Impact of MDR on Directive 2001/83/EC: What you need to know

White Paper

March 2021

ASPHALION

Introduction

The Medical Device Regulation 2017/745 (MDR)[1] has been out and about for almost four years after its entry into force in May 2017. This new legal framework has had a massive impact on the medical devices sector and, even though the different economic operators, notified bodies (NBs) and competent authorities had an extra year to get ready before it fully replaces the Medical Device Directive 93/42/EEC (MDD)[2] (after the date of application was postponed due to the COVID-19 outbreak by means of Regulation (EU) 2020/561[3]), there are still lots of uncertainties regarding the implementation of several of its articles.

Such is the case of **Article 117**, amending Directive 2001/83/EC (MPD)[4] on medicinal products for human use, which **introduces new requirements for integral drug-device combinations (DDCs)**. Mainly, this article indicates that marketing authorisation application (MAA) dossiers for medicinal products (MP) integrally combined with a medical device shall include proof of conformity of the device component with its applicable requirements as per Annex I of MDR. Depending on the device risk classification, this proof of conformity could either be a signed *EU Declaration of Conformity* or a *CE Certificate* issued by a NB, where available. For devices of risk class higher than Class I for which a *CE certificate* is not available, a report with a **Notified Body Opinion** proving conformity of the device component with its requirements shall be obtained before the MAA dossier is submitted for evaluation to the Competent Authority (CA). But what are the ins and outs of this report? How will this process be handled, and what will be the impact on the maintenance of the Marketing Authorisations (MA)?

This White Paper is aimed at clarifying the principal points that should be taken into account by Pharmaceutical Companies with regard to their integral DDCs while preparing the MAA dossiers or maintaining the granted licenses during life-cycle management in Europe. In order for the industry to be aware of the evolution of the implementation of Article 117, this White Paper reflects the critical aspects of MDR Article 117 that have not yet been clarified by the CAs and NBs.

Affected drug-device combinations

First, it is important to identify which DDCs are affected by Article 117. As indicated therein, the change affects the two groups of integrally combined products. The first group would include all those cases where the medicinal product component is driving the principal mode of action of the combination, as described in **Article 1(8)** of MDR. On the other hand, the second group, described in **Article 1(9)** of MDR, would include those cases of integral combinations where the device component is providing a drug delivery action, such as inhalers, pre-filled syringes or transdermal patches, as long as the device component is specific for the administration of the medicinal product in the given combination and is not reusable (Figure 1). It should be noted that Article 117 does not apply to combined advanced therapy medicinal products, neither to already authorised integral DDCs falling in either one of the two categories.

