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.

### 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 review.
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 medicinal substance. However, some requested nonclinical data such as that described 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.”

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 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. 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 consis-
tency 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 coro-
nary 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 Administra-
tion (FDA) published two DES guidance documents; 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 require-
ments, product development pathways; systemic pharmacol-
ogy, 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 assess-
ment of drug–stent combinations; and postapproval con-
siderations. It also refers to another FDA 43-page guidance
document 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 defi-
cencies, general biocompatibility considerations, test article
certification, good animal husbandry, factors affecting the
ability to pool data from US and non-US studies, and label-
ing for a DES.

In contrast to the EMEA DES guideline, which was devel-
oped 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 involve-
ment 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
asp).

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, includ-
ing 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 evo-
lution 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 evolu-
tion of this process and the manner in which these guide-
lines are being developed and by whom. Those marketing
their products in the US and Europe will also need to under-
stand the differences between US and European regulatory
review processes and data requirements.

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