

# The Notified Body Consultation Procedure: Part 2

Manufacturers of medical devices incorporating ancillary substances should have a clear understanding of the consultation procedure that their Notified Body will have to follow. Part 1 of this article discussed the regulatory requirements and important guidance documents. Part 2 covers aspects of the process itself, required documentation and fees.

## Early review of guidance

The medical device directives specify the requirements for the Notified Body consultation procedure, but not the actual process for meeting the requirements. Thus, manufacturers should begin the consultation process by reviewing the European MEDDEV guidance on borderline products, drug-delivery products and ancillary substances.<sup>1</sup> Section C of the guidance describes the Notified Body actions that should be taken to initiate the consultation procedure, the documentation to be provided by the Notified Body to the Competent Authority for medicinal products, and the consultation process itself. Particular attention should be paid to section C.3; it outlines the documentation required, which will be unfamiliar to most medical device manufacturers. This makes early planning a necessity for preparing documentation that will be acceptable to drug regulatory authorities and accurately reflects device safety and performance characteristics, so as to avoid costly delays during the review process.

Equally important is the early identification of guidance documents from national Competent Authorities, which may potentially be consulted. The UK Medicines and Healthcare products Regulatory Agency (MHRA) and the Irish Medicines Board (IMB) are mentioned in this article and also in Part 1 as



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examples of Competent Authorities that provide consultation on ancillary substances and have developed guidance on how they manage the process. Other Competent Authorities may have similar guidance available. If the European Medicines Agency (EMA) is to be consulted, the current<sup>2</sup> and draft EMA guidance<sup>3</sup> on the consultation procedure should be reviewed. The draft EMA guidance is useful for planning purposes because it contains updated links and references.



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## Selecting a Notified Body

The Notified Body is responsible for contacting the Competent Authority or EMA to initiate the consultation procedure. As stated in the MEDDEV guidance document, the Notified Body should ensure that the data supplied by the manufacturer include a specific segment on the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device. The Notified Body also must verify the usefulness of the ancillary substance as part of the medical device, taking into account the intended purpose of the device. This is a critical responsibility and step in the consultation procedure because the Competent Authority or EMA will need to take this verification into consideration in reaching an opinion on the quality and safety of the substance.

If a manufacturer is in the early phase of a project involving a medical device incorporating an ancillary substance, and has not yet contracted a Notified Body, the potential benefits of selecting one with experience and established procedures for managing the consultation procedure should be considered. For a consultation on an ancillary medicinal substance, the manufacturer can select any national Competent Authority to provide an opinion on the substance and should make this selection in close cooperation with the Notified Body. A Competent Authority that is likely to provide the most efficient and cost-effective consultation and, if possible, which has experience in authorising a medicinal product that incorporates the same medicinal substance, should be selected. A Notified Body with experience in working with several Competent Authorities will be able to provide an opinion on this critical aspect of the process.

## Timelines

The opinion of the national Competent Authority or the EMA must be provided within 210 days after the receipt of valid documentation. This requirement is specified in the Medical Devices Directive (MDD; 93/42/EEC) in Section 4.3, Annex II, and Section 5, Annex III, and in the Active Implantable Medical Devices Directive (AIMDD; 90/385/EEC) in Section 4.3, Annex 2, and Section 5, Annex 3.

It is important to note that this timeframe is based upon the receipt of documentation that the regulatory authority considers acceptable for providing an opinion; therefore, project timelines should consider the possibility that additional time may be needed during the submission process to satisfy the authority. A Notified Body with experience in the consultation procedure is likely to be more accurate in estimating the actual time needed to complete this process than one without this experience.

## Pre-submission activities and meetings

Although there are similarities among regulatory authorities on pre-submission activities, some differences exist. For this reason, if the consultation will be provided by a national Competent Authority, any guidance issued by the authority should

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be reviewed in advance of the submission to understand what is expected during the pre-submission period. For example, section 2.1, Pre-submission meetings and notification, of the MHRA consultation procedure guidance<sup>4</sup> states that in order to facilitate allocation of the consultation to assessors in the relevant therapeutic assessment team, it is helpful to send a pre-submission notification email to the contacts on the first page of the guidance when a submission date has been identified. The IMB consultation procedure guidance<sup>5</sup> describes pre-submission activities in section 3.1 of its guidance document, stating that the Notified Body should request in writing a consultation with the IMB ideally six months before the intended submission.