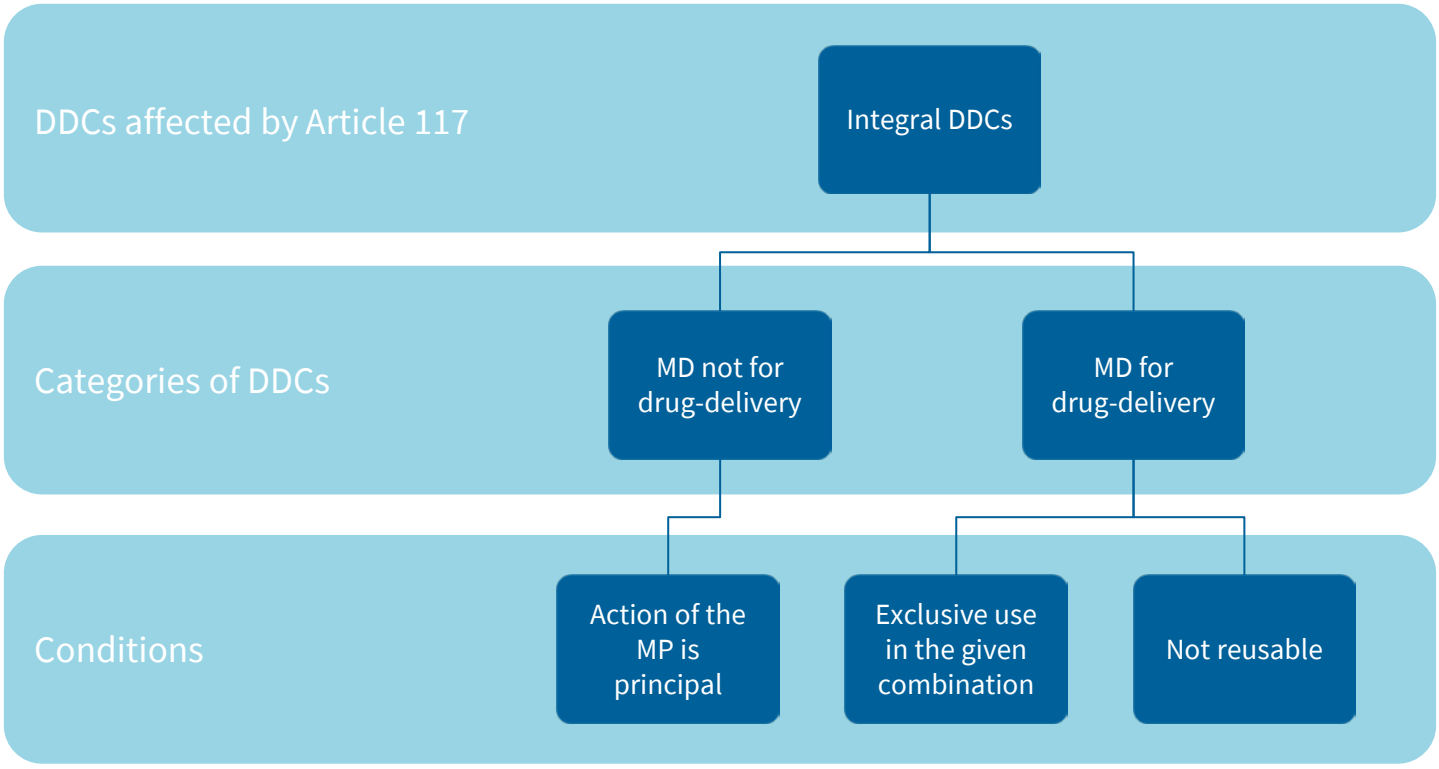

Figure 1 | Integral DDCs and conditions for them to be affected by Article 117.

The notified body opinion

Now that we have identified the affected DDCs, let us analyse more in depth one of the major changes brought by Article 117: The **Notified Body Opinion (NBOp)**. The **NBOp** replaces the CE Certificate for the device component of an integral DDC for which no CE Certificate has been issued by a NB and that would require the NB's assessment if placed as an independent product on the market; that is, devices of risk higher than class I (including Class I which are sterile, with measuring function and/or reusable surgical instruments) without a CE Certificate (Figure 2).

