21 October 2019 Rev.1
EMA/37991/2019
Human Medicines Evaluation Division

Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)

This Question and Answer (Q&A) document provides practical considerations concerning the implementation of the medical devices and the in vitro diagnostic medical devices regulations.

This document has been produced to provide guidance to Applicants as regards aspects falling within the scope of the Agency's activities and should be read in conjunction with the new medical devices Regulation (EU) 2017/745, and the new in vitro diagnostic medical devices Regulation (EU) 2017/746. The medical devices regulation (MDR) and in-vitro diagnostics regulation (IVDR) replace the three existing Directives (93/42/EEC, 98/79/EC and 90/385/EEC) for medical devices. The Regulations entered into force on 25 May 2017; however, they will have a transition period to allow manufacturers, notified bodies and authorities to comply with the changes and will come into full application on 26 May 2020 for medical devices and 26 May 2022 for in vitro diagnostics. These regulations lay down roles and responsibilities for EMA and National Competent Authorities (NCA) for medicinal products, as follows:

- For medical devices incorporating a medicinal substance (with action ancillary to the device)[1] the notified body shall seek a scientific opinion from either the NCAs or EMA. The notified body shall seek the opinion of EMA for medicinal products falling exclusively within the scope of centralized procedure[2], or that incorporate human blood or plasma derivatives
- For devices that are composed of substances or of combinations of substances that are systemically absorbed by the body in order to achieve their intended purpose, the notified body shall seek a scientific opinion from either the NCAs or the EMA[3]
- For companion diagnostics, the notified body shall seek a scientific opinion from either the NCAs or the EMA[4]
- The European Commission may consult EMA when deliberating on the regulatory status of products in borderline cases involving medicinal products[5].

[1] Regulation 2017/745 Annex IX 5.2
[2] Annex I, Regulation (EC) No 726/2004
[3] Regulation 2017/745 Annex IX 5.4
[4] Regulation 2017/746 Annex IX 5.2, Annex X 3(k)

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- For medicinal products with an integral medical device[6], there are new requirements to provide an opinion from a notified body

This update of the questions and answers focuses on aspects relating to the implementation and applicability of the requirements of Regulation (EU) 2017/745 to medicinal products with an integral or co-packaged medical device.

This is a living document and the questions and answers are being updated continuously, and will be marked by "NEW" or "Rev." with the relevant date upon publication.

[5] Regulation 2017/745 Article 4, Regulation 2017/746 Article 3
[6] Regulation 2017/745 Article 117

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1. Medicinal product medical device combinations ('combination products')

1.1. What regulatory framework does a product incorporating both medicinal product and medical device fall under? New Oct 2019

Medicinal products and medical devices that are placed on the market together are generally known as "combination products".

The regulatory framework for devices incorporating medicinal substances as an 'integral part' is laid down in Article 1(8) of MDR:

- Where the action of the medicinal substance is **ancillary**, the product is regulated as a medical device and must be CE marked. As the action of the medicinal product is considered ancillary, a scientific opinion must be provided from a medicines authority before a notified body can issue a certificate for the combined product. For more information and a list of products previously reviewed by EMA, please see EMA webpage on Ancillary medicinal substances in medical devices
- Where the action of the medicinal substance is **principal**, the combination product is regulated under the medicinal products framework. In that case, the relevant general safety and performance requirements of the MDR apply to the device part.

The regulatory framework for administration devices is laid down in Article 1(9) MDR:

- If the administration device is marketed as a **single integral product** intended **exclusively for use in the given combination** and is **not reusable**, the combination product is regulated under the medicinal products framework. In that case, the relevant general safety and performance requirements of the MDR apply to the device part.
- In all other cases, the administration device is regulated under the medical device framework. When the medical device is not physically combined with the medicinal product the device will need to be CE marked. See section 2. of the Q&A's for additional information concerning co-packaged medical devices.

Throughout this document, products that, in accordance with Article 1(8) and 1(9) are regulated under the medicinal products framework, are referred to as integral Drug-Device Combinations (integral DDCs). Additional information and examples of these products are provided in section 2. of the Q&A's.

1.2. How do I choose a notified body for my co-packaged /integral device? New Oct 2019

A notified body (NB) within the European Union (EU) is an entity designated by an EU competent authority to assess the conformity of medical devices before being placed on the market. Companies are free to choose the notified body they engage with; the only criterion is that the notified body must be designated to carry out the conformity assessment procedure for the particular medical device type(s) for which a certification is sought. Applicants can check the NANDO (New Approach Notified and Designated Organisations) website, by clicking on 'Legislation' and select the relevant Directive/Regulation to search for a notified body designated for the product types and technical competences needed.