If consultation is sought from the EMA, manufacturers should refer to the section on pre-submission activities of the draft EMA guidance, which includes a link to the EMA web page on Ancillary medicinal substances. The EMA also requires that the Notified Body provide an “intention to submit letter” at least six months before the expected date of submission. Both current and draft versions of the EMA guidance state that the letter should include the date of expected submission and the scientific explanation that the action of the medicinal substance incorporated in the medical device is only ancillary to that of the device. Both versions state that the scientific explanation should be in line with the MEDDEV guidance; however, the draft guidance refers to the current version—2.1/3 rev 3, December 2009—instead of the obsolete version.

Depending upon the authority involved with the consultation, a pre-submission meeting may be required or may be optional. For example, the EMA strongly recommends a pre-submission meeting at least six months before the expected date of submission. The IMB requires a pre-submission meeting, which should be held at least two months before the expected date of submission. The MHRA states that meetings associated with an imminent consultation may be arranged as part of the consultation procedure. It also states that a scientific advice meeting to discuss the consultation at an early stage, which is chargeable, may also be arranged.

### Data requirements and format

The documentation that should be provided by the Notified Body to the Competent Authority or EMA is described in the MEDDEV guidance on ancillary substances; however, important reference is made to any relevant national guidance where consultation is provided by a Competent Authority or to EMA guidance where consultation is provided by that agency.

As stated in the MEDDEV guidance, the information provided to the Notified Body should be based upon Annex I of Medicinal Products Directive (2001/83/EC), as amended by Directive 2003/63/EC. This latter directive contains a revised Annex I of Directive 2001/83/EC, Analytical, Pharmacotoxicological and Clinical Standards and Protocols in Respect of the Testing of Medicinal Products, which is currently in force.


Although the format requested by the various regulatory authorities may differ, the data requirements and information requested is

consistent with that described in the MEDDEV guidance. For example, the first section, General information, should include a general description of the medical device, including the manufacturer’s claim regarding the purpose of incorporation of the ancillary medicinal substance or the ancillary human blood derivative, together with a critical appraisal of the results of the risk assessment.

The section Quality documentation is divided into two sections, the first providing information on the ancillary medicinal substance or the ancillary human blood derivative. This section should include relevant parts of the Common Technical Document (CTD) Module 3, in accordance with the format described in Volume 2B, Notice to Applicants, Medicinal products for human use, Presentation and format of the dossier Common Technical Document (CTD). Guidance is also provided on how to provide information on the active substance. The section should also include CTD Module 2.3, Quality Overall Summary in accordance with Volume B, Notice to Applicants.

The second section describes the information to be provided on the ancillary substance as incorporated in the medical device. The remaining sections cover nonclinical documentation, clinical evaluation and labeling.

### Payment processes and fees

Section 4.5, Fees, of the draft EMA guidance includes updated links to fees charged for the consultation procedure. For example, the fee charged for an initial request concerning an ancillary substance that is new to the EMA centralised procedure is €76,000; a known ancillary blood derivative from a known source, €57,200; or a known ancillary medicinal substance from a known source, €38,100. Small and medium enterprises can apply for fee reductions. Readers should refer to the websites of the Competent Authority of interest to obtain a current list of fees. 

### References

1. Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative (MEDDEV 2.1/3 Rev. 3, December 2009); [http://ec.europa.eu/consumers/sectors/medical-devices/documents/borderline/index\\_en.htm](http://ec.europa.eu/consumers/sectors/medical-devices/documents/borderline/index_en.htm)
2. EMEA recommendation on the procedural aspects and dossier requirements for the consultation to the EMEA by a Notified Body on an ancillary medicinal substance or an ancillary human blood derivative incorporated in a medical device (Doc. Ref. EMEA/CHMP/401993/2005, 24 April 2008); [www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/10/WC500004337.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004337.pdf)
3. European Medicines Agency recommendation on the procedural aspects and dossier requirements for the consultation to the European Medicines Agency by a Notified Body on an ancillary medicinal substance or an ancillary human blood derivative incorporated in a medical device or active implantable medical device (Draft, 21 October 2010); [www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2010/10/WC500098403.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/10/WC500098403.pdf)
4. United Kingdom Medicines and Healthcare products Regulatory Agency guidance on the consultation procedure; [www.mhra.gov.uk/howweregulate/devices/medicaldevicesdirective/drug-deviceconsultations/index.htm](http://www.mhra.gov.uk/howweregulate/devices/medicaldevicesdirective/drug-deviceconsultations/index.htm)
5. Irish Medicines Board guidance on the consultation procedure; [www.imb.ie/en/medical-devices/premarket-activities/drugdevice-combination-products.aspx](http://www.imb.ie/en/medical-devices/premarket-activities/drugdevice-combination-products.aspx)