EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 December 2012
EMA/CHMP/92924/2011
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on '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 derivate incorporated in a medical device or active implantable medical device ' (EMA/CHMP/578661/2010)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	EUCOMED Medical Technology
2	Federal Institute for Drugs and Medical Devices EU and International Affairs (BfArM)
3	Irish Medicines Board (IMB)
4	International Plasma Fractionation Association (IPFA)
5	Medicines Evaluation Board, The Netherlands (CBG-MEB NL)
6	Medical Product Agency, Sweden (MPA)
7	Ministry of Health, Welfare and Sport, The Netherlands
8	ZLG Central Authority of the Länder for Health Protection with regard to Medicinal Products and Medical Devices

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	Eucomed welcomes this guidance document. The document is informative, provides a good overview of the process, and flows very well. Eucomed also welcomes the opportunity to have a pre-submission meeting in order to assist in the preparation of an application. This meeting will be mutually beneficial and will help ensure the application contains all necessary information to ensure a favourable opinion.	
	Eucomed is however concerned it may not always be possible to meet the requirement for a notified body to provide an "intention to submit letter" at least 6 months before the expected date of submission. Likewise, it may be necessary that a pre-submission meeting takes place less than 6 months prior to the expected date of submission.	The text has been amended to reflect "preferably" 6 months. This timeframe allows sufficient time to perform some internal procedures such as the Rapporteurship appointment which is handled at next CHMP meeting. In addition, pre submission-meetings 6 months in advance to the intended submission date allows the applicants sufficient time to amend any deficiency to their dossiers and applications that could have been identified. This requirement was set in line to pre-submission meetings for medicinal products in the centralised procedure.
	Eucomed is concerned regarding the publication of a public assessment report (CPAR). Eucomed believes this report should not be published until such time as the product in question is CE marked. There may be instances where the CE mark process is not complete	We acknowledge the concerns of publication prior to CE mark of the device. The text has been modified and now states "at the time the notified body has reached a decision on the granting of the CE mark". Notified bodies will be requested to

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	within the timeframe the EMA intend to publish this report. The publication of such information will lead to concerns on disclosure of information. Currently Notified Bodies do not disclose information. Further information/examples on the type of information intended to be included in this report should be made available to allow Device manufacturers the opportunity to review and assess.	inform EMA of this date.
	The text contains a requirement which goes beyond the text of the directive concerning the compulsory referral to the Agency for medicinal products that fall within the scope of 67 Annex I to Reg. EC 726/2004. The “mistake” is due to the fact that a similar statement is present in MEDDEV 2.1/3 rev.3 and was not detected at the time of the development of the MEDDEV. Eucomed is asking the Commission to modify the text of the MEDDEV accordingly.	The text is maintained in line with MEDDEV 2.1/3 rev 3 (Dec 2009). A reference to the MEDDEV has been inserted.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
67-68	1	**Comment:** The text of the Directive, referred at lines 99-107 and 123-129 does not indicate that the referral to the Agency is compulsory for medicinal products other than for medicinal products derived from Human blood or human plasma. This was erroneously indicated also in MEDDEV 2.1/3 rev. 3 and needs to be amended. The option of referring to the Agency remains, but it cannot be considered compulsory. **Proposed change:** In the case of ancillary human blood derivative, it is mandatory for the notified body to consult the European Medicines Agency as the competent authority for the consultation	The text is maintained in line with MEDDEV 2.1/3 rev 3 (Dec 2009). A reference to the MEDDEV has been inserted.
75-78	3	**Comment:** Section 1 requires that the notified body (NB) will convey its final decision to the Agency, this is of particular relevance for medicinal substance consultations where the NB having given due consideration to the Agency opinion may make a decision to certify the product. The MEDDEV guidance 2.1/3 rev3 (C3g) suggests that the NB should consult the relevant device competent authority of this before issuing the certificate. Whilst not a legislative	The European Medicines Agency informs of every opinion on a consultation procedure to the medical device competent authority of the member state where the notified body is based. The opinion to the competent authority is sent at the same time as to the notified body. This has been common practice, although not previously reflected in the guideline. The following reference has been included in section 4.3 of the document: *"The CHMP opinion is sent to the Notified body and to the national competent authority on medical devices of the*

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		requirement this is worth including in the current text and it may be considering as possible good practice for the EMA to inform the relevant device competent authority of its negative opinion directly. **Proposed change (if any):** Addition to line 78. - If a notified body following a negative opinion for a medicinal substance decides to issue the certificate it should consult with the relevant device competent authority before doing so. .	*member state in which the notified body is based."*
76	1	**Comment:** The statement in line 76 should be aligned with the Directive text quoted in line 123 and 135/136 **Proposed change:** For ancillary human blood derivatives …	Not agreed. Lines 75-78 in the introduction have been written based on the different texts included in the Annex II point 4.3 of MDD and AIMDD directives. Different wording is followed for cases when the consultation to EMA is mandatory than when is optional. The text in lines 75-78 differentiate the sentences applicable to both mandatory and optional scope (i.e. "the NB will give due consideration…" or "the NB will convey …") from the sentences only applicable to mandatory scope (i.e. "for Ancillary blood derivatives, the NB may not deliver …."). The text in lines 123 and 135/136 only applies to mandatory consultation to the Agency.
95 and 98	1	**Comment:** Incorrect citation of MDD and AIMDD: delete "as amended" in order to be consistent with MDD and AIMDD wording.	Agreed. The text is modified.

