WHITE PAPER

MEDICAL DEVICES

Medicinal products & medicinal substances incorporated in medical devices

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I Introduction

The implementation of the European Medical Device Regulation, Regulation (EU) 2017/745 (MDR) and the publication of numerous guidelines could increase the already existing confusion about the association of medicinal product or medicinal substance with medical device. The objective of this whitepaper is to provide a support on the management of initial submission to EMA (European Medicines Agency) of such association according to version 1 of EMA Guideline recently

II Context

This whitepaper addresses the consultation process with EMA related to the association of medical device with medicinal product or medicinal substances. It is thus necessary to define these last two elements.

• A medicinal product shall be compliant with the provided definition in point 2 of Article 1 of Directive 2001/83/EC :

"Any substance or combination of substances presented for treating or preventing disease in human beings.

Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product."

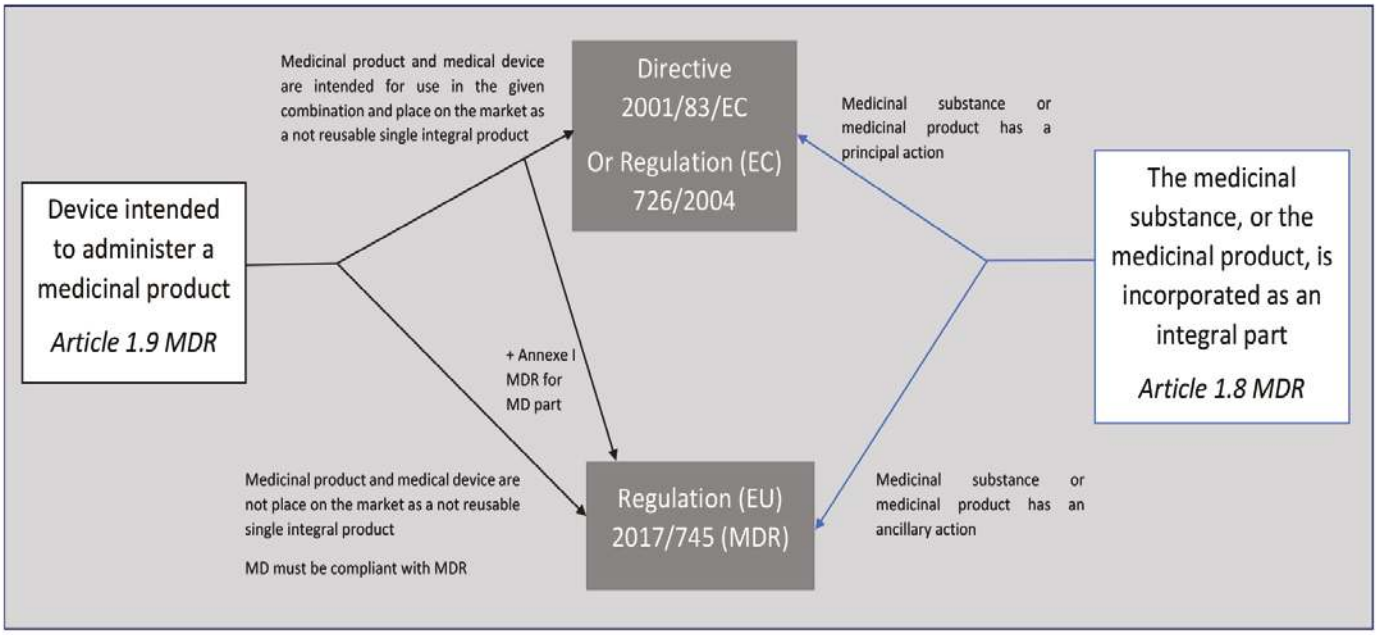
• Is considered as medicinal substance, a substance which, if used separately [of the medical device], would be a medicinal product as defined in the article quote upper, Article 1.8 MDR.

As reminder, a medical device is defined according to point 1 of Article 2 of Medical Device Regulation (EU) 2017/745 (MDR).

III Which regulation is applicable ?

Depending on how the Medical Device (MD) and the medicinal substance or the medicinal product are combined, the applicable regulations are different, and the finished product may be subject to several regulations at the same time.

