

# The Evolving Process of European Combination Product Review, Part I

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A new European guideline on drug-eluting stents (DES)<sup>1</sup> introduces for the first time detailed information that European drug authorities should review concerning the medicinal substance that is incorporated into this type of drug-device combination product. Part I of this article discusses European requirements that apply to DES. Part II will discuss the new guideline, other stent guidelines and evolving process of drug-device regulatory review in Europe.

## European requirements

The European regulation of drug-device combination products regulated by the Medical Device Directive (MDD) (93/42/EEC), is defined in Article 1, Definitions, Scope, paragraphs 3 and 4 of the Directive. Under Article 3, a device that is intended to administer a medicinal substance is governed by the MDD, and the medicinal substance is governed by the Medicinal Products (MP) Directive 2001/83/EC. However, if a device is placed on the market in such a way that the device and the medicinal substance form a single integral product that is intended exclusively for use in the given combination and is not reusable, that single product is governed by MP Directive. Even though the entire product is regulated as a drug product, the relevant essential requirements of Annex I of the MDD apply with regard to the safety and performance related device features.

Under Article 4, where a device incorporates as an integral part a substance which, if used separately, may be considered to be a medicinal product and is liable to act

on the body with action ancillary to that of the device, that device must be assessed and authorised in accordance with the MDD. That is, the product is regulated under medical device legislation and not medicinal product legislation. Article 4a applies to devices incorporating as an integral part a medicinal product constituent or a medicinal product derived from human blood or human plasma; these products are beyond the scope of this article. The issues examined in this article concern primarily the type of drug-device product described in Article 4 of the MDD.

Medical devices covered by Article 4 are Class III products under the MDD, which is the highest risk category (based on the classification rules found in Annex IX of the MDD, Section 4, Special Rules, subsection 4.1, Rule 13). The requirements for assessing a medical device covered by Article 4, that is, one that forms an integral unit with a medicinal substance that acts with ancillary action to that of the device, are specified in the essential requirements of the MDD, which are found in Annex I. Section 7.4 in Annex I states that the safety, quality and →



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→usefulness of the medicinal substance must be verified, taking into account the intended purpose of the device. This is done by analogy with the appropriate methods specified in Directive 75/318/EEC on the Approximation of the Laws of Member States Relating to Analytical, Pharmacotoxicological and Clinical Standards and Protocols in Respect of the Testing of Medicinal Products. Changes that have been made to these requirements are discussed later in this article.

### Guidance on the consultation process

The manner in which the verification of the safety, quality and usefulness of the medicinal substance must be performed is specified in Section 4.3 of Annex II and in Section 5 of Annex III of the MDD. These sections require the Notified Body to consult one of the competent bodies responsible for implementing the medicinal products requirements stated in Section 7.4, before taking a decision on the adequacy of the design of the product. Furthermore, the Notified Body must give due consideration to the views expressed in this consultation when making its decision. The Notified Body must also convey its final decision to the competent body concerned.

To help all involved parties understand how the consultation process should be managed, the following European MEDDEV guidance document provides guidance on the process: Demarcation Between Directive 90/385/EEC on Active Implantable Medical Devices, Directive 93/42/EEC on Medical Devices, and Directive 65/65/EEC Relating to Medicinal Products and Related Directives (MEDDEV 2.1/3 rev 2, July 2001). Section B, The Consultation Process for Devices Incorporating a Medicinal Substance Having Ancillary Action, clarifies the language in the Directive, describes Notified Body actions that can be taken to initiate the consultation process, and discusses documentation that is to be provided by the Notified Body to the competent body for medicinal products.

For example, the guidance explains why the term “by analogy” is used in essential requirement 7.4. This term is used because verification of the safety, quality and usefulness of the medicinal substance refers to a substance that is not a medicinal product, but a medicinal substance that acts in an ancillary fashion within a device–medicinal substance combination.