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		Proposed change: "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 the Article 1 of Directive 2001/83/EC, and which is liable to act on the body…" "…by analogy with the methods specified in Annex I to the Directive 2001/83/EC."	
140 - 142	1	**Comment:** In some cases, this 6 months length of time would not be practical or consistent with standard medical device product lifecycles. By the time the briefing materials and presentation can be prepared for most pre-submission meetings, the submission itself is usually well developed and ready to submit within 1 month, assuming agreement by the regulatory agency. In cases where there is doubt about product classification, this recommendation to meet at least 6 months prior to the submission would be more applicable. Also, how would it be ensured that the appropriate CHMP representatives are present at this pre-submission meeting, consistent with rapporteurs assigned once the consultation begins? When meetings can be held within 1 or 2 months prior to submission, it could be easier to ensure continuity in representatives present. **Proposed change (if any):** N/A	The text has been amended to reflect "preferably" 6 months. This timeframe allows sufficient time to perform some internal procedures such as the Rapporteurship appointment which is handled at next CHMP meeting. In addition, pre submission-meetings 6 months in advance to the intended submission date allows the applicants sufficient time to amend any deficiency to their dossiers and applications that could have been identified. This requirement was set in line with pre-submission meetings for medicinal products in the centralised procedure.
149-150	1	**Comment:**	The CHMP assigns two rapporteurs to conduct the assessment

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		What is the criteria for assigning more than one rapporteur? Is it possible to provide examples? **Proposed change (if any):** N/A	on a normal basis in analogy of the Centralised procedure for medicinal products. In certain cases, where less extensive assessment could be needed (e.g. a further development of a medical device containing an ancillary medicinal substance previously assessed in a consultation procedure at the Agency), CHMP may exceptionally appoint only one rapporteur.
151	1	**Comment:** The requirement to submit an 'intention to submit' letter at least 6 months before the expected date of submission could significantly delay introduction of new products to the EU market. In some cases, projects are delayed and then restarted quickly based on other projects/ business considerations. In addition, there is often significant testing under way 6 months prior to submission; if the testing reveals that additional testing is required, sometimes the project can be delayed or cancelled. **Proposed change (if any):** N/A	The text has been reworded to "preferably 6 months". See above comment to Lines 140 – 142.
152	1	**Comment:** Will the scientific explanation be required for every new product, or just for each new product type? For example, this process could be considered burdensome in the case of a next generation product which uses the same medicinal substance, by the same manufacturer. **Proposed change (if any):** N/A	The scientific explanation is required for every Initial Consultation procedure. In case the changes leading to the next generation product were classified as major/minor amendments to the 'initial consultation' dossier ('post consultation procedures') and did not trigger a new 'initial consultation procedure', a new scientific explanation would not be needed.

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154	1	**Comment:** The relationship between MEDDEV 2.1/3 rev.3 and Appendix 2 is not clear.	The sentence has been reworded to better clarify.
155-221	4	***4.2. Data requirements and format of the application dossier*** A clarification was published in 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."* ***Non-applicability of the Active Substance Master File (ASMF) concept to biological active substances***	When a PMF is not certified (centralized certification), the information on the starting material (plasma) is part of the Module 3 of the plasma derived medicinal substance. As such, this information should be submitted within the module 3 and cannot be submitted separately. The same noted legal requirements apply.

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		"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-refer 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 European Medicines Agency for evaluation. The Committee for Medicinal Products for Human Use (CHMP) will give an opinion and therefore it should be provided with the relevant data for evaluation. **Comment:** This issue refers to a confidentiality matter. We are aware this is a legislation requirement. However, if the PMF is not certified (centralized certification), the applicant is supposed to document the PMF or information on the starting material (plasma). This means that the blood derivative manufacturer should provide all information to the applicant. Can the applicant refer to a blood derivative manufacturer file submitted in parallel by the blood derivative manufacturer himself in case the PMF information has never been submitted to the EMA but to a national authority, for evaluation? **Proposed change (if any):**	

