famhp
federal agency for medicines and health products

Guideline for applicants

for the consultation of the FAMHP by a Notified Body

on an ancillary medicinal substance incorporated in a medical device or active implantable device

Procedural aspects and document requirements

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1. Scope

This guideline concerns the procedural aspects relating to a consultation to the FAMHP by a Notified Body on an ancillary medicinal substance used in a medical device. In addition, guidance on the dossier requirements (content and format) for such a consultation is provided hereafter. The scope of this guideline is applicable to the following types of consultations:

- **Initial consultation** on an authorised ancillary medicinal substance being used for an established purpose (i.e. where the **medicinal substance** from the specified manufacturer **has not been evaluated** by any EEA member state or the EMA in connection with the previous marketing authorisation and/or a previous successful notified body consultation).
- **Initial consultation** on an authorised ancillary medicinal substance being used for an established purpose **from a known source** (i.e. where the **medicinal substance** from the specified manufacturer **has already been evaluated** by an EEA member state or the EMA in connection with a previous marketing authorisation and /or a previous successful medicines authority consultation)
- **Supplementary consultation on an authorised ancillary medicinal substance** when changes are made to the medicinal substance, particularly relating to its manufacturing process, the notified body is required to consult with a competent authority in order to confirm that the quality and safety of that substance are maintained and 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.

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2. Introduction and legal basis

The objective of the consultation procedure is to verify the safety and quality of the medicinal substance including the benefit or risk of the incorporation of the substance into the device, taking in account the intended purpose of the device. The FAMHP will verify these the safety, quality and usefulness of the ancillary substance by analogy with the appropriate methods specified in Annex I to the Directive 2001/83/EC, as amended.

For medical devices incorporating a medicinal substance with action ancillary to the device, pursuant Regulation (EU) 2017/745 article 1(8), the notified body shall request a scientific opinion from either a National Competent Authority (NCA) or the European Medicines Agency (EMA) (Regulation (EC) No 2017/745, Annex IX, section 5.2). The notified body shall seek the opinion of EMA for medicinal products falling exclusively within the scope of centralized procedure (Annex I, Regulation (EC) No 726/2004) or that incorporate human blood or plasma derivates.

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

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3. Procedure and required documents

3.1. Pre-submission activities

3.1.1. Consultation Request

The notified body should request, in writing with an "**Intention to Submit Letter**" (ISL), a consultation with the FAMHP.
This request should be made by preference at least 6 months before the intended submission and should be addressed to the STA unit of the FAMHP. (sta.meddev@fagg-afmps.be)
Ideally, the ISL should be directly accompanied by the following documents:

- **Explanation for classification**

  This document should be compiled by the Notified Body in conjunction with the device manufacturer using the template provided (Annex 2). Applicants may wish to refer to the following documents for guidance on classification:
  - Regulation (EU) 2017/745 chapter V

- **Verification of the usefulness of the medicinal substance in the medical device ("assessment of the usefulness")**

  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' (in Annex 3), where necessary.

  After the reception of the documents listed before have been reviewed, the FAMHP will inform the Notified Body whether or not they are willing to accept the application and a date for a pre-submission meeting will be scheduled in accordance with the firm, the concerned Notified body and the FAMHP within a period of 6 months maximum.

  The documents regarding the explanation of classification (cfr: Annex 2.) and the assessment of usefulness (cfr: Annex 3.) can be provide after the ISL, but must be available at the latest 2 months before the scheduled pre-submission meeting.

3.1.2. Pre-submission meeting

The FAMHP strongly recommends a pre-submission meeting with the relevant notified body (NB) and device manufacturer. This meeting should preferentially 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 formal consultation application. At this meeting regulatory and procedural guidance can be provided to the NB and device manufacturer and the specific documents above mentioned can be discussed. However, scientific advice will not be provided since this falls outside the scope of a pre-submission meeting.

