COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

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

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KEYWORDS

Consultation, notified body, ancillary medicinal substance, ancillary human blood derivative, medical device

Note: The changes introduced by Directive 2007/47/EC will apply from 21 March 2010 and will be implemented in this recommendation by that date.
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EXECUTIVE SUMMARY

This recommendation aims to provide interested parties with appropriate guidance on procedural aspects as well as format and data requirements to facilitate the consultation procedure to the European Medicines Agency (EMEA) by notified bodies on:

- Medicinal products within the meaning of Article 1 of Directive 2001/83/EC incorporated, as an integral part in a medical device and which are liable to act upon the body with action ancillary to that of the device.

- Medicinal product constituents or medicinal products derived from human blood or human plasma within the meaning of Article 1 of Directive 2001/83/EC incorporated, as an integral part in a medical device and which are liable to act upon the human body with action ancillary to that of the device.

These substances are referred to hereinafter respectively as ancillary medicinal substances and as ancillary human blood derivatives.

This recommendation applies to any application for consultation submitted to the EMEA by notified bodies.

1. INTRODUCTION

This recommendation is intended to provide the relevant parties with information about procedural aspects of the consultation procedure to the EMEA by notified bodies on an ancillary medicinal substance or an ancillary human blood derivative incorporated as an integral part in a medical device, as well as guidance on data requirements and format of such applications for consultation.

This recommendation applies when substances are liable to act upon the body with actions ancillary to that of the device.

This recommendation provides for two procedures:

a) Voluntary consultation of the EMEA in the case of ancillary medicinal substances

In this case, it is at the discretion of the Notified Body to choose the Competent Authority designated by the Member States with whom he consults before taking a decision. The Notified Body will give due consideration to the views expressed in the consultation when making its decision and it will convey its final decision to the competent body concerned.

The Directive does not refer to consultation of the EMEA in this context. However, in the past years, it has been the interpretation that EMEA “may be consulted, where the substance involved has been included in a medicinal product which has been evaluated by the EMEA.”

b) Mandatory consultation of the EMEA in the case of ancillary human blood derivative

In this case, the Notified Body has to seek the opinion from EMEA.

The Notified Body will give due consideration to the opinion of the EMEA when making its decision and may not deliver the certificate if the EMEA’s scientific opinion is unfavourable. It will convey its final decision to the EMEA.

2. **SCOPE**

The scope of this paper is to describe the format and content of the applications for consultation that the notified body in conjunction with the manufacturer of the medical device should submit to the EMEA, as well as procedural aspects for consultation of the EMEA on an ancillary medicinal substance or an ancillary human blood derivative incorporated in a medical device.

3. **LEGAL BASIS**

   a) Medical devices incorporating, as an integral part, a substance which, if used separately, may be considered to be a medicinal product and which is liable to act upon the body with action ancillary to that of the device (Article 1 (4) of Directive 93/42/EEC).

   Annex I, Section 7.4, first subparagraph, to Council Directive 93/42/EEC, as amended, states that, where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 65/65/EEC (this reference has to be understood as Directive 2001/83/EC as amended) and which is liable to act upon the body with action ancillary to that of the device, the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, by analogy with the appropriate methods specified in Directive 75/318/EEC (this reference has to be understood as Annex I to Directive 2001/83/EC as amended).

   Section 4.3 of Annex II (full quality assurance system) and Section 5 of Annex III (EC type-examination) to Council Directive 93/42/EEC, as amended, requires that, in the case of devices referred to in Annex I, section 7.4, first subparagraph, the notified body shall, as regards the aspects referred to in that section, consult one of the competent bodies designated by the Member States in accordance with Directive 65/65/EEC (this reference has to be understood as Directive 2001/83/EC as amended) before taking a decision. The notified body will give due consideration to the views expressed in this consultation when making its decision. It will convey its final decision to the competent body concerned.

   b) Medical devices incorporating as an integral part, a substance which, if used separately, may be considered to be a medicinal product constituent or a medicinal product derived from human blood or human plasma and which is liable to act upon the human body with action ancillary to that of the device (Article 1 (4a) of Directive 93/42/EEC).