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		N/A	
159-162	2	**Comment:** Our experience with dossier for consultation procedures has shown, that CTD-format should be used generally. The assessment of quality and safety including the clinical benefit/risk profile by the competent authority is easier and more efficient when CTD-format is used. When following the format of the MEDDEV guidance 2.1/3 rev. 3 often documents where missing or documents didn't follow guidance for the evaluation of medicinal products (CHMP-guidance, ICH-Guidance etc.) **Proposed change (if any):** N/A	CTD format is requested for the information on the ancillary medicinal product itself (i.e. Section 2 - module 2.3 and Section 3 – module 3). The other sections do not follow CTD structure.
169-171	6	**Comment:** There is a risk for understanding that the Notified Body (NB) must send in a report to the EMA not only if the verification for medicinal substance is done by the EMA but also when the verification is done by a competent authority. This is not the case when the NB seeks a scientific opinion from one of the competent authorities as stated in line 99-102. **Proposed change (if any):** Add a clarification after line 173: "There is no requirement to send a report to EMA in the case the Notified Body seeks a scientific opinion from one of the competent authorities regarding the medicinal substance.	Not agreed. The current guidance only covers consultation procedures to EMA. Consultation to National Competent Authorities are outside the scope of this document. The request of a report from the notified body on the 'verification of the usefulness' is in accordance with Annex I, section 7.4 of the Dir. 93/42/EEC and Annex I, Section 10 of Dir 90/385/EEC which states: "*the notified body shall, after having verified the usefulness of the substance as part of the medical device and taking into account of the intended purpose of the devices, seek a scientific opinion from one of the national competent authorities designated by the Member States or to the*

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			European Medicines Agency …".
217-219	1	**Comment:** Eucomed regrets that the referenced hurdle of data exchange between EU authorities still exists. EMA should be encouraged to bring this administrative obstacle to the attention to the Commission in order to take appropriate actions to improve the review process in the future.	Noted.
236-237	1	**Comment:** Is the reduced review timeframe limited to substances/derivatives with CEP/PMF? There may be other examples where a shortened procedure may also be appropriate. **Proposed change (if any):** N/A	The reduced review timeframe is limited for the two cases specified in the guideline. The reduced timeframe for 'a known medicinal substance from a known source' refers to ancillary medicinal substances from the same manufacturer that have been previously assessed by the CHMP. Please note that PMF only covers the quality and safety of the starting materials of plasma derived medicinal products and not the quality of the ancillary substance itself. PMF only replaces a part of the module 3 of the ancillary substance. Certification of PMF by EMA does not quality for accelerated assessment.
238 - 239	1	**Comment:** What CHMP meeting is being referred to here? Is this the pre-submission meeting that is strongly recommended at least 6 months prior to the submission (line 140-142)? Or is this referring to a different CHMP	Pre-submission meeting is a meeting with EMA staff prior to the submission to clarify regulatory, procedural aspects and dossier requirements for the submission. It is not related with CHMP meetings.

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		meeting? **Proposed change (if any):** N/A	CHMP is the Committee for Medicinal Product for Human Use. This committee meets every month at fixed dates (available on EMA website). CHMP is responsible to assess the justification provided by the notified body for an accelerated consultation procedure and to agree on it. This should be done prior to the start of the procedure (i.e. at least in the CHMP meeting prior to the start of the procedure).
241	1	**Comment:** Can we clarify who the opinion will be provided to? Will it be the notified body and/or manufacturer? **Proposed change (if any):** N/A	The opinion is provided to the notified body, as applicant for this procedure. A new sentence has been added: "*The CHMP opinion is sent to the Notified body …*"
244-251	1	**Comment:** Will this report only be published once the product in question is CE marked? The publication of such information will lead to concerns on disclosure of information. Currently Notified Bodies do not disclose information. Further information/examples on the type of information intended to be included in this report should be made available to allow Device manufacturers the opportunity to review and assess. **Proposed change (if any):** This report should only be published once the product in question is CE marked.	Agree. The text has been modified to reflect "*at the time the notified body has reached a decision on the granting of the CE mark*". It is already stated that "*The relevant medical device manufacturer and ancillary medicinal substance manufacturer will be consulted through the notified body on the CPAR before publication.*"

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252-263	5	**Comment:** An addition is suggested in section “4.4. Post-consultation phase”. Namely, a description of the appropriate procedure in case the EMA has obtained information on the ancillary substance, which could have an impact on the established benefit/risk profile of the addition of the substance in the medical device. (Which procedure assumingly will be: providing the notified body with advice, whether this information has an impact on the established benefit/risk profile of the addition of the substance in the medical device or not. This updated scientific opinion can then be taken into account by the notified body in reconsidering its assessment of the conformity assessment procedure.) **Proposed change (if any):** N/A	A paragraph has been included.
252-263	7	**Comment:** In section 4.4. “Post-consultation phase” a reference to an essential provision of Directive 2007/47/EC amending Directives 90/385/EEC and 93/42/EEC is missing. This provision contains an obligation for the pharmaceutical authority (in this case EMA) to provide the notified body with an advice, if new knowledge might arise, which could influence the benefit/balance risk of the combination product. The Netherlands Ministry of Health, Welfare and Sports considers this an important provision, which bridges the formerly existing ‘safety gap’ between the	See comment above.

