



Drug-device combination products

Navigating regulatory challenges
and pitfalls in the EU

1 Introduction

Drug-device combinations (DDCs) are products that include both a medical device and medicinal product constituent part.

There are two main types of combination products:

- ▶ **Integral:** The medical device and medicinal product form one single integrated product.
- ▶ **Co-packaged:** The medical device and medicinal product are separate items packed together in the same secondary packaging.

In the EU, combination products can be regulated under either the Medicinal Product Directive (Directive 2001/83/EC)¹ as a medicinal product or the Medical Device Regulation (2017/745; MDR)² as a medical device.

For co-packaged combination products, the medical device and the medicinal product are regulated individually under their respective regulations. However, for integral combination products, the regulation that will govern the combination product is determined based on the product's principal mode of action.

Integral combination products are regulated as medicinal products in the cases where:

- ▶ The action of the medicinal product is principal and not ancillary to that of the device.
- ▶ The device is intended to administer a medicinal product, and the two constituent parts form a single, non-reusable integral product.

Combination products that fail to meet either of these criteria are regulated as medical devices.

The types of DDCs within the scope of this paper are single integral combination products. These include medicinal products presented in devices such as prefilled syringes, dual-chamber syringes and autoinjectors/pens.

With the introduction of the MDR in May 2021, replacing the previous Medical Device Directive (93/42/EEC; MDD), the requirements that combination product manufacturers must fulfill have undergone significant changes.

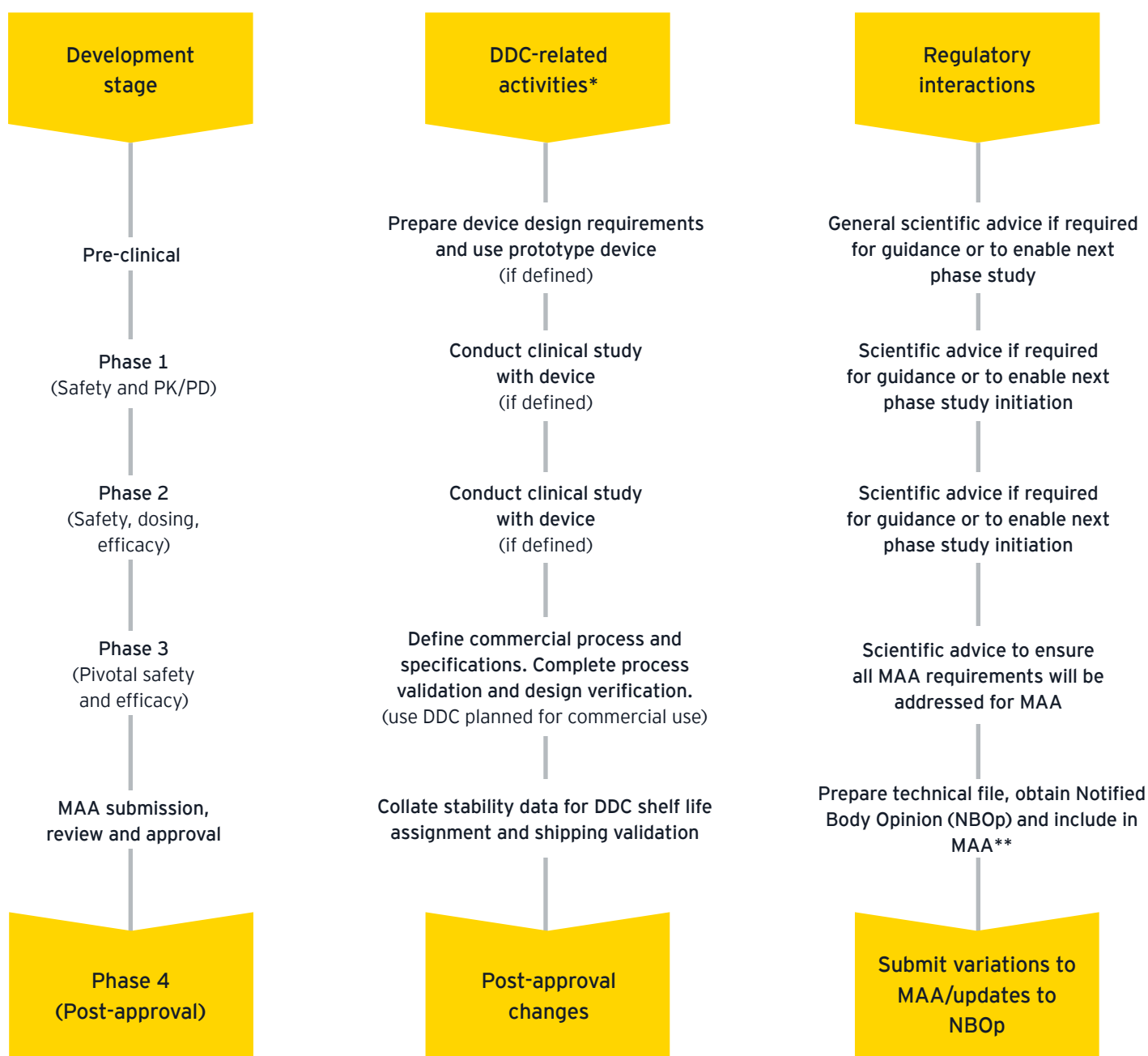
Previously, to obtain approval for an integral DDC wherein the primary mechanism of action was via the medicinal product, the applicant was required to submit a marketing authorization application (MAA) in accordance with Notice to Applicants v2b³. Information on the device and combination aspects of the DDC was described within the MAA, usually at a high level.

