HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Drug-Device Consultations

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This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

CONTENTS

1 SCOPE

This guideline concerns the procedural aspects relating to a consultation to the HPRA by a Notified Body on an ancillary medicinal substance used in a medical device. In addition, guidance on the dossier requirements for such a consultation is provided.

2 INTRODUCTION

Section 4.3 of Annex II and section 5 of Annex III to Council Directive 93/42/EEC requires that a Notified Body consult a Competent Authority for medicinal products or the EMA when ancillary medicinal substances are used in medical devices, as defined in Annex I, section 7.4, before taking a decision on providing CE Mark certification. This guideline concerns the procedural aspects and dossier requirements for a consultation with the HPRA, which is the Competent Authority for medicinal products in Ireland. The guideline is aligned with the draft 'Guideline on the procedural aspects and dossier requirements for the consultation to the EMA by a notified body on an ancillary medicinal substance used in a medical device' (EMEA/CHMP/401993/2005).

The objective of the consultation procedure is to verify the safety and quality of the medicinal substance, taking account of the intended purpose of the device, by analogy with the appropriate methods specified for medicinal products in Directive 2001/83/EC, as amended.

The HPRA is currently in a position to accept applications for consultation where the ancillary medicinal substance is an authorised medicinal substance[i)] being used for an established purpose[ii)]. However, it is not in a position to accept applications where the ancillary medicinal substance is an authorised medicinal substance being used in a non-established purpose, a novel medicinal substance or if the substance is of biological origin[iii)].

It should be noted that the HPRA will not accept applications for consultation where the application has already been submitted to another Competent Authority.

(i) The term 'authorised medicinal substance' means present in a medicinal product that has been authorised by the HPRA or EMA

(ii) The term 'established purpose' means use in an authorised indication (as a medicinal product), or use for a purpose within the same ATC (Anatomical Therapeutic Chemical Classification System) code in the same anatomical location as the authorised indication. Applicants are encouraged to contact the HPRA if they have any queries in this regard.

(iii) Biological medicinal products are defined in the 'Guidance for applicants on biologicals' (http://www.hma.eu/215.html).

3 CONSULTATION PROCEDURE

3.1 Pre-submission

3.1.1 Consultation request

The Notified Body should request, in writing, a consultation with the HPRA. Ideally, this request should be made 6 months before intended submission and should be addressed to Customer Services in the HPRA. The request will be acknowledged and at a later date the HPRA will ask the Notified Body to submit the following documents:

- Application form

- Explanation for classification

  This document should be compiled by the Notified Body in conjunction with the device manufacturer using the template provided (Appendix 2). Applicants may wish to refer to the following documents for guidance on classification:

  - MEDDEV 2.4/1 Guidelines for the classification of medical devices
  - MEDDEV 2.1/3 Guidance document on 'Borderline products: medical devices/medicinal products' and 'combination products'

- Verification of the usefulness of the medicinal substance in the medical device

  The Notified Body is responsible for verifying and documenting the usefulness of the medicinal substance in the device. The aspect of 'usefulness' relates to the rationale for using the medicinal substance in relation to the specific intended purpose of the device. It refers to 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. The Notified Body may refer to relevant 'supportive scientific information' (Appendix 3), where necessary.
  A preliminary opinion regarding the usefulness of the medicinal substance in the medical device may be provided at this stage of the consultation procedure. However, the HPRA requires the final opinion of the Notified Body at the submission stage of the consultation procedure.

3.1.2 Pre-submission procedure

When the documents listed in section 3.1.1 have been reviewed, the HPRA will inform the Notified Body whether or not they are willing to accept the application. The HPRA will not accept applications if they do not agree with the scientific explanation for classification.

Having informed the Notified Body that an application can be accepted, the HPRA will indicate a proposed time frame for the procedure, stating when the assessment can be initiated and will agree a submission date with the Notified Body. If the Notified Body subsequently no longer requires the consultation, on the basis of the time schedule or for other reasons, the HPRA must be notified of this decision as soon as possible. If the dossier is received more than 1 - 2 weeks after the agreed submission date, changes to the initial time schedule may be made.