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		pharmaceutical and medical device authorities in the assessment of combination products on the EU market. Please see 93/42/EEC Annex I, 7.4., last paragraph: *When the relevant medicines competent authority (i.e. the one involved in the initial consultation) has obtained information on the ancillary substance, which could have an impact on the established benefit/risk profile of the addition of the substance in the medical device, it shall provide the notified body with advice, whether this information has an impact on the established benefit/risk profile of the addition of the substance in the medical device or not. The notified body shall take the updated scientific opinion into account in reconsidering its assessment of the conformity assessment procedure.* (Similar obligation is in 90/385/EEC Annex 1, 10. last para.) **Proposed change (if any):** Please incorporate above cited obligation to address also the required information flow from the EMA to the Notified Body.	
252-263	8	**Comment:** In section 4.4. “Post-consultation phase” an essential requirement of Directive 2007/47/EC amending Directives 90/385/EEC and 93/42/EEC is missing.	See comment above.

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		The medical device directives now contain an obligation for the medicines competent authority (here the EMA/the Agency) to provide the notified body with an advice in cases where new information on the ancillary substance has been obtained. Please see 93/42/EEC Annex I, 7.4., last paragraph: *When the relevant medicines competent authority (i.e. the one involved in the initial consultation) has obtained information on the ancillary substance, which could have an impact on the established benefit/risk profile of the addition of the substance in the medical device, it shall provide the notified body with advice, whether this information has an impact on the established benefit/risk profile of the addition of the substance in the medical device or not. The notified body shall take the updated scientific opinion into account in reconsidering its assessment of the conformity assessment procedure.* (Similar obligation is in 90/385/EEC Annex 1, 10. last para.) Proposed change (if any): Please incorporate above cited obligation to address also the required information flow from the EMA to the Notified Body.	
253-263	3	**Comment:** Section 4.4 on the 'Post-Consultation Phase' should include reference to the obligation of the Agency, in its capacity as the 'relevant medicines competent	See comment above

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		authority' as referred to in Annex I 7.4 (fifth subparagraph) of 93/42/EEC and corresponding text in Annex 1 10 of 90/385/EEC, shall advice the NB when following the original consultation it obtains information on the medicinal substance which could impact on the established benefit/risk profile on the addition of the medicinal substance to the device. **Proposed change (if any):** Include text to refer to and outline this requirement following line 263. In addition, section 3 on Legal basis should be amended if deemed necessary.	
253-263	1	**Comment:** Eucomed would welcome further guidance/clarification on when a change to a device would require a change assessment for the ancillary substance. Also, what timelines will be associated with this consultation process? In other terms, would there be a guidance for the application of Regulation 1234/2008/EC in this case? **Proposed change (if any):** N/A	Further guidance on specific procedural aspects and examples on post-consultation procedures will be provided in a Q&A document at the dedicated section on Ancillary substances in EMA website.
285 - 286	1	**Comment:** These lines appear to be a duplicate of lines 275-276 **Proposed change (if any):** Amend as necessary so only one reference to this directive is included	Agreed. These lines have been deleted.

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299	1	**Comment:** It is not clear: 1. Which declaration? 2. Expert in what?	A footnote has been included for clarification. When in Section 2 expert reports are used as critical summaries of the documentation, we request a signed declaration of ownership of the report and the CV of the expert. The expert shall have suitable technical or professional qualifications. A CV including brief information on their educational background, training and occupational experience shall be presented. The professional relationship of the expert to the medical device manufacturer/notified body shall be declared.
302	1	**Comment:** “product information and labelling”, this wording is not new but it already exists in the current version. However, it would be helpful to define “product information” in more detail. Does this refer to the Instructions for Use only (this should be covered by “labelling” already) or to other requested data?	Agreed. We refer to the instructions for use and package labels. The text has been updated to: “Labelling”
317	1	**Comment:** The acronym ‘CEP’ is not explained in the document and its relevance may not be understood. The acronym ‘CEP’ should be explained. Appropriate advice on the use of a CEP should be included or referenced. **Proposed change (if any):** N/A	Agree. The definition has been included in the text.

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346	1	**Comment:** Directive number for active implantable medical devices is incorrectly referenced as 30/385/EEC **Proposed change (if any):** Dir.90/385/EEC on active implantable medical devices and the Council Directive 93/42/EEC on medical devices	Agree. Correction has been performed.