2. Medicinal product with an integral medical device (integral DDC)

2.1. When is my medicinal product considered to form an integral product with the administration device?

If a medical device used to administer a medicinal product is placed on the market in such a way that the device and medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable.

The second paragraph of Article 1(9) of the MDR sets out three cumulative conditions that need to be satisfied at the moment of the placing on the market:

- the device and the medicinal product form a single integral product;
- intended exclusively for use in the given combination;
- which is not reusable.

For medicinal products meeting the above conditions, the single integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable, however the relevant general safety and performance requirements set out in Annex I to Regulation (EU) 2017/745 shall apply as far as the safety and performance of the device part of the single integral product are concerned.

Examples of integral products which are not reusable are pre-filled syringes, pre-filled pens, nebulizers pre-charged with a specific medicinal product, patches for transdermal drug delivery and pre-filled inhalers.

An example of combinations which are not integral products is a vial containing a drug solution with an (empty) co-packaged syringe.

2.2. What is Article 117 and what does it mean for medicinal products? Rev. Oct 2019

Article 117 of Regulation (EU) 2017/745 (amending Annex I to Directive 2001/83/EC, point 12 of section 3.2) requires that the marketing authorisation application for a integral DDC should include, where available, the results of the assessment of conformity for the device (i.e. the declaration of conformity or the relevant certificate issued by a notified body).

If the dossier does not include the results of the assessment of conformity, and a EU certificate from a notified body would be required if the device was used separately, then the applicant will be required to provide an opinion from a notified body on the conformity of the device part with relevant requirements of Annex I to Regulation (EU) 2017/745 as part of the marketing authorisation application.

Article 117 applies to medicinal products that form an integral product with a medical device, (also known as integral DDC). Article 117 does not apply in the case of combined advanced therapy medicinal products as defined under Article 2(1)(d) of Regulation (EC) No 1394/2007.

2.3. How will the medical devices Regulation and in particular Article 117 impact new marketing authorisation applications? Rev. Oct 2019

Marketing authorisation applications for an integral DDC submitted as of 26 May 2020, must demonstrate that the device part meets the relevant requirements of Annex I of Regulation (EU) 2017/745 as follows:

- If the device component has CE marking then the applicant is expected to provide, where available, a **Declaration of Conformity or the EU notified body certificate** allowing the manufacturer to affix CE marking to the device.
- If the dossier does not include a declaration of Conformity and EU notified body certificate and the device component is a risk classification of sterile class I, measuring class I, class IIa, class IIb or class III medical device, then the applicant must provide **an opinion from a notified body** on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to Regulation (EU) 2017/745.

Table 1. Summary of changes for **Marketing Authorisations Applications involving integral DDCs**

Type of integral device included in the MAA	New submissions as of 26th May 2020
Class I (sterile, measuring or reusable surgical instrument*), Class IIa, Class IIb Class III	The marketing authorisation dossier should include a **Declaration of Conformity or EU notified body certificate** for the medical device, where available. If the above mentioned documentation is not available then **an opinion** ** **from a notified body** must be provided for the medical device
Class I (non-sterile, non-measuring, or non-reusable surgical instrument)	The marketing authorisation dossier should include a **Declaration of Conformity** for the medical device, where available.
* the reader should note that integral DDC as referred to in second subparagraph of Regulation 2017/745 Article 1(9) are not reusable **opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to Regulation 2017/745	

2.4. When is it required to provide the notified body opinion / EU certificate / declaration of conformity with my Marketing Authorisation Application (MAA)? Rev. Oct 2019

Applications for a marketing authorisation of an integral DDC submitted as of 26 May 2020 must comply with the requirements of Article 117 of Regulation 2017/745.

The submission of evidence of compliance with the general safety and performance requirements of the MDR in the MAA of integral DDCs as required under Article 117will not apply to marketing authorisation applications submitted before 26 May 2020,.

2.5. At what stage do I need to submit the notified body opinion?

EMA/NCAs strongly recommend submitting the EU certificate / declaration of conformity / notified body opinion already as part of the dossier of the initial marketing authorisation application for the medicinal

product to facilitate a smooth running of the procedure. In case the applicant cannot provide the required documentation at the time of MAA submission, the applicant should discuss at the EMA/NCA pre-submission meeting their plans to provide the required documentation. The absence of the required documentation may result in additional clock stops during the procedure, as the documentation is necessary for the adoption of a favourable CHMP opinion.