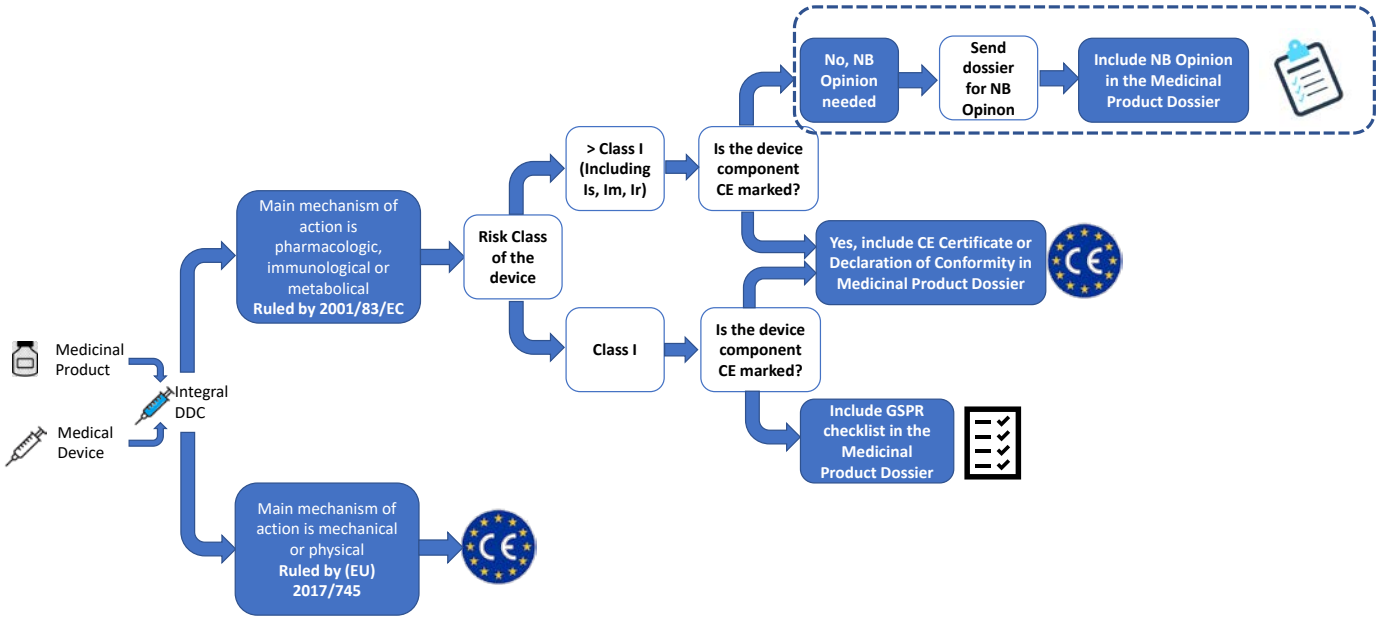

Figure 2 | Demonstration of conformity to requirements of the device component depending on its risk class and certification status.

The **NBOp** is a report obtained from a NB after an assessment of documentation regarding the medical device component of the integral DDC for which a MA will be requested, **indicating if the device fulfils all the applicable requirements**. In order to obtain this **NBOp**, it will be necessary to prepare a **dossier** and submit it to the NB. This dossier shall also include a detailed explanation of the DDC's intended use and users, so that the relation between device component and overall DDC is clear to the NB. Additionally, it shall include in-depth data related to the device component, including: description and specifications, design and manufacture, risk assessment, verification data of relevant safety and performance attributes, instructions for use (IFU) regarding the use of the medical device component and, of course, the list of applicable general safety and performance requirements (GSPRs) and relevant technical standards followed to demonstrate conformity, among others (Figure 3). Gathering all this information on the medical device component typically involves several departments of different companies, including R&D departments from the applicant's Company in charge of producing relevant design documentation related to the DDC, as well as relevant departments at the supplier's company, as the device component is often manufactured by a third party.

It shall be noted that the NB will only check that the device component is compliant with its applicable GSPRs, and not quality, safety or efficacy aspects of the assembled combined medicinal product (DDC), as this assessment shall be performed by the medicines' CA.

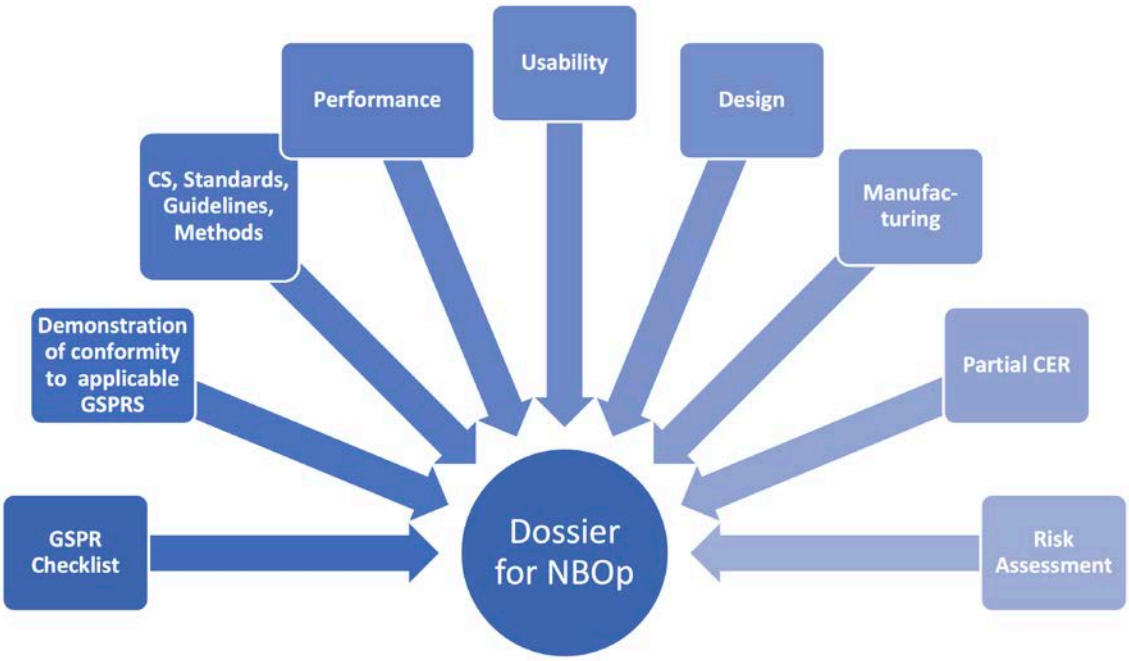

Figure 3 | Content to be included in the dossier for Notified Body Opinion.