3.1.3 Pre-submission meeting

Prior to submission the Notified Body and device manufacturer must attend a pre-submission meeting at the HPRA. This meeting should be held at least 2 months before the expected date of submission and is intended to assist the Notified Body and device manufacturer in preparing their application. At this meeting regulatory advice can be provided to the Notified Body and device manufacturer. However, scientific advice will not be provided.

3.2 Submission

Upon request from the HPRA the Notified Body should submit the application and fee. Once an application has been submitted, the HPRA will not accept any amendments to the application dossier unless they have been requested by the HPRA.

3.2.1 Documentation requirements

The application for consultation must be accompanied by the documentation listed below. One copy of each volume is required, each volume securely bound but readily separable, with the documents in the order given below, clearly identified and separated from each other. In addition, a single electronic copy of the documentation should be provided (files should be in pdf format with appropriate indexing). References to published literature should be accompanied by the full text of the published article/study.

The dossier should be comprehensive enough to permit independent/primary review. The Notified Body should ensure that all the required documentation is provided.

Additional information of specific relevance to the quality, safety and usefulness of a particular medicinal substance should also be included if not addressed in the sections below. The HPRA may request information not listed below if deemed necessary.

It should be noted that because of the wide range of medical devices which incorporate medicinal substances, a flexible approach to the data requirements will be adopted. Nevertheless the information should be based in principle, to the extent relevant, on Annex I to Directive 2001/83/EC as amended by Commission Directive 2003/63/EC. It is envisaged that, where well-known medicinal substances for established purposes are the subject of the consultation all aspects of safety and usefulness may not be required and many of the

headings will be addressed by reference to the literature, including standard textbooks, experience and other information generally available. Nonetheless the documentation requirements given in this section should be addressed. Applicants should consider the extent of population exposure to date if they wish to claim that a medicinal substance is well-known and being used for an established purpose. Furthermore, the quality of cited references should be of a high standard.

Volume 1 (Quality):

1 Cover letter

2 Comprehensive table of content

3 Application form

4 Good manufacturing practice documentation

- Where a medicinal substance is incorporated in the medical device a declaration is required from the manufacturer of the medical device containing the ancillary medicinal substance stating that the active substance manufacturer(s) operates in compliance with the detailed guidelines on good manufacturing practice for starting materials.

- Where a medicinal product is incorporated in the medical device, documentary evidence is required demonstrating that the medicinal product manufacturer(s) operates in compliance with the detailed guidelines on good manufacturing practice (refer to Section 2.4 of the application form). Applicants should note the following:

    - The manufacturer responsible for batch release of the medicinal product must be located in the EEA.

    - For manufacturing sites outside the EEA and where a mutual recognition agreement or other Community arrangement does not apply, the site must have been inspected for GMP compliance by an EEA medicines authority.

    - A declaration by the Qualified Person of each of the manufacturing authorisation holders where the active substance is used as a starting material is required stating that the active substance is manufactured in accordance with the guidelines on good manufacturing practice for starting materials as adopted by the Community. A declaration must also be provided by the Qualified Person of the manufacturing authorisation holder(s) responsible for batch release.

5 Product information and labelling (English only).

6 Quality summary (or expert report) for the ancillary medicinal substance as an integrated part of the medical device.

7 Quality overall summary (relevant parts) for the ancillary medicinal substance as an integrated part of the medical device in accordance with the format of Volume 2B (Presentation and content of the dossier) of the Notice to Applicants (Eudralex, The Rules Governing Medicinal Products in the European Union).

8 Module 3: Quality – relevant parts in accordance with the format of Volume 2B (Presentation and content of the dossier) of the Notice to Applicants (Eudralex, The Rules Governing Medicinal Products in the European Union) for the ancillary medicinal substance as an integrated part of the medical device. In preparing module 3 the following should be noted:

- Applicants should refer to the 'Guideline on summary of requirements for active substances in the quality part of the dossier (EMEA/CVMP/1069/02; CPMP/QWP/297/97 Rev 1)' when preparing section 3.2.S.
    - If a certificate of suitability (CEP) is to be submitted for the ancillary medicinal substance, refer to section 2.1 of this guideline.
    - If a European Drug Master File (EDMF)/Active Substance Master File is to be submitted, refer to section 2.2 of this guideline.