   Annex I, Section 7.4, second subparagraph, to Council Directive 93/42/EEC, as amended, states that, where a device incorporates, as an integral part, a human blood derivative, the notified body shall seek a scientific opinion from the European Agency for the Evaluation of Medicinal Products (EMEA), on the quality and safety of the derivative, taking account of the appropriate Community provisions and, in particular, by analogy with the provisions of Directives 75/318/EEC and 89/381/EEC (these references have to be understood as Annex I to Directive 2001/83/EC as amended.). The usefulness of the derivative as a part of the medical device shall be verified, taking account of the intended purpose of the device.

   Section 4.3 of Annex II (full quality assurance system) and Section 5 of Annex III (EC type-examination) to Council Directive 93/42/EEC, as amended, requires that, in the case of devices referred to in Annex I, section 7.4, second subparagraph, the scientific opinion of the EMEA must be included in the documentation concerning the device. The notified body will give due consideration to the opinion of the EMEA when making its decision. The notified body may not deliver the certificate if the EMEA's scientific opinion is unfavourable. It will convey its final decision to the EMEA.
4. PRACTICAL RECOMMENDATIONS

4.1 Pre-submission activities

The EMEA strongly recommends a pre-submission meeting with the relevant notified body and device manufacturer at least 6 months before the expected date of submission in order to assist them in preparing their application.

The pre-submission guidance for medicinal products on the EMEA website (http://www.emea.eu.int - Human Medicines/Applications Procedures/Pre-submission guidance) may be helpful for applicants. It is intended to prepare separate pre-submission guidance for consultations on ancillary medicinal substances and ancillary human blood derivatives incorporated in medical devices.

Prior to the submission, the Committee for Human Medicinal Products (CHMP) will appoint one or, if necessary, two of its members to act as Rapporteur(s). The notified body will need to provide an “intention to submit letter” at least 6 months before the expected date of submission. This 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. This should be in line with the MEDDEV guidance 2.1/3 rev 2, July 2001. (See format in Appendix 2)

4.2 Data requirements and format of the application dossier

Each application for consultation shall be submitted to the EMEA using the relevant application form, that can be found on the EMEA website and containing the information described in this document.

Guidance on data requirements and format of the application dossier can be found in Appendix 1. For its preparation the EMEA has taken as basis the MEDDEV guidance 2.1/3 rev 2, July 2001 and supplemented this with guidance of EudraLex Notice to Applicants Volume 2B (Presentation and content of the dossier – CTD). In addition, references to specific guidance available for plasma-derived medicinal products, biological/biotechnological products and new chemical entities are given.

For ancillary human blood derivatives, the notified body has to provide information to the EMEA regarding the "context" that the human blood derivative will be used in, in order to ensure that the EMEA can give an opinion on the quality and safety of the substance and at the same time assess its usefulness within that context and reach a conclusion on the risk/benefit ratio for its incorporation in the medical device.

For medicinal substances, with ancillary action that are incorporated in a medical device, the safety, quality and usefulness will be verified, taking account of the intended purpose of the device, by analogy with the appropriate methods specified in Directive 75/318/EEC (this reference has to be understood as Annex I to Directive 2001/83/EC as amended).

According to MEDDEV guidance 2.1/3 rev 2, July 2001, 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.

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2 CHMP Rapporteur/Co-Rapporteur appointment: Principles, Objective criteria and methodology (EMEA/124066/2005)

3 This refers to the intended use of the medical device and the contribution of the ancillary human blood derivative to such use.
A clarification was published on the CHMP Monthly Report for November 2005 on the Active Substance Master file (ASMF) and Plasma Master file (PMF) concepts in relation to medical devices incorporating biological medicinal products as ancillary substance.

This clarification states the following:

Notified bodies, medical device manufacturers and manufacturers of the ancillary biological substances are advised that the non-applicability of the Active Substance Master File (ASMF) concept to biological active substances and the non-applicability of the concept of open and closed parts to Plasma Master File (PMF) as per the CHMP Monthly report for October 2004 as stated below, are applicable to medical devices incorporating biological medicinal products, including blood derivatives with action ancillary to that of the devices.

Therefore, ASMF are not allowed for these types of substances and the PMF should be made available to the medical device manufacturer, as for any other part of the dossier of an ancillary blood derivative.