The process of obtention of the **NBOp** can take between 2 to 6 months, depending on the quality and completeness of the information provided to the NB and the timelines established by each NB, among other factors. Therefore, preparing a high-quality dossier is key to ensuring a short review process. It is also important to follow best regulatory writing practices to ease as much as possible the evaluation of the data by the reviewers. Particularly, it is recommended to present the dossier in Summary Technical Documentation (STED) format, providing the files fully legible and easily searchable without any kind of access protection.

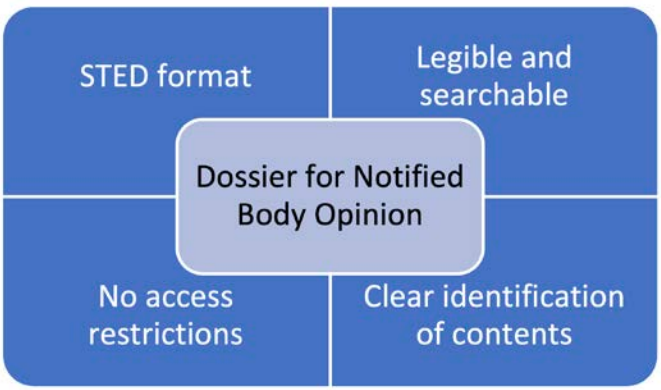

Figure 4 | Recommendations on Dossier for Notified Body Opinion.

The overall process for the obtention of the NBOp will follow the steps depicted in Figure 5: after quotation and contract processing, the dossier on the device component will have to be delivered by the Marketing Authorization applicant to the selected NB. Upon a preliminary review of overall completeness of the provided dossier, this NB can ask for further information on missing sections, activating a first clock-stop. Once all the necessary documentation has been provided by the applicant, the NB will start the assessment of the dossier. This will lead to a cyclic step of questions and answers, which may be repeated until the NB is satisfied with the responses received by the applicant, implying a second clock-stop. Once the questions are duly answered, the NB will issue the NBOp.