Under the MDR, a separate opinion from a designated notified body (NBOP) will need to be obtained and included within the MAA submission. This represents a significant investment of time and resources for a step now on the critical path to approval. If not addressed correctly, the process may directly impact the costs and time to approval.

This paper outlines the authors' overall process and real experiences. It highlights common pitfalls and how to avoid them – through case studies and mitigation strategies to give drug developers the best chance of success.

2 Overview of DDC-related activities and regulatory interactions

It is recognized that drug development is performed on a case-by-case basis and that there is no single approach for development and approval that can be applied for all products. However, to aid the upcoming discussion for illustrative purposes, a general approach has been applied. The key DDC requirements, a general overview of the drug device-related activities and associated regulatory interactions are summarized below.



* Human Factors/usability study to be initiated prior to any clinical implementation of the DDC.

** It is strongly recommended to submit the NBOp in the dossier of the initial marketing authorization application. If the required documentation cannot be provided at the time of MAA submission, the relevant documents must be provided before an opinion on the medicinal product application can be issued. The approach should be discussed in the EMA pre-submission meeting. Note that the absence of the required documentation may result in additional clock-stops during the MAA review procedure.

3 When do you need to obtain a NBOp for your DDC?

For a medical device to be placed on to the EU market, the device requires CE marking to affirm that the product complies with all the relevant medical device regulations regarding safety and performance.

For integral DDCs regulated as a medicinal product, the MDR has introduced the applicable Article 117. Under this article, manufacturers of integral DDCs must CE mark the device constituent part of their DDC and include the relevant documentation in their marketing authorization dossier.

However, if the device constituent part does not have a CE mark, the manufacturer must provide an opinion of the conformity of the device part with the relevant general safety and performance requirements (GSPRs) issued by a designated notified body. This includes the device element of a medicinal product – when integral (classified either as Class I [i.e., sterile], Class IIa, Class IIb or Class III), non-reusable and intended exclusively for use in the given combination. Moreover, submissions to European regulators for a DDC now need to include usability data, and a Notified Body (NB) will review the device component. Integral devices classified as Class I devices (i.e., non-sterile) are not subject to an NB opinion⁴.

The GSPRs of Annex I of the MDR lay out the requirements that devices must meet to state compliance to the MDR and are the backbone for establishing conformity to the regulation. GSPRs cover specific requirements related to risk, performance, design and manufacturer, and labeling and instructions for using the device.