EXTRACT FROM CHMP MONTHLY REPORT FOR OCTOBER 2004

Non-applicability of the Active Substance Master file (ASMF) concept to biological active substances

Marketing Authorisation Holders (MAH’s) and applicants are advised that the concept of Active Substance Master files, as laid down in Directive 2001/83/EC, as amended, cannot be applied in the context of biological medicinal products.

The characterisation and determination of biological active substances’ quality requires not only a combination of physic-chemical and biological testing, but also extensive knowledge of the production process and its control.

The MAH/applicant for a biological medicinal product could therefore not comply with the requirement to ‘take responsibility for the medicinal product’ without having full and transparent access to these quality-related data. The use of an ASMF would prevent such access, and should therefore not be allowed for biological active substances.

In addition, active substances, which are present in certain medicinal products such as vaccines or cell therapy medicinal products, do not fit with the concept of a ‘well-defined’ active substance.

Non-applicability of the ASMF concept of open and closed parts to Vaccine Antigen Master file (VAMF) and Plasma Master file (PMF)

The legislation does not provide for the use of open/closed parts in the Vaccine Antigen Master file (VAMF) and Plasma Master file (PMF). The concept of open (non-confidential) and closed (confidential) parts is specific to the Active Substance Master file.

Regarding the VAMF the legislation specifies that the VAMF holder cannot differ from the MAH/applicant for the concerned medicinal product: there is hence no rationale for an ‘open/closed’ parts system.

For the PMF the legislation specifies that where the MAH/applicant differs from the holder of the PMF, the PMF shall be made available to the MAH/applicant for submission to the competent authority.

It should be noted that it is not possible to cross-reference to the dossier of nationally authorised medicinal products in support of a notified body consultation procedure. This is because data held in national systems is not available to the EMEA for evaluation. The Committee for Human Medicinal
Products (CHMP) will give an opinion and therefore it should be provided with the relevant data for evaluation.

4.3 Consultation procedure to the EMEA

The Committee for Human Medicinal Products (CHMP), will appoint one or, if necessary, two of its members to act as Rapporteur(s). These CHMP members will each lead a team of experts in the evaluation of the submitted dossier. Input from other CHMP members is provided during the procedure.

The applicant for the consultation procedure is the notified body in accordance with the legal provisions of Directive 93/42/EEC, as amended. The consultation dossier for submission will be prepared in close collaboration between the medical device manufacturer and the notified body.

The CHMP will follow the same assessment timetable as used for a new application to the EMEA according to the Centralised Procedure as described in EudraLex Notice to Applicants Volume 2A, Chapter 4 i.e. a maximum 210 day timetable with the opportunity for clock stops for the applicant to reply to questions or communicated deficiencies.

The CHMP can be asked to shorten the procedure in the following cases:

- the device is for use in serious diseases (life threatening or heavily disabling diseases);
- a known medicinal substance or human blood derivative from a known source is used and when CHMP considers that the evaluation needed is less extensive;

After the evaluation period the CHMP/EMEA will issue an opinion on the safety, quality and usefulness of the medicinal substance incorporated in the medical device.

A Public Assessment Report on the Consultation procedure to the EMEA by notified bodies on ancillary medicinal substances incorporated in medical devices (CPAR) will be published on the EMEA website at the time the medical device obtains the CE mark. The relevant medical device manufacturer and ancillary medicinal substance manufacturer will be consulted through the notified body on the CPAR before publication. The general principles to be applied for the deletion of commercially confidential information in accordance with EMEA document EMEA/45422/2006 will apply.

4.4 Post-Consultation phase

When major or minor amendments to the documentation on an ancillary medicinal substance or ancillary human blood derivative incorporated in the medical device can affect the quality, safety and usefulness of the substance, the notified body should inform the EMEA on such follow-ups to the initial request. Such amendments will be classified and evaluated by analogy to the Variations Regulation (Commission Regulation (EC) 1085/2003).

4.5 Fees

Following the publication of Council Regulation (EC) No 1905/2005 of 14 November 2005 amending Regulation (EC) No 297/95 on fees payable to the European Medicines Agency (EMEA), and the adoption of the Implementing Rules by the EMEA Management Board, the applicable fees can be consulted on the EMEA website (http://www.emea.eu.int/htms/general/admin/fees/feesh.htm).

