The Evolving Process of European Combination Product Review, Part II

Maria Donawa

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A new European guideline on drug-eluting stents (DES)[1] 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 discussed European requirements that apply to DES.[2] This article discusses the new guideline, other stent guidelines, and the evolving process of drug–device regulatory review in Europe.

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The new DES guideline

As discussed in Part I of this article,[2] under the Medical Device Directive (MDD) (93/42/EEC) where a device incorporates a medicinal substance that is liable to act upon the body with action ancillary to that of the device, the quality, safety and usefulness of the substance must be verified by analogy with the methods specified in Annex I of the Medicinal Products (MP) Directive (2001/83/EC). The Active Implantable Medical Device Directive (AIMDD) (90/385/EEC) contains similar requirements.

In addition, in accordance with the requirements of Directive 2007/47/EC, which revises the MDD and AIMDD, the Notified Body selected by the manufacturer is responsible for verifying the usefulness of the medicinal substance and must seek a scientific opinion from the drug regulatory authority on the quality and safety of the medicinal substance, including the clinical benefit–risk profile of incorporating the substance into the device (consultation procedure). The drug regulatory authority can be a European national competent authority (NCA) responsible for implementing European drug regulations or the European Medicines Agency (EMEA). When issuing its opinion, the NCA or EMEA must 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."

On 30 May 2008, the Committee for Medicinal Products for Human Use of the EMEA adopted a new guideline on the clinical and nonclinical evaluation of medicinal substances contained in drug-eluting stents (DESs). The guideline comes into effect on 1 December 2008. Although voluntary, national drug regulatory authorities and the EMEA are expected to follow the guideline when conducting an evaluation of a DES medicinal substance during the mandatory consultation procedure.

The purpose of the new DES guideline, which is based on the requirements specified in the revising Directive, is to harmonise the preclinical and clinical assessment by NCAs and the EMEA during the consultation process with regard to the safety assessment of the medicinal substance, including its clinical benefit–risk profile. The document states that its scope is limited to the clinical and nonclinical aspects of the evaluation of the medicinal substance, following by analogy the methods specified in Annex I of the MP Directive. The guideline does not cover the information that should be developed on the quality of the medicinal substance.

General approach and contents

The 10-page guideline describes various "possibilities" related to varying degrees of knowledge of the medicinal substance contained in DES, ranging from significant knowledge to little or none. These possibilities are arranged in categories A to D and form the basis for determining the type of data that are needed for preclinical and clinical →

Dr Maria E. Donawa

physician, pathologist and pharmacist with more than 25 years' regulatory experience, worked with the US FDA before becoming President of Donawa Consulting, an international consultancy firm, which provides clinical research, quality management system, regulatory affairs, and European Authorised Representative services to medical technology companies.

assessment of the medicinal substance. They are categorised as shown in Table I, except that in the guidance document the letters follow each possibility.

The background section describes the factors that will affect the safety evaluation and determination of the benefit–risk profile of incorporating the substance into the device. For example, it is recognised that although the total amount of medicinal product incorporated in the DES is substantially lower than that used systemically in clinical applications, local safety aspects are a major point of concern and should be taken into account in the nonclinical evaluation programme. The guideline also states that the benefit–risk profile of the medicinal substance in the context of a DES is linked with the chosen stent platform, the surface coating and the drug carrier system (if present), and any interaction between these.

Guidance on the type of data needed for evaluation of the ancillary medicinal substance in DESs begins with Section 5, Bench Testing. This is a brief section that states that it must be demonstrated that the medicinal substance and device neither chemically nor physically interact adversely with each other. It makes other test suggestions, but points out that, "Bench testing and Biocompatibility testing are part of the review by Notified Bodies."

Nonclinical and clinical data

Section 6, Data for Nonclinical Evaluation, provides guidance on biocompatibility testing of the device and other nonclinical data from pharmacodynamic studies, nonclinical pharmacokinetic testing, multiple overlapping stents testing, preclinical toxicity studies, and testing of the medicinal substance if not an approved medicinal product. Most of this guidance covers aspects that would be expected to be examined by the NCA or EMEA in their evaluation of the safety and benefit–risk of the medicinal substance. However, some requested nonclinical data such as that described in Section 6.1, which is discussed below, are data that would be expected to be evaluated by the Notified Body.

Section 6.1, Biocompatibility Testing of the Device, states, "The manufacturer must submit results of biocompatibility testing of the bare stent platform performed to support the initiation of a human clinical study as described in the Essential Requirements." It also states, "The results of biocompatibility testing of all relevant materials including carrier and stent material shall be provided to the NCA/EMEA. The Manufacturer should document and discuss the extent of biocompatibility testing conform ISO 10993 (A,B,C,D)." The last sentence includes a typographical or grammatical error, but more importantly, the reason for submitting data on the bare stent platform to the NCA/EMEA is not clear. It would have been more understandable if there had been a request that the results of the evaluation by the Notified Body of these data be provided to the NCA/EMEA.

Section 7, Clinical Data, includes guidance on the type of clinical data that should be collected during clinical studies of DES. Specific guidance is provided on clinical pharmacokinetic testing, clinical surrogate measures and exploratory testing, confirmatory clinical trials, study endpoints, duration of follow-up, clinical safety evaluation, and postmarketing surveillance considerations. Most of the guidance in this section concerns the clinical data needed to evaluate medicinal substance safety or benefit–risk profile of the medicinal substance. In some cases, the requested data appear to specifically relate to the device; however, some overlap is to be expected regarding the clinical data evaluation of the medicinal substance and certain device aspects.