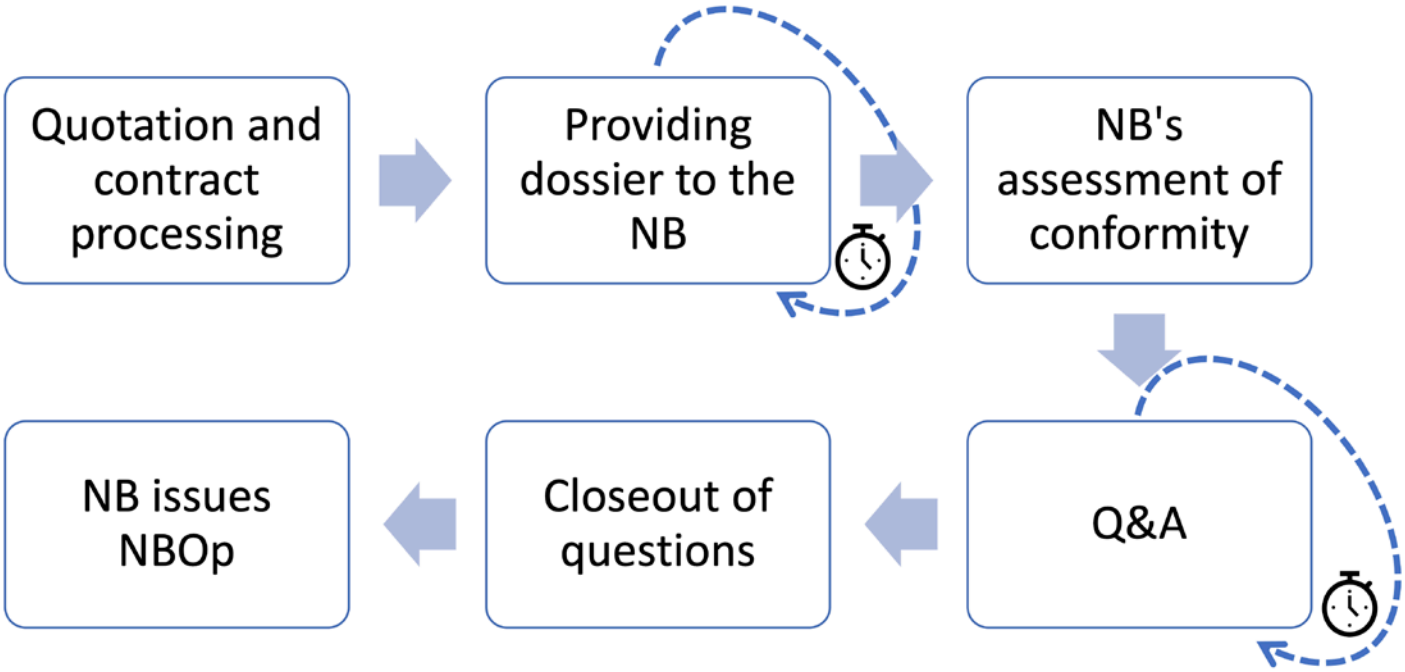

Figure 5 | Process of obtention of the Notified Body Opinion.

As indicated in EMA's Questions and Answers on Implementation of MDR and IVDR[5] the **NBOp** should be included in Module 3.2.R of the initial MAA dossier for the medicinal product. Thus, the request of a Notified Body Opinion should be planned well in advance of the time when the submission of the initial MAA is foreseen.

Since the CA in charge of evaluating the integral DDC will rely on the assessment of the device component performed by the NB, the **NBOp** will not only include a general statement of compliance of the device with the applicable requirements but also particular concerns and comments on specific critical points regarding the device component for the CA to assess. It will be the CA who will decide whether the critical points are indeed critical and will take special consideration when reviewing the MAA.

The **NBOps** issued until now show that NBs do not have a clear idea of how much detail they should contain (some are 30 pages long and others 120 pages long); consequently, *Team NB* aiming to harmonize this situation will soon publish a **NBOp** template for all NBs to use.

Life-cycle management

Even though Article 117 of MDR has no retrospective effect on the already marketed integral DDC products (i.e. it is not necessary to submit **NBOps** for non CE marked devices of integral DDCs which are already on the EU market), it must be taken into account that substantial changes to the design or intended purpose of the device component in the integral DDC will require of either a renewed *CE Certificate* (where risk class of the device is higher than I), or a renewed **NBOp**[5] to be submitted as part of the variation package.

Nevertheless, if no changes are made to the device component, the **NBOp** has no expiry date *per se*.

However, what is the definition of substantial change? According to EMA's Questions and Answers on Implementation of MDR and IVDR[5], a change to the device component is considered substantial "*if it affects the performance and safety characteristics of the device*". On the other hand, according to the recently published *Team NB* position paper on the interpretation of device related changes in relation to a **NBOp**, a change to the device component should be deemed substantial when it has an impact in terms of device safety or performance, compliance with the relevant GSPR(s) or device related claims and intended use. Moreover, *Team NB* Position goes even further indicating that changes to the medicinal product (for instance, changes to volume or viscosity) should also be assessed as potentially substantial with regard to device compliance with GSPRs, as these may also have an impact on the safety or performance of the device component.

Although there is still no agreement on the definition of substantial change by Medicines Competent Authorities and NBs, one thing is clear: the responsibility to decide whether a change introduced to the device component (either direct or indirect) is substantial or not lies with the Marketing Authorization Holder (MAH), and therefore also does the decision of requesting a new **NBOp**. In order to ease the decision-making process of whether or not a change to the device (or medicinal product) is substantial or not with regard to the compliance of the device component, *Team NB*'s position paper provides six different flowcharts which can help making a final decision regarding the weight of a change from a NB's perspective.

Impact on the dossier for medicinal products

The amendment of the MPD by Article 117 of MDR brings about additional challenges with regard to structure and content of the dossier of the DDC as a MP. Although currently at draft stage, in June 2019 *EMA* published a "Guideline on the quality requirements for drug-device combinations"[6], which specifically indicates what information related to the device component of the integral DDC should be included in each section of the MAA dossier of the MP.

In particular, according to this draft Guideline, the already mentioned proofs of device conformity (*EU Declaration of Conformity, CE Certificate* or **NBOp**), should be included in section 3.2.R, and additionally several aspects of the DDC should be addressed within the dossier of the medicinal product. For instance, description of the DDC, details on its manufacturing process or stability data on the device are points that shall be included in the information of module 3.2.P, among others (see Table 1 for more details).