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4 CHMP Rapporteur/Co-Rapporteur appointment: Principles, Objective criteria and methodology (EMEA/124066/2005)
Fee reductions are applicable for scientific services (e.g. consultation procedure) for medical device manufacturers with SME status as registered at the EMEA SME office. Refer to SME user guide for SMEs.

REFERENCES


EudraLex, Notice to Applicants Volume 2B (Presentation and content of the dossier – CTD).

EudraLex, Notice to Applicants Volume 2A, Chapter 4 (Centralised Procedure).
APPENDIX 1 DATA REQUIREMENTS AND FORMAT OF THE APPLICATION DOSSIER

Section 1 comprises:

- Application Form
- Product Information and Labelling (English only)
- Appendix 2 (Scientific explanation that the action of the medicinal substance or human blood derivative incorporated in the medical device is only ancillary to that of the device in line with the MEDDEV guidance 2.1/3 rev 2, July 2001)
- Critical summaries (or expert reports) of the Quality, Non-Clinical and Clinical data provided in line with MEDDEV guidance 2.1/3 rev 2, July 2001 for the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device.
- Module 2.3: Quality Overall Summary (relevant parts) for the ancillary medicinal substance or ancillary human blood derivative itself in accordance with the format of Volume 2B, CTD of the Notice to Applicants (EudraLex, The rules governing medicinal products in the European Union).
- Tabular summaries for non-clinical and clinical studies.

Section 2 comprises:

- Quality, non-clinical, and clinical documentation, following the headings and data requirements of Section B.3 of the MEDDEV guidance 2.1/3 rev 2, July 2001 for the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device.

Section 3 comprises:

- Module 3: Relevant parts, for ancillary medicinal substance or ancillary human blood derivative itself, in accordance with the format of Volume 2B, CTD of the Notice to Applicants (EudraLex, The rules governing medicinal products in the European Union).

Note: For non biological ancillary medicinal substances for which an active substance master file (ASMF) or a CEP is used, refer to the EMEA guideline on ASMF (EMEA/CVMP/134/02 or CPMP/QWP/227/02).

Note: For ancillary human blood derivatives for which a PMF already exists, the relevant information in module 3 already submitted as part of the PMF does not need to be provided with the information for the consultation procedure. In this case, a notification letter should accompany module 3 from the medical device manufacturer including the following:

1. Reference to the PMF number and date of the certification
2. Declare that the PMF Certificate, Evaluation report and PMF dossier are fully applicable for the ancillary human blood derivative
3. Declare that the PMF holder has submitted the PMF Certificate, Evaluation report and PMF dossier to the medical device manufacturer.
4. State that the PMF Certificate, evaluation report and PMF dossier are available at the EMEA, and therefore not attached to this notification letter. However, on request, the PMF dossier will be sent to the EMEA within 48 hours.
Useful guidelines to fulfil the data requirements
The following list of guidelines is not exhaustive and there may be other guidelines applicable.

1 General guidance:


- EudraLex **Notice to Applicants Volume 2B** (Presentation and content of the dossier – CTD).

- Guideline on Active Substance Master File Procedure (EMEA/CVMP/134/02; CPMP/QWP/227/02). Please note this guideline is not applicable for biological active substances.

2 Guidance for blood derivatives

Quality:

- Note for Guidance on Plasma-Derived Medicinal Products (CPMP/BWP/269/95)

- Note for Guidance on Assessing the risk for Virus Transmission - New Chapter 6 of the NiG on Plasma-derived medicinal products (CPMP/BWP/5180/03).

- Guideline on the Scientific Data Requirements for a Plasma Master File (PMF) (EMEA/CPMP/BWP/3794/03).

- Note for Guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses (CPMP/BWP/268/95)

- Relevant European Pharmacopoiea monographs.

- Guideline on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with regard to vCJD Risk (CPMP/BWP/5136/03).

- CHMP Position Statement on Creutzfeldt-Jacob Disease and Plasma-Derived and Urine-Derived Medicinal Products. (CPMP/BWP/2879/02)

Good Manufacturing Practice:

- Manufacture of medicinal products derived from human blood or plasma, Annex 14 to the EU Guide to *Good Manufacturing Practice*.