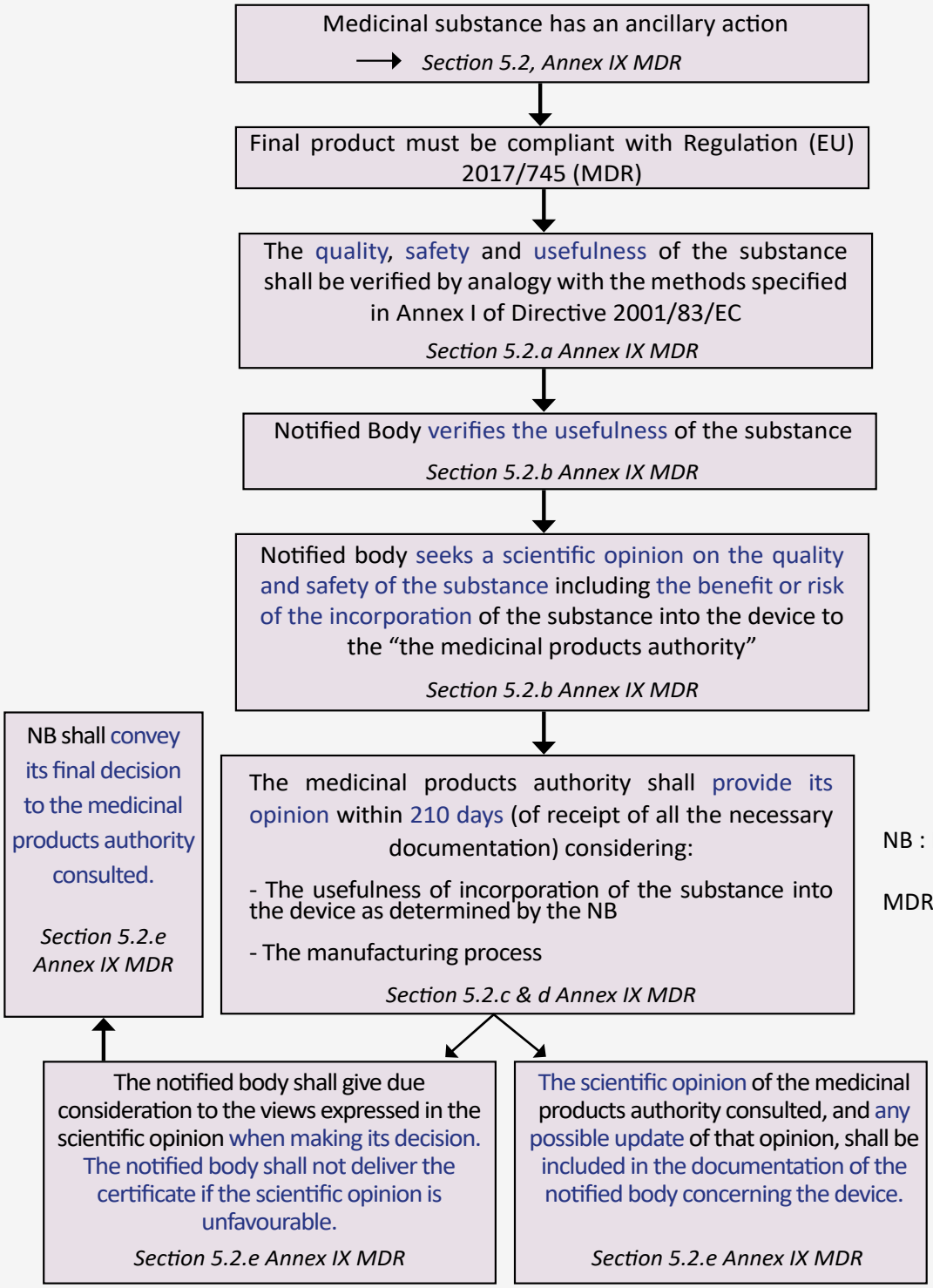
Below a tree structure to clarify the applicable regulations according to the cases:



In this whitepaper we will focus on the hypothesis that the medicinal product, or the medicinal substance, has an ancillary action, meaning that the principal action of the medical device is not obtained by the latter. So, are concerned medical devices as, soft tissue fillers incorporating local anaesthetics, bone cements containing antibiotic or heparin eluting coronary stents.

IV How is medical device incorporated substance evaluated according to the Regulation (EU) 2017/745 in the case of an ancillary action?

Section 5.2 of Annex IX (MDR) specifies the documentation assessment procedure for devices incorporating a medicinal substance. It is specified that "the quality, safety and usefulness of the substance shall be verified by analogy with the methods specified in Annex I to Directive 2001/83/EC", the steps are then detailed as follows:



If the requirements and obligations are well defined here, the operational details are not explained. The recently published revision of the EMA guideline (EMA / CHMP / 578661/2010 rev .1, Nov. 2019) makes recommendations on these different aspects.

V What does the EMA guideline recommend for an initial submission?