If a presentation (i.e. power point) is available, this should be send to the STA unit at least 2 weeks before the established date of the pre-submission meeting.
If the applicant has a list of specific questions which he likes to submit before this meeting, these should be sent to the same address as soon as possible and at least 1 month before the pre-submission meeting.

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The meeting slides and the list of question(s) are primarily intended to facilitate the pre-submission meeting and subsequently to assist the Notified Body and device manufacturer in preparation of their formal consultation application.

3.2. Submission

Once a formal consultation application has been submitted, the FAMHP will normally not accept any additional data or amendments to the application dossier unless they have been requested by the FAMHP or agreed upon at time of the pre-submission meeting with the NB and device manufacturer.

3.3. Documentation requirements

A single electronic copy of the documentation should be provided by eudralink or email. References to published literature should be accompanied by the full text of the published article/study.

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 FAMHP may request information not listed below if deemed necessary. Because of the wide range of medical devices which incorporate, as an integral part, an ancillary medical substance, a flexible approach to the data requirement is necessary. 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 2033/63/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 literature, including standard textbooks, experience and other information generally available. Nonetheless all headings should be addressed, either with relevant data or justification for absence of data. The latter may be based on the manufacturer's risk assessment.

Volume 1 : Quality documentation:

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 medicinal product manufacturer(s) operates in compliance with the detailed guidelines on good manufacturing practice: (https://ec.europa.eu/health/documents/eudralex/vol-4_en)

Applicants should note the following:

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

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- 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 EU. A declaration must also be provided by Qualified Person of the manufacturing authorisation holder(s) responsible for batch release.

5. Product information and labelling

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 medicinal device in accordance with the format of Volume 2B of the "Notice of 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 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 IMB 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 FAMHP.

     - Where data relating to any part of 3.2.P is omitted, justification is required.

Volume 2: Non-clinical documentation :

1. Cover letter

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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

Volume 3: Clinical documentation:

1. Cover letter

2. Comprehensive table of content

3. Application form

4. Product information and labelling (English only)

5. Explanation for classification (Annex 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

3.3.1. 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.

3.4. Consultation procedure

3.4.1. Initial consultation procedure:

The FAMHP 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 including the benefit or risk of the incorporation of the ancillary substance into the device.

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 FAMHP.
A longer clock stop will be granted at the discretion of the FAMHP and, in normal circumstances, a clock stop will not exceed 90 calendar days.
The FAMHP will review the responses to the queries and, if necessary, will address further queries to the Notified Body or EDMF holder. Once the further 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 FAMHP is not satisfactory, this may preclude a positive opinion being issued.

The FAMHP aims to issue a final assessment report with a final positive or negative opinion to the Notified Body within max. 210 days after formal validation of the initial consultation application. The opinion will be based on the quality and safety of the substance, including the 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.

3.4.2. Supplementary consultation procedure:

Before any change is made by the device manufacturer with respect to an ancillary substance incorporated in a device, in particular related to its manufacturing process, the manufacturer shall inform the notified body of the changes. Subsequently, that notified body shall seek the opinion of the medicinal products authority consulted initially, in order to confirm that the quality and safety of the ancillary substance remain unchanged. In this context the FAMHP shall take into account the data relating to the usefulness of incorporation of the substance into the device as determined by the notified body, in order to ensure that the changes have no negative impact on the risk or benefit previously established concerning the incorporation of the substance into the device. The FAMHP will provide its opinion to the concerned Notified Body within max. 60 days after receipt and validation of all the necessary documentation regarding the changes.
Where the FAMHP, as consulted NCA, obtains information on the ancillary substance, which could have an impact on the risk or benefit previously established concerning the incorporation of the substance into the device, it shall advise the notified body as to whether this information has an impact on the risk or benefit previously established concerning the incorporation of the substance into the device. The notified body shall take that advice into account in reconsidering its assessment of the conformity assessment procedure.

3.5. Fees and payment.

The applicant pays a fee on the basis of the invoice that is sent by the Budget and Management control Department of the FAMHP. For each payment, please indicate the structured communication mentioned on the invoice. This will allow the FAMHP to link the payment to the correct invoice, even if a third party executes it. Without the structured communication, we will consider the invoice as unpaid.