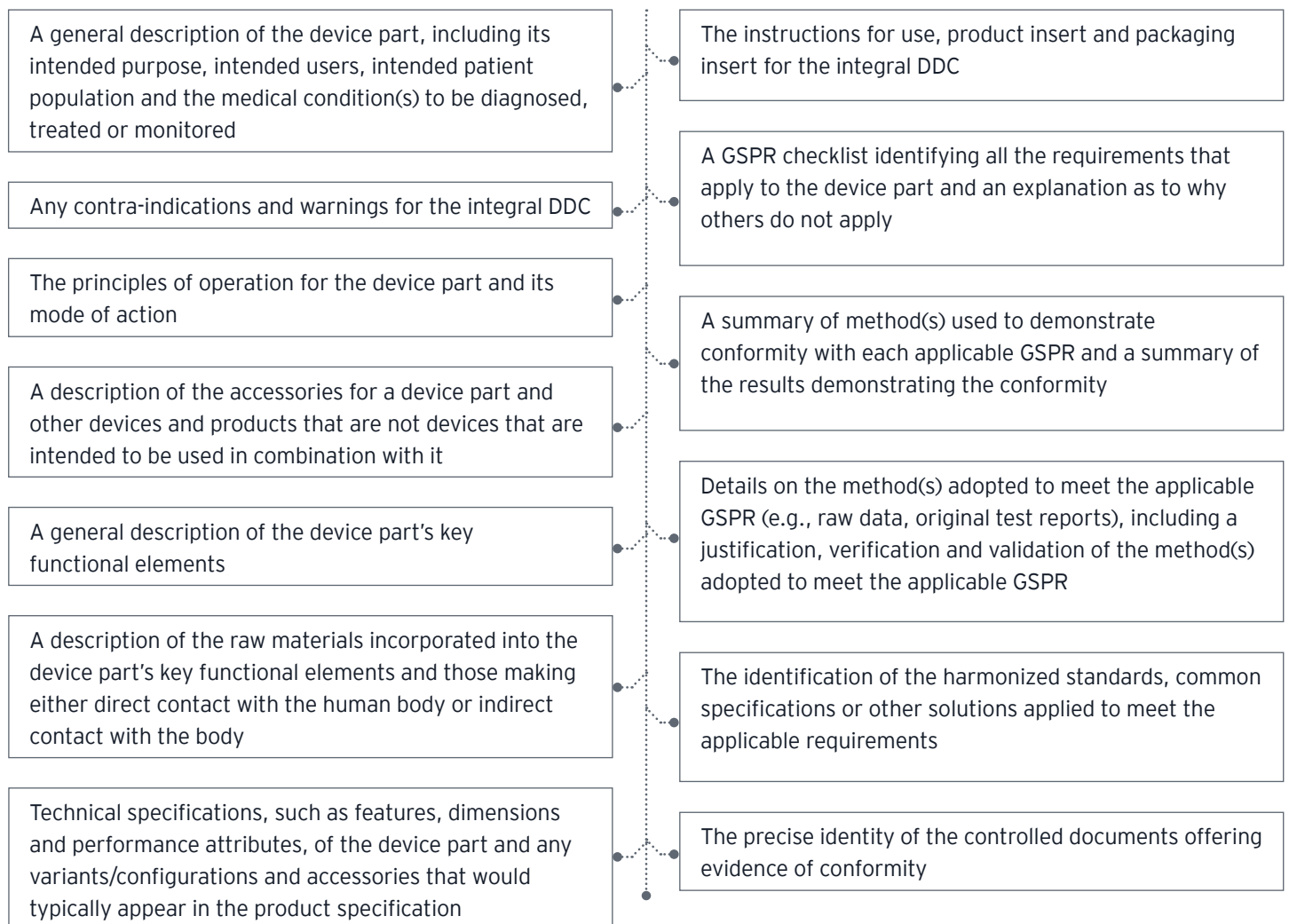
Manufacturers must ensure they have identified all the relevant and applicable GSPRs for their combination product and have a sufficient level of evidence to demonstrate that the requirements have been met.

It is important to note then when identifying the applicable GSPRs, the focus should not only be on the device part but also on that part's interoperability and compatibility with other devices, products or substances.



4 What should you include in your NBOp submission?

A full technical file as described in Annex II of the MDR is required for CE marking of medical devices. A full technical file is not required for an NBOp, but a significant amount of documentation will still need to be prepared. Team-NB has provided guidance on the structure and content of the submission file⁵. Based on the guidance, the submission file should contain the following:



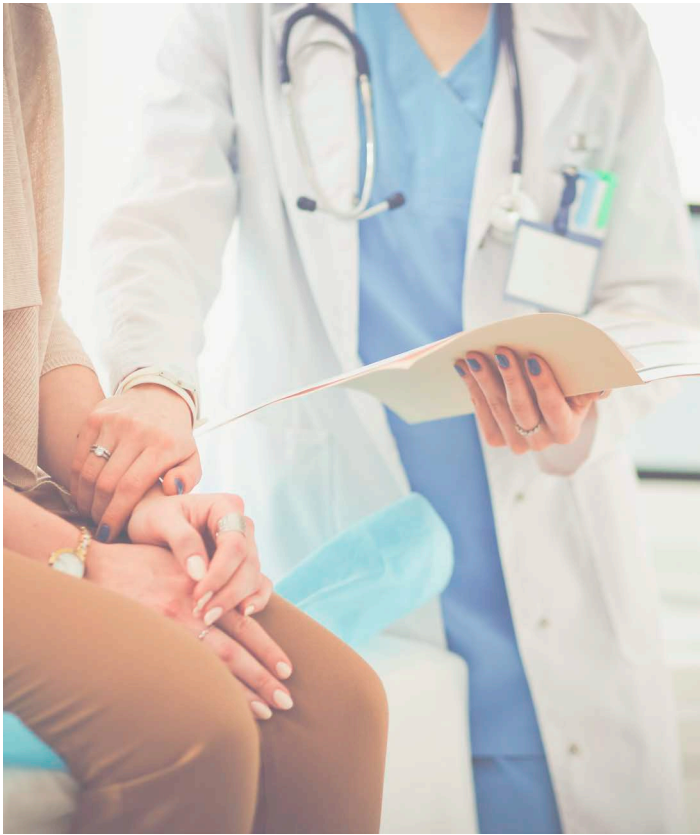
In many circumstances, integral DDC legal manufacturers use suppliers or subcontractors to design, develop and manufacture the device constituent part. This can introduce several challenges and delays when preparing your NBOp submission. For instance, the supplier holds most of the information needed to prepare the submission and does not want to provide full access to their data due to confidentiality reasons, commercially sensitive data or the supplier is slow in providing the information needed for the submission. It is imperative to have contractual agreements

and robust supplier management processes in place that clearly define data sharing arrangements, roles and responsibilities and timelines between both parties for developing the NBOp submission.

In cases where your supplier or subcontractor is unwilling to share the necessary technical data directly with you, you may be able to agree with both your NB and supplier to allow your supplier to share the data directly with the NB.

5 Under what circumstances would you need to submit a new or updated NBOp?

If you make a substantial change to your product that could affect the performance and safety characteristics of the device part or the intended use of the device, consider when MAA variation would be required and when NBOp would need to support the change and maintain registered information (i.e., notification vs. prior approval/Type II). Regardless, all changes will require internal management of change governed by MAH QMS as per EU cGMPs and ICH Q10 requirements.



NBOp submissions can require a significant amount of time and resources to prepare. Therefore, they require sufficient planning to minimize delays to the EMA variation application, especially in scenarios where you may have multiple integral DDCs requiring a new or updated NBOp at the same time.

We recommend manufacturers consider the following activities to make the process more efficient:

- 1** Map out all planned and upcoming changes to the device constituent parts for your integral DDCs to know when the change is expected to occur. This will make it easier to plan for when an NBOp may be required.

- 2** For each change, assess whether the change would be considered significant or substantial and necessitate an NBOp. NBs cannot advise or provide consultation to manufacturers on whether a specific change requires an NBOp. MDCG has provided guidance on significant changes, which is a useful source for helping to decide on the impact of a planned change⁶. You should also consider incorporating this process into your QMS to ensure standardization and consistency when carrying out this assessment.

- 3** If you use a supplier for the device constituent part of your integral DDC, you should make sure that you have contractual agreements in place to ensure an appropriate level of communication and action regarding changes to the device.

6 What should you consider when selecting a NB to issue your NBOp?

The introduction of the MDR brought about more stringent requirements for NBs to meet to get their designation. As a result, the number of NBs designated for medical device certification has reduced to less than half (currently 23 MDR-designated NBs) compared with the number available for the MDD.

When selecting a NB to issue an NBOp, consider several factors:

Is the NB designated to provide services for your device class? NBs have a designated scope of devices that they can provide service for. NBOG codes are assigned to different device classes and are used to determine the scope of the NB's designation. An integral DDC manufacturer should determine the codes that apply to their device part and verify that the prospective NB is designated for those codes.

Does the NB have experience with providing NBOps? As NBOp is a new requirement, the experience that NBs have with them may be limited. Therefore, to ensure a more frictionless process, it will be important for an integrated DDC manufacturer to understand the NB's experience when undergoing its selection process.