Step 1: The Notified Body verifies the usefulness of the substance

The quality, safety and usefulness of the substance shall be verified by analogy with the methods specified in Annex I of Directive 2001/83/EC

Section 5.2.a, Annex IX MDR

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Notified Body verifies the usefulness of the substance

Section 5.2.b, Annex IX MDR

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Notified body seeks a scientific opinion on the quality and of the substance including the benefit or risk of the incorporation of the substance into the device to « the medicinal products authority »

Section 5.2.b, Annex IX MDR

WHO ?

The Notified Body

Before initiating any approach with the EMA

HOW ?

Writing a report (which will be submitted in section 1 of the application dossier). «usefulness» is defined in MEDDEV 2.1 / 3 Rev 3 as the suitability of the medicinal substance to achieve its intended action, and whether the potential inherent risks (aspects of «safety») due to the medicinal substance are justified in relation to the benefit to be obtained within the intended purpose of the device.

NB: The reference to an ASMF (Active Substance Master File) is not authorized

V What does the EMA guideline recommend for an initial submission?

Step 2: The Notified Body seeks a scientific opinion from the «medicinal products authority»

Who is the «medicinal products authority» mentioned in Regulation (EU) 2017/745?

The authority consulted by the Notified Body depends on the type of substance:

- Substance falling within the scope of Annex I of Regulation (EC) 726/2004 -> EMA submission is mandatory
- Other substances -> choice of submitting authority at the discretion of the Notified Body

The EMA may however be consulted if the substance is already included in a medicinal product evaluated by the EMA. (MEDDEV 2.1 / 3 rev 3)

Notified Body verifies the usefulness of the substance

Section 5.2.b, Annex IX MDR

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Notified body seeks a scientific opinion on the quality and of the substance including the benefit or risk of the incorporation of the substance into the device to « the medicinal products authority »

Section 5.2.b, Annex IX MDR

↓

The medicinal products authority shall provide its opinion within 210 days (of receipt of all the necessary documentation) considering:

- The usefulness of incorporation of the substance into the device as determined by the NB
- The manufacturing process

Section 5.2.c & d, Annex IX MDR

NB shall convey its final decision to the medicinal products authority consulted.

Section 5.2.e Annex IX MDR

WHO ?

Pre-submission meeting : Notified Body AND medical device manufacturer with EMA

Intention to submit letter to EMA : Notified Body

Submission to EMA : Notified Body in close collaboration with the medical device manufacturer

WHEN ?

Pre-submission meeting : At least six months before the expected date of submission

Intention to submit letter : At least six months before the expected date of submission and 10 days before a CHMP* meeting at EMA in order to be included in the agenda of the meeting**

Submission : After the reception of the letter from the Agency confirming the start of the procedure, the applicant must immediately send the final documentation

HOW ?

Pre-submission meeting : Consult the site for the procedure and contact the EMA.

Intention to submit letter : Format according to Annex 2 of EMA guideline, to be sent to : pa-bus@ema.europa.eu
Receipt of a unique product identifier (UPI) to be reminded in each correspondence

Submission :

Elements:
- *Application form* : Format submission available on the EMA website HERE
- *Application dossier* : The format and the data to be communicated are explained in various documents, a consolidated version is provided in Annex I to the EMA Guideline

Format : The electronic submission process (e-soumission) in XML format is mandatory

* Le CHMP (Committee for Medicinal Products for Human Use) is the committee of the European Medicines Agency responsible for medicines for human use.

** Meeting dates available at the following link : https://www.ema.europa.eu/en/documents/other/chmp-meeting-dates-2019-2020-2021_en.pdf

V What does the EMA guideline recommend for an initial submission?