3.5.1. Fee payment procedure

1. The company receives an **invoice** for all validated requests for national Scientific-Technical Advice and/or consultation procedures submitted in the prior quarter.

2. The invoice will mention the **references** of the request(s).

3. The fact that the FAMHP does not work with a **Purchase Order (PO) number** is not a valid reason for not paying an invoice.

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4. You will always receive the invoice at **the billing address**. Please provide your invoicing email address in the cover letter included in the submission of the consultation procedure.

5. Any **bank costs** for payments from abroad cannot be charged to the FAMHP. These costs are for the account of the payer.

6. In case the applicant should ask for a **withdrawal** of a consultation request after the validation of the request, the fee is due.

7. When a formally submitted STA request is declared **invalid** by the FAMHP at the end of the validation phase of the procedure, the fee will not be charged to the applicant.

3.5.2. Fees applicable

The FAMHP is currently applying the rates for NB consultation procedures as indicated in table 1 below in accordance with the FAMHP's fee regulations of 2023. The fees are subject to indexation on an annual basis.

With the entry into force of the MDR, (Regulation (EU) 2017/745), device manufacturers may want to request in concertation with their Notified Body a (re)consultation with no, minor or major dossier revisions or changes to their device-drug combination product as compared to what was previously CE certified under the old EU Medical Device Directives. In the context of such transition from MDD to MDR, the FAMHP wants to highlight that due to the large difference in the nature of such dossiers, the fee that applies, will largely be dependable on the workload of the dossier and will therefore be confirmed at the time of the consultation request.

Consultation by a notified body – initial consultation	48.038,25 €
Consultation by a notified body – variation (i.e. supplementary consultation)	21.002,81 €

Table 1: fees for NB consultation procedures with the FAMPH. These fees are intended to cover the FAMHP's workload related to the entire consultation procedure, including any pre-submission meeting requests from the applicant as well as the renumeration of any external experts that the FAMHP needs to consult during the coordination of such procedure.

4. Notifications from a notified body

Following completion of the consultation procedure the Notified Body should convey its final decision to the FAMHP. The Notified Body will give due consideration to the views expressed in the initial consultation when making this decision. Pursuant Regulation (EC) No 2017/745, Annex IX, section 5.2, paragraph (e) the Notified Body shall not deliver the certificate if it has received an unfavourable opinion from the FAMHP and shall convey it's final decision to the FAMHP. In all other cases, the Notified Body is requested to inform the FAMHP before issuing the certificate whenever the Notified Body would not be in favour of following some of the FAMHP's scientific opinions provided during the consultation.

The same principles apply for supplementary consultations where changes have been made with respect to an ancillary substance incorporated in a device. Pursuant Regulation (EC) No 2017/745, Annex IX, section 5.2, paragraph (f), the notified body shall not deliver the supplement to the EU technical documentation assessment certificate if the scientific opinion provided by the FAMHP is unfavourable. The notified body shall convey its final decision to the FMAHP as consulted NCA.

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

5. Medical device vigilance

Manufacturers of medical devices, including those containing an ancillary medicinal substance, should consult the Regulation (EU) 2017/745 chapter VII.

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Annex 1 : References

- 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
- Regulation (EU) 2017/745 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
- 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)

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Annex 2 : Explanation for classification

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

- Regulation (EU) 2017/745 medical devices (e.g. Annex VIII)

Explanation for classification of medicinal substances integrated in medical devices as ancillary substances according to regulation (EU) 2017/745.

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 Regulation (EU) 2017/745**
COMPONENT A	**Principal action:** <title that clearly describes the action> Scientific explanation (brief):	Refer to relevant section of the Regulation above and to respective example, e.g. *– 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 Regulation 2017/745 and to respective example, e.g. *– 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**

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Annex 3: assessment of usefulness

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

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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 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.

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