Advice is also provided on how documentation relating to the medicinal substance should be provided by the manufacturer to the Notified Body. For example, it should be in the form of a separate section and in the format described in the medicinal products document, Notice to Applicants. Section B.3 of the MEDDEV guidance document states that the information provided should be based in principle and to the extent possible on the annex to Directive 91/507/EEC, which modifies Directive 75/318/EEC. This provides (in sections a to q) a comprehensive checklist covering document headings such as General information, Qualitative and quantitative particulars of

the constituents, Description of method of manufacture, Controls of starting materials, and other headings. Readers should refer to the MEDDEV guidance document for the complete list of headings.

What is of particular interest to the discussion in this article is that the guidance points out in Section B.1 that the ultimate responsibility for the decision on whether or not the pertinent legal requirements are met belongs to the Notified Body.

### Clarification in the revising Directive

On 21 September 2007, Directive 2007/47/EC was published, which revises the Active Implantable Medical Device Directive (90/385/EEC) and the MDD (93/42/EEC). The revisions will take effect in March 2010. Readers should be aware of the changes made to essential requirement 7.4 regarding a device that incorporates as an integral part a medicinal substance that is liable to act on the body with action ancillary to that of the device. As mentioned previously, the current version of the MDD requires that the safety, quality and usefulness of the substance must be verified, taking into account the intended purpose of the device, by analogy with the appropriate methods specified in Directive 75/318/EEC. The requirement for consulting with medicinal product competent bodies is included in the conformity assessment annexes.

The revising text in essential requirement 7.4 of 2007/47/EC includes the requirement for verification of the safety, quality and usefulness of the medicinal substance. However, it provides more specific provisions than those currently included in Section 4.3 of Annex II and in Section 5 of Annex III of MDD (93/42/EEC) for the process of Notified Body consultation with the medicinal product competent bodies. The revising text states that the Notified Body “shall, having verified the usefulness of the substance as part of the medical device and taking account of the intended purpose of the device, seek a scientific opinion from one of the competent authorities designated by the Member States or the European Medicines Agency (EMA) acting particularly through its committee in accordance with Regulation (EC) No 726/2004 on the quality and safety of the substance including the clinical benefit–risk profile of the incorporation of the substance into the device. When issuing its opinion, the competent authority or the EMA shall take into account the manufacturing process and the data related to the usefulness of incorporation of the substance into the device as determined by the Notified Body.”

In addition, the revising text includes a new provision in Section 7.4 related to changes made to the ancillary substance. It states that where changes are made to an ancillary substance incorporated in a device, in particular related to its manufacturing process, the Notified Body shall be informed of the changes and shall consult the relevant medicines competent body (that is, the one involved in the initial consultation) to confirm that the

quality and safety of the ancillary substance are maintained. The competent body shall take into account the data related to the usefulness of incorporation of the substance into the device as determined by the Notified Body. This is to ensure that the changes have no negative impact on the established benefit–risk profile of the addition of the substance in the medical device.

Additional responsibilities for feedback from the medicines competent body are also included. The last paragraph of Section 7.4 states that when the relevant medicines competent body (that is, the one involved in the initial consultation) has obtained information on the ancillary substance that could have an impact on the established benefit–risk profile of the addition of the substance in the medical device, it shall provide the Notified Body with advice, whether this information has an impact on the established benefit–risk profile of the addition of the substance in the medical device or not. The Notified Body shall take the updated scientific opinion into account in reconsidering its assessment of the conformity assessment procedure.

### An evolving process

The new DES guideline describes the information that should be provided by Notified Bodies to drug regulatory

authorities during the consultation procedure for DES. It also represents an evolution of the consultation procedure not only because of the manner in which the guideline was developed, but also regarding the specific guidance provided. Significant improvements were made to the draft guideline; however, there are still review issues that may need to be resolved to avoid any unnecessary duplication of regulatory review by drug regulatory authorities and Notified Bodies. Part II will discuss the new EMEA guideline, other stent guidelines, and the trend that the EMEA guideline may represent regarding the review of drug-device combination products in Europe.

### Reference

1. Guideline On the Clinical and Nonclinical Evaluation During the Consultation Procedure On Medicinal Substances Contained In Drug-eluting (Medicinal Substance-Eluting) Coronary Stents, [www.emea.europa.eu/pdfs/human/ewp/11054007enfin.pdf](http://www.emea.europa.eu/pdfs/human/ewp/11054007enfin.pdf). [mdt](#)

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