Step 3: The medicinal products authority provides its opinion

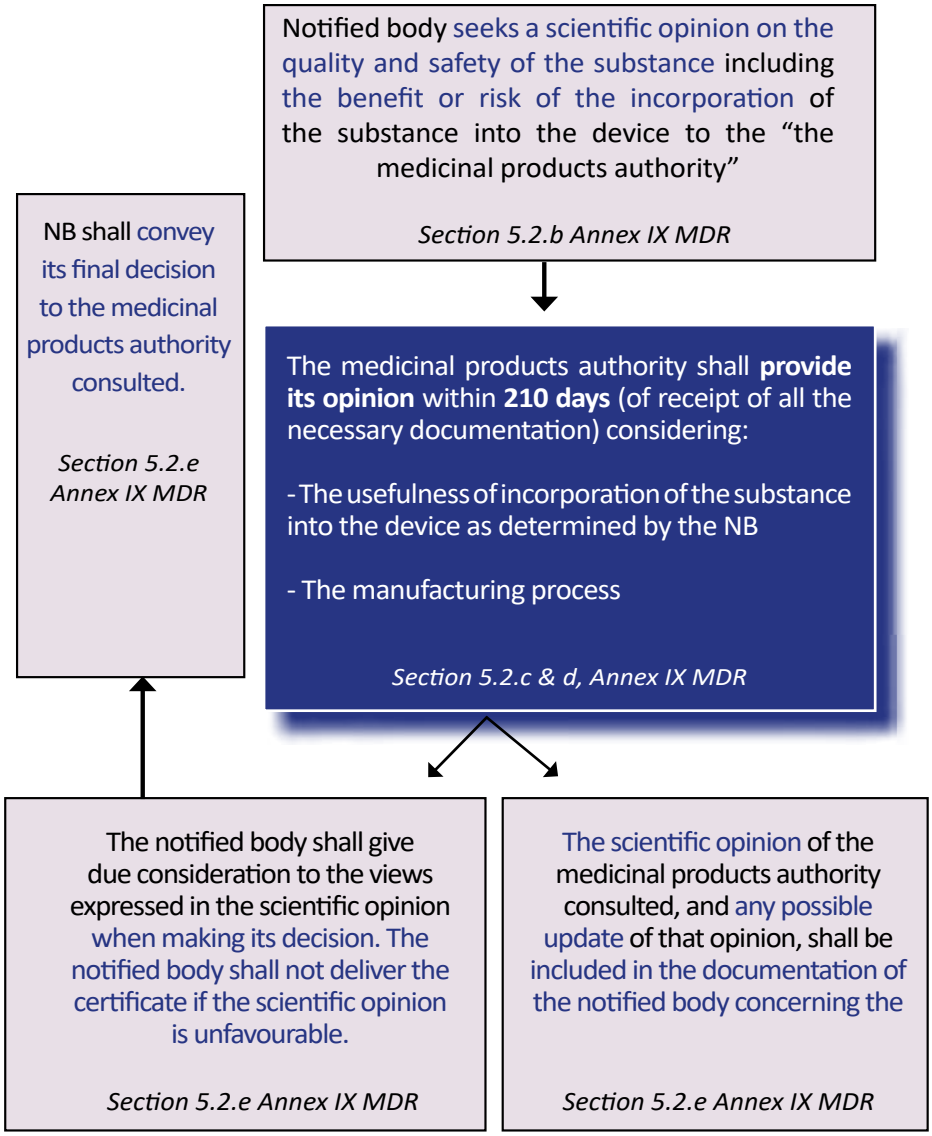
The CHMP will follow the same evaluation calendar as the one used for a new submission as part of a centralized procedure (EudraLex notice to applicants Volume 2A, Chapter 4), i.e. an evaluation in 210 days, with the possibility of clock stops to allow the Notified Body to answer questions posed by the CHMP (on average one year of evaluation is expected in total).

A request for an accelerated assessment procedure may be made in the following cases:

- The device is used for the treatment of serious illnesses (fatal or disabling illnesses)

- The medicinal substance is known and used and the CHMP therefore considers a less in-depth evaluation.

Requests for an accelerated assessment procedure must be justified and made at least 2 to 3 months before the date of submission using the Agency form.



WHO ?

EMA if the substance fall under the Annex of Regulation (EC) 746/2004

The competent authority designated by the Member State or the EMA according to the choice of the Notified Body

WHEN ?

After the evaluation period, the CHMP gives an opinion on the quality and safety of the substance(s) including the clinical benefit/risk profile of the incorporation of the substance(s) into the medical device.

HOW ?

The CHMP opinion is sent to the Notified Body and to the competent authority for medical devices of the Member State in which the Notified Body is based.

A public assessment report on the consultation procedure (Consultation procedure Public Assessment Report, CPAR) will be published on the EMA website as soon as the Notified Body has given its decision on CE certification.

NB: The manufacturer of the medical device and the manufacturer of the medicinal substance will be contacted, through the Notified Body, on the CPAR before its publication.

VI. Conclusion

The combination of a medicinal substance and a medical device is often questionable. The consolidation of the various guides allows to clarify the actors and the critical points. In addition to the qualification of the finished product, which is a strategic point of development, the solicitation of new actors is to be considered from the design phase. Indeed, the submission strategy can have a critical impact on the evaluation timeline, a good anticipation and a thorough knowledge of the EMA calendars are therefore essential. It is therefore essential to inform the Notified Body as soon as possible of the presence of a medicinal product or a medicinal substance so that it can plan the different stages with the authority of the medicinal product which will carry out the evaluation.

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