Table I: Categories that form the basis for determining the type of data that are needed for preclinical and clinical assessment of the medicinal substance.

- A: the medicinal substance is already used in a CE-marked DES with the same indication and the manufacturer claims comparable medicinal substance release characteristics. This possibility is further divided into A1, A2, A3 and A4 depending on the similarity of the stent material, surface coating and drug carrier systems of the device under evaluation compared with a CE-marked DES
- B: the medicinal substance is already used in a CE-marked DES with the same indication, but the manufacturer claims different medicinal substance release characteristics
- C: the medicinal substance is known to the competent authority as an active pharmaceutical ingredient or formulated medicinal product in an authorised medicinal product, but not as a component of a previously CE-marked DES
- D: the medicinal substance is a new active substance and therefore not known to a competent authority either as an active pharmaceutical ingredient or formulated.

Draft Coronary Stent Clinical Evaluation Guideline

The new DES guideline states that it should be read with the "CETF guideline on clinical evaluation of coronary stents (ref 5)…" However, this document is not listed in Section 8, References (Background Guidance, Norms and Scientific), of the DES guideline and there is no reference 5. The guideline to which the DES refers is a guideline[3] that is currently a draft document developed by the Medical Devices Clinical Evaluation Task Force (CETF) and intended to be annexed to MEDDEV 2.7.1 on the "Evaluation Clinical Data: A Guide for Manufacturers and Notified Bodies." CETF is a working group of the European Commission's Medical Devices Experts Group, which supports the implementation of the medical device Directives.

The European Commission published a page on its website announcing the availability of the draft guideline and inviting interested parties to submit comments by 22 April 2008. The page can no longer be found on the site; however, a link is provided in this article.[3] The information on the page indicated that in the case of DESs, a guideline on the evaluation of medicinal substances contained in DES was under development by the EMEA. In addition, it was explained that to provide a consolidated guidance on the clinical evaluation of DESs, an objective was to align the two draft guidelines and tentatively

merge them in a single document. At the time of writing, the final version of the CETF guideline had not been published.

The purpose of the CETF guideline is to establish consistency in the clinical evaluation of coronary stents among manufacturers, Notified Bodies and Competent Authorities, in anticipation of the implementation of Directive 2007/47/EC in March 2010. The guideline covers all coronary stents, including DESs and other innovative stents. With regard to DESs, reference is made to the EMEA draft guideline because when the CETF guideline was published the EMEA DES guideline was still in draft form. The CETF draft guideline is a brief document of eight pages. It lists in general terms, the type of preclinical assessment that should be conducted and provides general advice on clinical investigations of coronary stents. Reference is made to the European harmonised standards covering technical aspects of nonactive surgical implants: EN 126006-3, EN 14299-3 and EN 14630.

US draft DES Guideline

In March 2008, the United States Food and Drug Administration (FDA) published two DES guidance documents;[4,5] the main document and a companion document that provides detailed guidance on DES nonclinical and clinical studies. The main document is 84 pages and covers regulatory requirements, product development pathways; systemic pharmacology, toxicology, and safety data for the drug substance alone; chemistry, manufacturing and controls information for the drug substance and for the finished product; nonclinical studies of the finished DES; finished product manufacturing, sterilisation, package integrity, and shelf life; clinical assessment of drug–stent combinations; and postapproval considerations. It also refers to another FDA 43-page guidance document[6] that provides guidance on nonclinical tests and labelling for intravascular stents.

The draft companion document is 30 pages and provides guidance on Investigational Device Exemption and Premarket Approval applications, presentation of data in a Master Table, DES clinical study summaries, responses to outstanding deficiencies, general biocompatibility considerations, test article certification, good animal husbandry, factors affecting the ability to pool data from US and non-US studies, and labelling for a DES.

In contrast to the EMEA DES guideline, which was developed by the EMEA and then made available for comments, the US DES guidance documents were prepared by a working group that included members of the FDA Center for Devices and Radiological Health, Center for Drug Evaluation and Research, and the Office of Combination Products in the Office of the Commissioner of the FDA.

Evolution of the consultation procedure

The review of drug–device products in Europe, in particular the consultation process, is evolving with the active involvement of various parties in an effort to improve the process. For example, the European guidance document, Interface With Other Directives Such As Medical Devices/Medicinal Products (MEDDEV guidance document 2.1/3 rev.2) is being revised and will include clarification on the contents of the information to be provided to drug regulatory authorities during the consultation procedure. A European Commission expert group is working on the clarification of what is meant by "by analogy." The Irish Medicines Board has published a Guide to Drug–Device Consultations (www.imb.ie/default.aspx).

Although the EMEA DES guideline was made available for comments, it appears to have been developed without the formal involvement of the medical device sector, including device Competent Authorities and Notified Bodies. This should be avoided in future and any subsequent guidelines by EMEA concerning medical devices should be coordinated with the medical device sector before initiation of the work. In addition, the CETF and EMEA guidelines were produced independently, although it appears that these two groups will now work together to harmonise the two documents or may even combine them.

The release of the EMEA guideline marks a distinct evolution in the review process of drug-device combination products that are regulated as medical devices. Readers should make every effort to keep up-to-date with the further evolution of this process and the manner in which these guidelines are being developed and by whom. Those marketing their products in the US and Europe will also need to understand the differences between US and European regulatory review processes and data requirements.

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Maria E. Donawa

Donawa Consulting, Piazza Albania 10, I-00153 Rome, Italy, tel. +39 06 578 2665, e-mail: medonawa@donawa.com

www.donawa.com

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