Do you have existing relationships with the NB? Due to the reduction in available NBs, the workload for the remaining NBs has increased significantly. As a result, many NBs face significant backlogs and are limiting the number of new customers they take on. Where possible, it may be advantageous for an integral DDC manufacturer to leverage its existing relationships.

How much is the NB charging to provide the NBOp, and is it within your budget? As NBs are independent organizations, the cost for their services, including an NBOp, varies from one NB to another. An integral DDC manufacturer should obtain quotes from a variety of prospective NBs to ensure that the cost is acceptable based on the service provided.

What are the NBs' proposed timelines for the NBOp process? NBs will have different estimated timelines for the NBOp process. For example, BSI has stated that their estimated timelines are six to nine months, and they do not offer expedited service. Therefore, it is important for an integral DDC manufacturer to plan ahead when it comes to NBOps to minimize the impact that these timelines could have on the overall MAA submission.

It is useful to note that you do not need to use the same NB for all your NBOps. However, securing a NB will require extensive vendor management activities that may further burden the manufacturer. Therefore, if you know that you will require several NBOps for multiple integral DDCs, it may help to agree upfront with a single NB for them to carry out the work and then plan the activities accordingly.

Streamlining the NBOp process as much as possible will be key. Additionally, some NBs may offer pre-submission meetings to agree on timelines and the level of documentation they will require for their review, which could help to accelerate the overall process.

7

What device-related information needs to be included within your MAA?

The content of the MAA should be as described in Notice to Applicants v2b. The device-related information requirements have been recently clarified and should be further aligned

with the EMA Guideline on Quality Documentation for Medicinal Products when used with a Medical Device (July 2021)⁷.

Manufacturing process

The manufacturing process for medicinal products should be in accordance with GMP and described in sufficient detail within the MAA.

Case study

During the review of the MAA, the agency requested further detail on the DDC assembly process. The entire process description section (3.2.P.3.3 Description of Manufacturing Process and Process Controls and 3.2.P.3.4 Controls of Critical Steps and Intermediates) had to be rewritten within a short period. Further to this, during the preparation of the content, it became apparent that no controls were in place for room-temperature operations for this temperature-sensitive product.

Mitigation strategy

Ensure that the manufacture of the DDC is described in sufficient detail to allow the reviewers to understand the process and controls. Include how the components are verified as suitable for use upon receipt, how each assembly step is performed (including whether manual or automated) and how the success of each step is measured. Describe the analytical procedures in place for controls. For temperature- or light-sensitive products, describe the controls in place to ensure controlled exposure to temperature and light.

Controls

Suitable specifications for the finished product DDC should be defined. These should include essential performance requirements, and the acceptance criteria should be assigned based on industry standards, available release and stability data, experience and the target population.

Case study

The specifications for self-administration were not suitable for the target population (unwell patients with reduced strength).

Mitigation strategy

Specification assignment should account for the target population administering the product.

Validation

Evidence that the manufacturing process is robust and capable of consistently manufacturing the DDC to the required quality should be included in the MAA.

Case study

Upon MAA submission, data supporting the validation of drug manufacture was included; however, validation data for the integral DDC assembly was limited and referred to data generated during process development. During the review, the agency requested validation data for the complete process (including the DDC assembly) was provided.

Mitigation strategy

Ensure process validation activities include the complete manufacturing process, including DDC assembly. In some cases, alternative approaches to the traditional three consecutive batches have been agreed upon. If such an approach is planned, then it is advised this is agreed with the agencies in scientific advice before MAA submission.

Stability

Sufficient data to support shipment parameters, shelf-life assignment and in-use procedures of the DDC should be described within the MAA.

Case study

A product presented in a vial, prefilled syringe and autoinjector was submitted for approval. The applicant requested to assign shelf life based on development data and what they had determined as the worst-case presentation. The applicant was requested to generate real-time stability data on all presentations for shelf-life assignments during the review.

Mitigation strategy

Shelf-life assignment should be based on real-time data from each major presentation. If an alternative approach is planned, it should be supported by a risk assessment and agreed upon with the agencies before MAA submission.

8 What key considerations should you factor into your vigilance activities for your DDC?

For integral DDCs regulated as a medicinal product, the device vigilance requirements of the MDR are not applicable, nor is the requirement for details of the device constituent part or the manufacturer to be included in EUDAMED.