Section of the Dossier	Information to include
1.3 Product information	Summary of Product Characteristics (SmPC) • Section 1: the name of the MP should include the device presentation in line with EDQM standard terminology for pharmaceutical form. • Section 4.2: directions for proper use of the DDC should be described. A device tradename may be stated. • Section 6.3: Information on DDC in-use shelf-life, if relevant. • Section 6.4 DDC storage conditions. • Section 6.5: type of device and its component materials. • Section 6.6: product-specific information for preparation or handling, including disposal. Package Leaflet • Information consistent with the SmPC. • Clear and simple instructions on the intended use of the DDC. • Information related to the use of the DDC consistent with the Instructions for Use (IFU). Package leaflets and labels • May only include symbols or pictograms if necessary, to clarify information compatible with the SmPC which may be useful for the patient. • CE mark should not be included on the labelling for the DDC.
3.2.P.1 Description and composition	3.2.P.1 Description and Composition • Brief description and function of the device(s).
3.2.P.2 Pharmaceutical development	3.2.P.2 Pharmaceutical development • Information relevant to development of the device as integrated into the medicinal product including the rationale for its selection. • Suitability of the device for its intended use (device performance and medicinal product protection). • Any interaction of the device with the medicinal product should be discussed and justified. • A risk assessment summary for the DDC based on the principles detailed in ICH Q9 and/or DIN EN ISO 14971 is recommended. 3.2.P.2.1 Components of the Drug Product • High-level description of the DDC including cross-references to relevant sections. 3.2.P.2.2 Drug Product • Intended used and suitability of the device within the context of the DDC, therapeutic indication and relevant target patient population should be regarded. • Summary of device development with cross-reference to relevant data (M4 and M5), where required. • Equivalence of the overall performance of DDC prototype(s) used during pivotal clinical development with the DDC indented for marketing, where appropriate. 3.2.P.2.3 Manufacturing Process Development • Brief description of the DDC manufacturing process development. • Description of development, justification and suitability of sterilization processes of any devices or DDC, where relevant. • Comparison of manufacturing process of DDC from clinical studies to commercial DDC. • Description of the development of the control strategy for the DDC manufacturing process. 3.2.P.2.4 Container Closure System (CCS) • Description and Rationale for DDC o Brief description of the CCS including the rationale for all container and device components and materials of construction. o Brief details of critical functional components and brief description and rationale for any related technologies.

	○ If the device includes a graduation marking, the requirements of Quality of Medicines, Q&A on the EMA website should be considered. • Functional Performance ○ Dose accuracy and precision, mechanical functionality and/or functionalities directly related to the intended use of the device with the medicinal product and its impact on quality, safety and efficacy should be considered. ○ Precision and accuracy of dosing should be demonstrated throughout the shelf life (beginning, middle and end) and under the conditions recommended in the SmPC (in-use). ○ In-use stability studies should be designed to demonstrate accurate and reproducible drug delivery as per the posology stated in SmPC by simulating the use of the DDC (various orientations) under relevant storage conditions. ○ Usage studies should be provided (shaking, priming, dropping test, etc.). • Compatibility between Device and Drug Product ○ Physical and chemical compatibility should be assessed based on interaction studies (extractable and leachable, sorption, precipitation of drug substance in solution, stability, etc.). Any material and processing aids in direct contact with the drug product should be considered. ○ Toxicological assessments of processing aids in direct contact with the drug product should be performed. ○ Compatibility from a chemical and physical stability perspective (different orientation, in-use conditions and during simulated transportation studies). ○ Suitability of the device for the drug product (rheological properties of the DP) should be discussed and justified. 3.2.P.2.5 Microbiological Attributes • For sterile product, the integrity of the DDC throughout use and shelf-life, as it relates to preventing microbial contamination should be demonstrated.
3.2.P.3 Manufacture	3.2.P.3.1 Manufacturers • Manufacturer names/addresses for DDC assembly, packaging, DDC sterilization, labelling and quality control sites, as well as for the EU batch release site(s). 3.2.P.3.3 Description of manufacturing process and process controls • Description in detail of operations relating to the combination of device(s) and drug product, critical processes, technologies and/or packaging operations that directly affect product quality. • Description of any operation performed on the devices by the DDC manufacturer (subassembly steps, washing, coating, sterilisation, dehydrogenation, etc.). Information on the sites should be presented in this section or in section 3.2.P.7. • Description of the filling steps and final assembly of the device into the DDC, critical process parameters, in-process controls and acceptance criteria for critical steps. • Position of applied labels which include printed markings on the container should be specified and acceptable tolerances for label positioning defined as critical in-process controls (IPCs) in sections 3.2.P.3.3 and 3.2.P.3.4. 3.2.P.3.4 Control of critical steps and intermediates • Critical steps and any holding time should be defined and justified. • Any device-specific intermediates should be defined along with specifications, test methods and their validation. 3.2.P.3.5 Process validation and/or evaluation • Assembly and sterilisation of the device(s) (if applicable) and any filling steps should be covered in the process validation for the manufacture of the DDC.