      The EDMF holder must give permission to the HPRA to access the data in the EDMF in relation to a specific drug consultation, in the form of a 'Letter of Access'.
    - Where data relating to any part of 3.2.S is omitted detailed justification is required.
- Applicants should refer to the requirements for section 3.2.P of Module 3 in Volume 2B (Presentation and content of the dossier) of the Notice to Applicants (Eudralex, The Rules Governing Medicinal Products in the European Union) when preparing the dossier for the medical device with the ancillary medicinal substance incorporated. In the context of a consultation the term 'drug product' can be taken to mean the medical device and ancillary medicinal substance together as a finished product.
    - This section must contain a detailed account of the manufacturing process of the finished product including information relating to the incorporation of the medicinal substance into the device and all subsequent processing. However, an account of the manufacturing process of the device prior to incorporation of the medicinal substance is not usually required unless requested by the HPRA.
    - Where data relating to any part of 3.2.P is omitted justification is required.

Volume 2 (Non-clinical):

1 Cover letter

2 Comprehensive table of content

3 Application form

4 Product information and labelling (English only)

5 Non-clinical overview (or expert report) for the ancillary medicinal substance as an integrated part of the medical device.

6 Tabular summaries for non-clinical (pharmacology, pharmacokinetics and toxicology) studies.

7 Non-clinical documentation for the ancillary medicinal substance as an integrated part of the medical device, following the headings and data requirements of Section B.3 of the guideline MEDDEV 2.1/3 rev. 2 [(a), (b), (h) – (o)].

Volume 3 (Clinical):

1 Cover letter

2 Comprehensive table of content

3 Application form

4 Product information and labelling (English only)

5 Explanation for classification (Appendix 2)

6 Verification of the usefulness of the medicinal substance in the medical device

7 Clinical overview (or expert report) for the ancillary medicinal substance as an integrated part of the medical device.

8 Tabular summaries for clinical studies (efficacy, safety and individual).

9 Clinical documentation for the ancillary medicinal substance as an integrated part of the medical device, following the headings and data requirements of Section B.3 of the guideline MEDDEV 2.1/3 rev. 2 [(a), (b), (m) – (p)].

3.2.2 Validation criteria

Each application will be validated to ensure all required documentation is supplied. If documentation is not supplied, justification for its absence needs to be supplied prior to validation. Incomplete submissions will not be validated.

3.3 Consultation procedure

The HPRA will review the dossier and will prepare an assessment report detailing the assessment of the dossier by analogy with the appropriate methods specified for medicinal products in Directive 2001/83/EC, as amended. The report will include an overall opinion on the quality and safety of the drug substance.

In addition, any queries to be addressed by the device manufacturer or the EDMF holder will be listed. The assessment report will be sent to the Notified Body, however any queries on the restricted part of the EDMF will be sent to the EDMF holder, and the Notified Body will be informed. Once the report has been issued the clock will be stopped for 60 calendar days to allow the applicant to reply to queries. If a longer clock stop is needed the applicant should send a justified request to the HPRA.

A longer clock stop will be granted at the discretion of the HPRA and, in normal circumstances, a clock stop will not exceed 90 calendar days.

The HPRA will review the responses to the queries and, if necessary, will address further queries to the Notified Body or EDMF holder. Once the queries have been sent the clock will be stopped for 60 days with the opportunity for a longer clock stop as mentioned above. Following receipt of these responses a final assessment report will be prepared. It should be noted that where the response to queries raised by the HPRA is not satisfactory, this may preclude a positive opinion being issued.

The HPRA aims to issue a final assessment report with a final positive or negative opinion to the Notified Body within 210 days of validation of the application dossier. The opinion will be based on the quality and safety of the substance, including the clinical benefit/risk profile of the incorporation of the substance into the device, and will 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.

Once an opinion has been issued the consultation procedure is considered to be closed.

4 NOTIFICATIONS FROM A NOTIFIED BODY

Following completion of the consultation procedure the Notified Body must convey its final decision to the HPRA. The Notified Body will give due consideration to the views expressed in the consultation when making this decision. If the Notified Body decides to issue a certificate when it has received a negative opinion from the HPRA, it should consult with the competent authority for devices before issuing the certificate. The HPRA must be informed if the Notified Body decides to issue a certificate when it has received a negative opinion from the HPRA.