Although manufacturers should still follow the applicable pharmacovigilance requirements, it is recommended that integral DDC manufacturer has the technical knowledge and processes built into their QMS for handling, evaluating and investigating, where necessary, all device-related complaints.

It will also be important for integral DDC manufacturers to review their pharmacovigilance agreements with suppliers to ensure that they take into consideration additional data that may need to be collected and communicated, such as device malfunctions and device-related events.

9 What labeling and UDI requirements are applicable for your DDC?

For integral DDCs regulated as medicinal products, the labeling and UDI requirements of the MDR are not applicable. Therefore, a device-part-related UDI should not be applied to the packaging or labeling of the integral DDC. With regards to labeling, the integral DDC manufacturer should follow the labeling requirements for a medicinal product.

For co-packaged combination products, where the device part is required to be CE marked and must comply with the MDR requirements, the information required on the label, including the device manufacturer, CE mark and UDI, should be provided on the device or its packaging contained within the overall outer packaging. The medicinal product information (patient information leaflet, product labeling

and SmPC) should not include any information related to device labeling, such as the device UDI, CE mark, device manufacturer or authorized representation or references to device-vigilance reporting.

If the device part of a DDC is CE marked, the product labeling for the integral DDC should follow the labeling requirements for medicinal products as outlined in the working group on Quality Review of Documents (QRD) templates. If a UDI is already directly marked on the device part it does not need to be removed. The UDI should not appear on the labeling or outer package of the medicinal product.



10 What are key considerations to factor into the lifecycle management of your DDC?

MAA

Changes to an approved DDC are categorized based on risk to public health and the impact on the medicinal product's quality, safety and efficacy. Changes to the content of the MAA are made in accordance with Commission Regulation (EU) No 1234/2008 (the "Variations Regulation")⁸.

Case study

An autoinjector MAA was authorized; however, to support launch activities, an additional manufacturing site was required. A process transfer was completed, and comparability was demonstrated. This information was used to file a post-approval variation.

Unfortunately, the agency identified gaps in the process validation activities, and additional process validation was requested. This resulted in an approximately six-month delay to the implementation of the new site.

Mitigation strategy

Consider including a post-approval change management protocol within the original MAA. Any issues with the protocol would then be reviewed and addressed as part of the MAA review. Additionally, once the protocol is executed, the supporting variation may be reviewed as a lower variation category (as the protocol has been reviewed as part MAA) and would be able to support rapid approval for launch.

Consultation procedure for ancillary medicinal substances in medical devices (Art 1(8)) 4.1.

According to Article 52(9) MDR, as clarified by MDCG Guidance 2020-12, NBs are required to request a consultation with a Competent Authority as part of the conformity assessment under the MDR for ancillary

medicinal substances already consulted under the medical device Directive 93/42/EEC.

It is possible to take the opportunity of an upcoming variation to request an opinion in accordance with the MDR. Please consult the table below to determine whether a full initial consultation or a follow-up (variation) consultation should be submitted.

Table: EMA consultation for ancillary medicinal substances under MDR where a consultation already took place under the Directive 93/42/EEC

Procedure type	Timetable	Conditions	Documentation
Type IA variation	30 days	Previous opinion issued by EMA No change to device No change to ancillary No change to NB assessment or only 'administrative' changes	<ul style="list-style-type: none"> Full package including description of the manufacturing process and the data relating to the usefulness of incorporation of the substance into the device (according to section 5.2 Annex IX of the MDR)
Type IB variation	First phase 30 days (with possibility to RSI and assessment of responses up to 60 days)	Previous opinion issued by EMA Minor variation (as classified by analogy to Commission Regulation (EC) No 1234/2008) or/and change to NB's assessment of conformity (this includes where the NB is different to MDD consultation)	<ul style="list-style-type: none"> Declaration from manufacturer and NB detailing which elements are changed, if applicable
Type II variation	First phase 60 or 90 days (with possibility to RSI and assessment of responses up to 210 days)	Previous opinion issued by EMA Major variation (as classified by analogy to Commission Regulation (EC) No 1234/2008)	
Full initial consultation	Up to 210 days	Previous opinion issued by a different CA	In addition to above: <ul style="list-style-type: none"> NCA opinion from previous consultation

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