European Medicines Agency

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON PROCEDURAL ASPECTS AND DOSSIER REQUIRMENTS FOR THE CONSULTATION TO THE EMEA BY A NOTIFIED BODY ON AN ANCILLARY MEDICINAL SUBSTANCE USED IN A MEDICAL DEVICE

Table 1: Organisations that commented on the draft Guideline as released for consultation

Add name followed by link to individual received comment (upon publication by Web Services)

	Name of Organisation or individual	Country
1	Novartis Pharma AG	Switzerland
2	Voisin Consulting	France
3	Eucomed	Belgium
4	IPFA *	Netherlands
5	Pfizer	France

* no specific comments have been received

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW	OUTCOME
The scope of this document should be limited to those situations where EMEA already has a statutory role (i.e. Directive 2000/70/EC).	The scope of this guideline is in accordance with Directive 93/42/EEC as amended (Annex I section 7.4, Annex II section 4.3 and Annex III section 5) and in line with the guidance document MEDDEV 2.1/3 rev 2 (Section B.2 indent d).
The text of Directive 93/42/EEC (hereinafter referred to as MDD) is currently under revision. Once the final text has been adopted it will be possible to review this document against the roles allocated to the EMEA under the revised MDD. We note that MEDDEV 2.1/3 Rev. 2, referred to in this document, has been agreed to be in need of revision	Until the revision of the Medical Device Directive 93/42/EEC is applicable and the Demarcation guideline MEDDEV 2.1/3 rev 2 is revised, those two documents are used as references. The guideline will be updated in due course with any changes arising from such revision.
DMFs: the current document does not adequately describe how a submission involving a drug master file should be handled. In particular the detail relating to the closed part of the file needs to be addressed. CEPs: appropriate advice should be included on what is needed if a Certificate of suitability of the European Pharmacopoeia is used	Clarification and relevant reference to current guidelines have been included.
The current proposal relating to time scales does not take adequate account of the time scales in the development and product lifetime for medical devices: lifetimes of medical devices are often measured in months and not in years. Medical device's life cycle is about 5 years (vs 10 years for the medicinal product) and the average time for the Notified Body to assess the design/technical file of a medical device is 90 days.	The timetable for the consultation procedure is a maximum of 210 days by analogy with the evaluation of the medicinal product in the centralised procedure. Flexibility will be allowed in duly justified cases. Clarification to this extent has been included in the guideline.
Fees are not compatible with those, which are applied by Member States authorities for doing the same job. Fees should be reduced accordingly.	The fees stipulated by Council Regulation (EC) No 1905/2005 amending Regulation (EC) No 297/95 on fees payable to the European Medicines Agency are proportionate to the work carried out by the EMEA. However, a 90% fee reduction for scientific services (i.e. ancillary consultation procedure) for SME registered at the SME office at the EMEA is applicable. (For more information on SME status visit http://www.emea.europa.eu/SME/SMEoverview.htm
There is ongoing activity at EMEA on guidance for drug eluting stents and the relationship between the two documents should be clarified	The clinical guidelines referenced in Appendix 1 of this guideline includes the draft guideline on drug eluting stents.
There is no discussion in this document of the mechanism to be used for notification of changes to information supplied in the original submission. This does not appear to be covered by the Variations Regulations. Appropriate advice will need to be provided	Additional information on the post-consultation phase has been included.

Due account should be taken of medical devices manufacturers' use of standards (EN, ISO, IEC etc) rather than pharmaceutical guidelines in a number of areas. This includes sterilization, quality systems, biocompatibility, risk management and clinical investigations. This document should not seek to impose requirements from the pharmaceutical sector that are less appropriate than the standards applied.	The CHMP guideline refers to the MEDDEV 2.1/3 rev 2 which already include reference to the mentioned guidance on applicable standards.
Out of the scope are drug delivery devices, e.g. inhalers. Can the same procedure be followed in such cases? What about in the case of novel inhaler and a novel active ingredient where the device is reusable or might even be marketable with more than one drug product (hence the device needs a CE marking)?	This consultation procedure on ancillary substances is not applicable to drug delivery devices. According to Article 1(3) first paragraph of Directive 93/42/EEC, delivery systems are considered medical devices, however, according to the second paragraph of the same article, those devices placed on the market in such a way that the medical device and medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable, are governed by Directive 2001/83/EC.
In case of use of an approved medicine in the combination, the application should be simplified considering that quality and safety data have already been assessed for the medicinal product	The current dossier requirements are already reduced in line with the Demarcation guideline MEDDEV 2.1/3, Section B.3.
What are the criteria on which the EMEA establishes the "usefulness" of the combination product?	EMEA does not establish the "usefulness" of the medical device. Meddev 2.1/3 rev 2 guideline is to be followed for usefulness of the ancillary medicinal substance or ancillary human blood derivative incorporated in a medical device.
Guidance for combination products (medicinal product/medical device) on how the device data should be presented into the required CTD format would be welcomed	This guidance is not applicable within the guideline hereby discussed. However, data on medical devices contained in medicinal products governed by Directive 2001/83/EC should be included in Module 3.2.R. (E.g. CE mark certificate, or sufficient data on the device should it not be CE marked.)