2.6. How does Article 117 of the medical devices regulation impact currently authorised integral DDCs? Rev. Oct 2019

Article 117 of MDR is not intended to apply retrospectively to integral DDCs already authorised or to those MAAs that have been submitted prior to 26 May 2020.

However, if after the granting of the marketing authorisation there is a substantial change to the design or intended purpose of the device component, or a new device is introduced, any required certificate/declaration of conformity/NB opinion should be submitted as part of the variation/extension application, as appropriate to EMA/NCA (see also Q0).

2.7. Will I need to provide a (new or updated) EU certificate / declaration of conformity / notified body opinion if there are changes to the device submitted through a variation /extension?

There are two cases where a new or updated EU certificate / declaration of conformity / notified body opinion is needed.

a) Addition or full replacement of the device component

In cases where a device component of a an DDC will be replaced or a new device will be added for applications submitted as of 26 May 2020, a new EU certificate / declaration of conformity / notified body opinion will need to be provided as part of the variation/extension application, as appropriate.

This requirement applies to all marketing authorisations, including those already compliant with Article 117 MDR at the time of the initial MAA.

b) Substantial design changes to the device component

In cases where the MAH introduces substantial changes to the medical device component, a new (updated) EU certificate / declaration of conformity / opinion from a notified body will need to be provided as part of the variation/extension application, as appropriate.

Changes to the device component are considered substantial if the changes affect the performance and safety characteristics of the device.

It is the responsibility of the marketing authorisation holder to determine if the changes are substantial and EMA/NCAs expect that the MAHs liaise with the notified body and submit to EMA/NCA the necessary documentation as part of a variation/extension application.

This requirement applies to all marketing authorisations, even those that had complied with Article 117 MDR with their initial MAA.

If the variation does not affect the medical device then a new/updated notified body opinion/ certificate is not required.

In line with the advice provided in the EMA Q&A for Post-authorisation procedural advice for users of the centralised procedure, given the relatively short timelines for variation/extension procedures, for medical devices the documentation to support the CE mark or the notified body opinion should be

submitted as part of the documentation at time of submission of the variation/extension to avoid any delays.

2.8. What is the impact of the MDR on medicinal products including an integral medical device for a Mutual Recognition Procedure submitted on or after the 26 May 2020? New Oct 2019

As the Mutual Recognition Procedure (MRP)/Repeat Use Procedure (RUP) is a new application for marketing authorisation in the concerned member states, the dossier must comply with the regulatory requirements applicable at the time of the application. If the requirements have changed since the national, Decentralised or Mutual Recognition procedure then the dossier will need to be updated. Therefore if the application for the MRP/RUP is submitted on or after 26 May 2020 and the authorisation includes an integral medical device then the GSPR and Article 117 of the MDR will need to be met and the supporting documentation such as the Declaration of Conformity, certificate of conformity or notified body opinion should be included in the dossier. A variation application to add a new Notified Body Opinion, declaration of conformity or certificate to formally update the dossier will be required in the reference member state and, where applicable, existing concerned member states before the commencement of the Mutual Recognition/Repeat Use procedure.

2.9. Are the requirements for UDI (unique device identifier) applicable to integral DDCs? New Oct 2019

No. if the device is governed by the medicinal products legislation, then MDR obligations related to UDI are not required and should not be applied to the package of the combination product. This is reflected in the MDCG 2019-2 guidance on application of UDI rules to device-part of products referred to in Article 1(8), 1(9) and 1(10) of Regulation 2017/745.

Even if the integral device is CE marked, it is expected that the labelling for the integral DDC should follow the labelling requirements for medicinal products outlined in the QRD (working group on Quality Review of Documents) templates. For integral devices with a CE mark, the UDI may be assigned to the device itself, however the UDI should not appear on the labelling or outer package of the medicinal product.

3. Medicinal product with a co-packaged device

3.1. How will the implementation of the Medical Device Regulation affect the device? New Oct 2019

Applicants will need to ensure that their co-packaged medical device is CE marked in accordance with the relevant legislation on medical devices to continue placing the product on the market. This also applies if a specific medical device is referenced in the SmPC.

- Devices certified by a notified body can benefit from a transition period provided for in MDR Article 120 (2), which allows devices with a valid certificate under the Medical Device Directive 93/42/EEC (MDD) and Active Implantable Medical device Directive 90/385/EEC (AIMDD) to be placed on the market up to the latest **27 May 2024**, although they will need to comply with certain requirements of the MDR from 26 May 2020 (see FAQ's published by the CAMD MDR/IVDR transition subgroup: FAQs – MDR Transitional provisions).
- Self-declared Class I devices must be in compliance with the MDR by **26 May 2020**.