3.2.P.5 Specification	3.2.P.5.1 Specification(s) • Description of DDC appearance. • Performance tests relevant to the intended use of the DDC. • Other critical test parameters related to Critical Quality Attributes (CQAs) of the DP.
3.2.P.7 Container Closure System	3.2.P.7 Container closure system *(where the device is part of the container closure system)* • Description of the CCS including materials of construction of each primary packaging and device component. • Specifications and test procedures (description, identification and functional tests), critical dimensions, technical drawings and photographs of primary and functional secondary packaging materials. Secondary packaging should be designed with consideration to the use and mechanical resistance of the DDC. • Information on sites and processes for sterilization and/or subassembly of device(s), or reference to section 3.2.P.3. For purchased empty, sterile, ready-to-use components, information in line with the EMA Sterilisation guideline or reference to the NB Certificate of Conformity for CE-marked devices should be provided. • Evidence of compliance with the Ph. Eur. monographs and/or food contact directives, as appropriate.
3.2.P.8 Stability	3.2.P.8 Stability • Functionality tests (dose delivery per actuation, syringeability, communication with software, etc.). • In-use stability testing performed under conditions of use as stated in the SmPC. Effect of storage orientations should be considered. • Microbial quality, sterility, content/potency and purity for the entire shelf-life and in-use period, as appropriate. • Simulated transport studies that encompass chemical (degradation) and physical (vibration) stability, where relevant.

3.2.R Regional Information	• Index with cross references to studies or information provided in 3.2.P or M5.
	• Demonstration of compliance of the device component with the applicable GSPRs, depending on the certification status and classification of the device:
	  ○ CE marked devices: EU Declaration of Conformity issued by the manufacturer or Certificate of Conformity issued by a NB (if available).
	  ○ Non-CE marked Class I devices: Applicant's confirmation that the device component meets the GSPRs.
	  ○ Non-CE marked devices with class higher than I (including sterile, with measuring function or reusable): NBOp.
	  (See Figure 2).
	• Summary on Usability Studies (with cross reference to full information on M5).
	• Discussion and justification for the use of platform technology

5.3 Clinical Study Reports	• Usability Studies (with a summary in 3.2.R)

Table 1 | Summary of data requirements on the device component to include in modules 1, 3 and 5 of iMAA for integral DDCs.

Conclusions

Taking into account that the countdown for the full implementation of MDR has already started, MAHs of integral DDC should already be assessing how this regulation is going to impact their products and what measures they will have to undergo to be ready for the new scenario. Mainly, they should be focusing on preparing the dossier for the NBOp (in case of a new authorization or if major changes are being performed to the device component of already authorized DDCs, as long as the device component is not CE certified by a NB), and on ensuring whether all the relevant information related to the device component that should be included in specific modules of their integral DDCs MAA dossiers is available and has been appropriately added.

References

1. REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. (2017).
2. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices. (1993).
3. REGULATION (EU) 2020/561 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 23 April 2020 amending Regulation (EU) 2017/745 on medical devices, as regards the dates of application of certain of its provisions. (2020).
4. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. (2001).
5. EMA. Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746). (2019).
6. EMA. Guideline on the quality requirements for drug-device combinations (Draft). (2019).

Asphalion Expertise

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Asphalion collaborates with Pharmaceutical, Biotechnological and Medical Technology organizations facilitating product development and regulatory affairs solutions for their projects.

Asphalion has extensive knowledge on medical devices and closely monitors every new and movement around the MDR and its accompanying guidance documents in order to be able to better advise and guide manufacturers, developers, regulatory affairs experts, entrepreneurs, and other professionals stakeholders on their implementation.

If you have any questions do not hesitate to contact us!

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