster responses to information requests.

6. EMA Submission

In uncertain cases regarding the necessity of a NBOp, the EMA offers opportunities for clarification. Companies appreciate prompt responses to queries about NBOp requirements. In most of these cases companies received favorable responses indicating that an NBOp was unnecessary, provided a justification was included in the appropriate dossier section (Module 3.2.R). However, clearer guidance and alignment with other stakeholders such as Team NB is needed for consistency in addressing these queries The recent update to the EMA Q&A guidance [6] has proven helpful and is expected to be reinforced by the finalized Variation guidance [9].

Industry acknowledges that including the NBOp in the initial MAA or Variation application submission is best practice. Survey feedback indicates that 61% of submissions to the Health Authorities (HAs) included a NBOp already in the initial application. Instances of NBOps provided during ongoing procedures were predominantly linked to initial MAAs. Additionally, such cases were also reported for line extensions and Variation Type II procedures.

Overall, these reviews with the EMA/NCAs have proceeded smoothly, with few to no questions related to device functionality being raised by the HAs.

However, in addition to enhanced guidance, companies would greatly benefit from a designated communication channel, such as a dedicated email address or portal, for queries specifically related to NBOps. Industry stakeholders also emphasize the necessity for a legislative framework that facilitates a Scientific Advice process involving NBs and the EMA/NCAs with clear roles and expectations.

7. Conclusion

The experiences of EFPIA member companies with Article 117 of the MDR reveal both significant progress and ongoing challenges in the regulatory landscape for iDDCs.

- There is a critical need for enhanced training and awareness of the relevant GSPRs among all stakeholders.
- Industry stakeholders emphasize the necessity for a legislative framework that facilitates a Scientific Advice process involving NBs and the EMA/NCAs.
- Improved communication between NBs and the EMA is essential to clarify roles and expectations.

The drive towards innovative technologies, including connected iDDCs integrated with artificial intelligence, also intensifies concerns regarding NBs' capabilities to meet acceptable timelines. Evaluating these novel products efficiently requires not only specialized NB expertise but also reinforces the critical need for enhanced collaboration, proactive dialogue, and aligned guidance among EMA, MDCG, and NBs discussed earlier. Without such improvements, the current system may struggle to adapt, potentially creating bottlenecks for cutting-edge therapies. Enhanced interaction and collaboration among the EMA, MDCG, and NBs are vital for aligned interpretations and consistent guidance, which can reduce duplicative efforts and expedite approval timelines. Harmonised procedures and transparency, as requested by European Parliament in the resolution adopted in October 2024 on the need to revise the MDR and In Vitro Diagnostic Medical Devices Regulation (IVDR), are just as valid for iDDCs and the NBOp process [8].

Ultimately, fostering this collaborative environment among industry, NBs, and regulatory bodies is crucial for overcoming the outlined regulatory challenges, improving outcomes for patients, and enhancing the efficiency of the regulatory process for innovative therapies in the European market

8. References

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