Non-Clinical and Clinical safety:


The Committee on Proprietary Medicinal Products (CPMP) changed its name to Committee for Human Medicinal Products (CHMP) on 1 May 2004.

3  Guidance for biological/biotechnology products

Quality:

- Relevant CPMP/CHMP* Guidelines published on the EMEA website.
  
  (http://www.emea.europa.eu- Human Medicines/Human Guidelines (Eudralex vol 3)/Quality and Biologicals/ Biologicals);


- Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01).

Good Manufacturing Practice:

- Manufacture of Biological Medicinal Products for Human Use, Annex 2 to the EU Guide to Good Manufacturing Practice.

Non Clinical and Clinical safety:


4  Guidance for new chemical entities

Quality:

- Relevant CPMP/CHMP Guidelines published on the EMEA website.
  
  (http://www.emea.europa.eu - Human Medicines/Human Guidelines (Eudralex vol 3)/ Quality and Biologicals/ Quality)


Good Manufacturing Practice:

- Relevant Annexes to the EU Guide to Good Manufacturing Practice.

Non-Clinical and Clinical safety:


APPENDIX 2 SCIENTIFIC EXPLANATION FOR QUALIFICATION

A – Scientific explanation that the action of the medicinal substance or human blood derivative incorporated in the medical device is only ancillary to that of the device in line with the MEDDEV guidance 2.1/3 rev 2, July 2001

Date: DD/MM/YYYY

Notified body (Applicant): <Name>
Medical Device Manufacturer: <Name>
Medical Device: <Name>

Ancillary medicinal substance: <INN> <Common Name>
Ancillary human blood derivative <INN> <Common Name>

1. Description of Medical Device

Type of product, ancillary medicinal substance/ancillary human blood derivative, brief description, principal intended action:
Make reference to medical device / medicinal product definitions

Intended use:

Product presentation / composition:
Description of the product (e.g. Quantitative and qualitative composition, route of administration and/or mode of action, pharmaceutical form (where relevant)).

2. Method by which the principal intended action is achieved

<table>
<thead>
<tr>
<th>Combination product (medical device part(s) + ancillary medicinal)</th>
<th>Principal intended action according to applicant*</th>
<th>Reference to MEDDEV guidance 2.1/3 rev 2, July 2001**</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>substance(s) / ancillary human blood derivative(s)</th>
<th>Medical device part(s)</th>
<th>Principal action: &lt;title that clearly describes the action&gt;</th>
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<tbody>
<tr>
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<td>Refer to relevant section of the Guideline and to respective example, e.g.</td>
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<tr>
<td></td>
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<td>A.3.1 – Examples for medical devices</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-“- Haemostatic products, for example…</td>
</tr>
<tr>
<td></td>
<td>Ancillary medicinal substance(s) / Ancillary human blood derivative(s)</td>
<td>Ancillary action: &lt;title that clearly describes the action&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Refer to relevant section of the Guideline and to respective example, e.g.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A.5 – Medical devices incorporating a medicinal substance with ancillary action</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“Examples of such medical devices are: …</td>
</tr>
</tbody>
</table>

*/ Provide cross-reference to supportive scientific information in Section B

** In addition reference to other regulatory texts can be made where relevant

3. Regulatory status (if existing)

Status in EU member states (including EEA countries) and outside EU if applicable
Provide examples of similar products that have already been marketed in EU or outside EU

4. Current use

Description of how medical device is used alone or in combination with the ancillary medicinal substance or ancillary human blood derivative (in EU or outside EU)
5. Other relevant aspects

B- Supportive scientific information

This section is the most important to reach a conclusion on the ancillary action of the medicinal substance or of the ancillary human blood derivative in the medical device. In particular scientific information demonstrating the ancillary nature of the medicinal substance or of the human blood derivative (in line with the demarcation guideline, MEDDEV guidance 2.1/3 rev 2, July 2001) in the combination product has to be provided. Scientific information should cover:

- The mode of action of the components (medical 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 / similar combination product.
- Explanation why the medicinal substance is added to the medical device: identification of those patients that would benefit from this combination product versus medical device alone
- Consideration of the potential risks associated with the addition of the medicinal substance to the medical device (immune reactions, carcinogenicity...)

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