Should the Notified Body seek another consultation with a competent authority other than the HPRA after an opinion has been issued by the HPRA, the HPRA should be informed of the outcome of this consultation. Furthermore, the Notified Body may withdraw the request to the HPRA during the consultation and may seek a consultation with another competent authority, in which case it should inform the HPRA.

5 MEDICAL DEVICE VIGILANCE

Manufacturers of medical devices, including those containing an ancillary medicinal substance, should consult HPRA Guidance Note 7 – The Vigilance System for Medical Devices.

APPENDIX 1 REFERENCES

Directive 93/42/EEC concerning medical devices amended by Directive 2000/70/EC and Directive 2001/104/EC

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended

Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC (Annex I)

Eudralex, The Rules Governing Medicinal Products in the European Union, Notice to Applicants Volume 2B (Presentation and content of the dossier)

Guideline on summary of requirements for active substances in the quality part of the dossier (EMEA/CVMP/1069/02; CPMP/QWP/297/97 Rev 1)

Guideline on the chemistry of new active substances (CPMP/QWP/130/96 Rev 1)

MEDDEV 2.1/3 rev. 2 Guidance document on 'Borderline products: medical devices/medicinal products' and 'combination products'

MEDDEV 2.4/1 rev. 8 Guidelines for the classification of medical devices

APPENDIX 2 FORMAT FOR EXPLANATION FOR CLASSIFICATION

Explanation for classification of medicinal substances integrated in medical devices as ancillary substances according to the Demarcation Guideline MEDDEV 2.1/3 rev. 2.

Date: **DD/MM/YYYY**
Notified body: **<Name>**
Applicant: **<Name>**
Product: **<Name>**

1. Intended Purpose of the Product

1.1 Type of product, brief description, and principal mechanism of action:
Make reference to medical device / medicinal product definitions

1.2 Indication, therapeutic purpose and intended use:

1.3 Product presentation / composition:
Quantitative and qualitative composition, route of administration and/or mode of action, pharmaceutical form and description of the product.

2. Method by which the principal intended action is achieved

Components	Intended action according to applicant*	Reference to Guideline MEDDEV 2.1/3 rev. 2**
COMPONENT A	**Principal action:** <title that clearly describes the action> Scientific explanation (brief):	Refer to relevant section of the Guideline above and to respective example, e.g. *A.3.1 – Examples for medical devices* -"- Haemostatic products, for example…
COMPONENT B	**Ancillary action:** <title that clearly describes the action> Scientific explanation (brief):	Refer to relevant section of the Guideline and to respective example, e.g. *A.5 – Medical devices incorporating a medicinal substance with ancillary action* "Examples of such devices are: ...

***** *Provide cross-reference to 'Supportive scientific information' in Appendix 3.*
****** *In addition - reference to other regulatory texts can be made where relevant.*

3. Regulatory status of similar products
Status in EU member states and in non-EU regions if applicable
Provide examples of similar products that have already been marketed in EU or in non-EU regions

4. Current medical use
Of the medical device or component devices alone or in combination (including use in the EU and/or in non-EU regions)

5. Other relevant aspects

APPENDIX 3 SUPPORTIVE SCIENTIFIC INFORMATION

Supportive scientific information is important with regard to the ancillary action of the medicinal substance in the device and its usefulness in the device. In particular scientific information demonstrating the ancillary nature of the medicinal active substance (as defined in the guideline MEDDEV 2.1/3 rev. 2) in the combination product has to be provided. Scientific information should cover:

- The mode of action of the components (device and medicinal product) on their own and in the combination product.

- Any reference / summaries of pre-clinical or clinical experience/trials with the combination product / medicinal product alone / device alone.

- Explanation why the medicinal substance is added to the device: identification of those patients that would benefit from this combination product versus device alone

- Consideration of the potential risks associated with the addition of the medicinal substance to the device (immune reactions, carcinogenicity...)

This list is not exhaustive and is only intended for guidance.