SPECIFIC COMMENTS ON TEXT

1. GUIDELINE SECTION TITLE

Line no.[1] + paragraph no.	Comment and Rationale	Outcome
1 & 2 Scope and introduction	1. The Introduction and Scope should be amended to reflect the current responsibilities of the EMEA with regard to stable blood derivatives used as ancillary substances in medical devices. 2. It should be made clear that the requirements described in this document relate only to those procedures involving mandatory consultation procedures to the EMEA. 3. Clarification on whether the scope of the guideline limited to device/blood derivates combinations or to all device/medicinal product combinations. 4. Clarification on whether the guideline concerns only device/**centrally authorized medicinal product**, and if the guideline will be transposed in a similar way by the NCA's. 5. How to proceed in case of novel ancillary substances, not marketed in EU but present on another market (i.e. US)	See the comment on scope under general comments above. Clarification has been included in the guideline. This guideline is only applicable to the consultation procedures carried out at EMEA, whether mandatory or not. According to section B.3 of MEDDEV 2.1/3 rev 2, the evaluation of new active substances and for known medicinal substances in a non-established purpose would be performed in accordance with the principles of evaluation of new active substances. Therefore, comprehensive data is required to address items stated in that section.
3 Legal Basis	This section will need to be revised when the final text of the MDD is made available. In particular : a. The text refers exclusively to Annex III; it should also refer to section 4 of Annex II of the MDD.	Agreed, text has been modified accordingly.

[1] Where applicable

	b. The text refers to “appropriate methods specified for medicinal products in Directive 2001/83/EC”. The correct reference should be to Annex I of Directive 2001/83/EC, as amended c. It would be advisable to define the terms “usefulness” and “risk/benefit ratio” with respect to the inclusion in the device of the substance. The use of the terms in the text should be applied consistently. In the first paragraph, last sentence, insert “human” before “blood derivatives”. The words **“MAIN GUIDELINE TEXT”** appear to be inappropriate or misplaced.	Agreed, text has been modified accordingly. Regarding the definition of usefulness, Meddev 2.1/3 rev 2 guideline is to be followed. Agreed, text has been modified accordingly. Agreed, text has been modified accordingly.
4.1 Pre-submission activities	While the concept of having a pre-meeting is useful, the timing involved in this activity is incompatible with the speed of innovation in the medical devices sector. Paragraph 3: the requirement for “scientific explanation for classification of medicinal substances integrated in medical devices as ancillary substances” should be re-worded. It is assumed that what is needed is an explanation as to why the combination product is a medical device rather than a medicinal product. Please confirm or clarify. Please discuss consultation on submissions of variations.	Already addressed in the general comments. See above. Agreed, text has been modified accordingly. Additional information on the post-consultation phase has been included.
4.2 Data requirements and format + Appendix I	See earlier comments in respect of the scope of the document and the need for adequate information on the use of DMFs and CEPs. There is no differentiation between novel and known substances in terms of data requirements. The possibility of supplying abridged information in the second case should be permitted. Last Paragraph of 4.2: a mechanism should be introduced whereby Competent authorities exchange relevant assessment reports. The current text apparently prohibits cross reference to dossiers authorized nationally, which could be a particular difficulty when more than one	Clarification and relevant reference to current guidelines have been included. The full documentation on quality is required in order to facilitate the assessment of the dossier. Clarification on the documentation to be submitted for human blood derivatives for which a PMF is used, or non-biological ancillary medicinal substances where an active substance master file (ASMF) or a CEP are used have been included. The full data are generally required. The completeness of the dossier is to be assessed on a case by case basis and therefore the pre-submission meeting is

	previously authorized ancillary medicinal substance is included in a medical device.	recommended.
	Confirm the MRP authorizations can be cross-referenced. Please what to do in case of national submissions.	It is not possible to cross-refer to the dossier of nationally authorised medicinal products for the reason stated in the guideline. This includes MRP authorizations.
	It would be appreciated if the guideline could develop the EMEA requirements in terms of the performance of "bridging studies" in order to assess these aspect and also provide clarification on clinical trials for combined products (study population, risk/benefit assessment)	Individual guidelines would be needed, e.g. guideline on drug-eluting stents.
	Appendix I: It is assumed that duplication of data in different formats is not required. Notified Bodies should be able to submit either in CTD or in MEDDEV format.	Most data are to be submitted in Meddev format, only data on ancillary medicinal substance are to be submitted in CTD.
	First section: for "separate volume" read "one volume". Third bullet: See previous comment on "scientific explanation".	Agreed, text has been modified accordingly.
	Fourth and fifth bullets: please clarify the exact expectation implied here, because there appears to be considerable overlap.	Agreed, the text has been modified accordingly.
	Second section: The two bullet points do not make the data requirements and presentation clear. Also references to Quality section are redundant (given in more than 1 bullet point is not necessary)	Clarification has been included in the guideline.
4.3 Consultation procedure to the EMEA	First paragraph: This should reflect consideration of the preference of the Notified Body for specific rapporteurs.	According to the new rules on appointment procedure any preferences from the third parties are **not** accepted, hence the link to the new procedure "CHMP Rapporteur/Co-Rapporteur appointment: principles, objective criteria and methodology" was added.
	See previous comments concerning duration of consultation procedure.	
	Third paragraph: Additional guidance should be provided on the mechanism for seeking accelerated processing of the application.	The preparation of the "Pre-Submission Guidance for applications for ancillary medicinal substance used in medical device" will cover several topics such as accelerated assessment.
	Fifth paragraph: information is required on the proposed content of the public report. It is assumed that Notified Bodies and manufacturers will have the right to redact confidential information prior to publication	Correct, clarification has been included in the guideline.

4.4 Fees	See general remarks.	
Appendix 2A	Section 1: Product presentation/composition: the terminology use should be more appropriate to a device/ drug combination, and provide further explanation of what is required for “quantitative and qualitative composition”; delete “pharmaceutical form”. Section 4: It is not understood exactly what is required.	Clarification has been included in the guideline.
Appendix 2B	See comments to section 4.1; paragraph 3. Second bullet: it should be permitted to include information on similar device/drug combination products.	Agreed, text has been modified accordingly. Agreed, text has been modified accordingly.