EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

27 February 2019
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 medicines, 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)
[5] Regulation 2017/745 Article 4, Regulation 2017/746 Article 3

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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

The first set of Q&A focuses on aspects relating to the implementation of Article 117 of Regulation 2017/745.

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.

[6] Regulation 2017/745 Article 117

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

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1. Article 117 of the medical devices regulation (EU) 2017/745

1.1. What is Article 117 and what does it mean for medicinal products?

Article 117 of Regulation 2017/745 (amending Annex I to Directive 2001/83/EC, point 12 of section 3.2), introduces a new requirement for notified body involvement in a medicinal product with an integral medical device. The marketing authorisation dossier for a medicinal product with an integral medical device is expected to include 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 device is not CE marked and a EU certificate from a notified body would be required if the device was used separately, then the applicant must provide an opinion from a notified body on the conformity of the device part with relevant requirements of Annex I to Regulation 2017/745 as part of the marketing authorisation application.

This applies to medicinal products that form an integral product with a medical device, where the action of the medicinal product is principal i.e. those that fall under second subparagraph of Article 1(8) and where a medical device is used to administer a medicinal product, i.e. second subparagraph of Article 1(9) of the medical devices Regulation. Throughout this document the term 'medicinal product with an integral medical device' is used to cover products falling under second subparagraphs of both Article 1(8) and Article 1(9).

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.

1.2. 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 the medicinal products Directive, however the relevant general safety and performance requirements set out in Annex I to Regulation 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.

Examples of combinations which are <u>not</u> integral products: a vial containing a drug solution with an (empty) co-packaged syringe.

1.3. How will the medical devices Regulation and in particular Article 117 impact new marketing authorisation applications?

Marketing authorisation applications for a medicinal product with an integral medical device submitted as of 26 May 2020, must demonstrate that the device part meets the relevant requirements of Annex I of Regulation (EU) 2017/745.

If the device component has CE marking then the applicant is expected to provide a **Declaration of Conformity and/or EU notified body certificate** allowing the manufacturer to affix CE marking to the device. Providing this documentation will facilitate the assessment of the device component with respect to meeting the requirements of Annex I of Regulation 2017/745. 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 2017/745.

Table 1. Summary of changes for **Marketing Authorisations Applications involving medicinal products with integral medical devices**

Type of MA including medical devices	New submissions as of 26th May 2020 with **NON CE** marked device	New submissions as of 26th May 2020 with **CE** marked device
Medicinal products with integral medical device/s Class I (sterile, measuring or reusable surgical instrument*), Class IIa, Class IIb Class III	Demonstrate that the medical device meets the relevant general safety and performance requirements of Annex I of the medical devices Regulation 2017/745. In addition **an opinion** ** **from a notified body** must be provided for the medical device component	Demonstrate that the Medical device meets the relevant general safety and performance requirements of Annex I of the medical devices Regulation 2017/745. In addition a **Declaration of Conformity and EU notified body certificate** is expected to be provided for the medical device component, where available. If the above mentioned documentation is not available then **an opinion** ** **from a notified body** must be provided for the medical device component
Medicinal products with integral medical device/s Class I (non-sterile, non-measuring, or	Demonstrate that the Medical device meets the relevant general safety and performance requirements of Annex I of the medical devices Regulation 2017/745.	Demonstrate that the Medical device meets the relevant general safety and performance requirements of Annex I of the medical devices Regulation 2017/745. In addition a **Declaration of Conformity** is expected to be provided

Type of MA including medical devices	New submissions as of 26th May 2020 with **NON CE** marked device	New submissions as of 26th May 2020 with **CE** marked device
non-reusable surgical instrument)		for the medical device component, where available.
* the reader should note that integral combinations 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		

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

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

Article 117 will not apply to marketing authorisation applications submitted before 26 May 2020.

1.5. 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.

1.6. How does Article 117 of the medical devices regulation impact currently authorised medicinal products with an integral medical device?

It is not intended to apply retrospectively the requirements of the medical devices Regulation to medicinal products with an integral medical device already authorised or to those MAAs that have been submitted prior to 26 May 2020.

However, if after 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 Q1.7).

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

1.7. 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 or notified body opinion is needed.

a) Addition or full replacement of the device component

In cases where a device component of a medicinal product with an integral medical device 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 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 the necessary documentation as part of a variation to EMA/NCA.

This requirement applies to all marketing authorisations, even those that had complied with Article 117 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 procedures, for medical devices the documentation to support the CE mark or the notified body opinion must be submitted as part of the documentation at time of submission of the variation to avoid any delays.