EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 February 2011
EMA/690489/2010

Overview of comments received on 'Procedural advice on the consultation of Notified Bodies in accordance with Article 9 of Regulation (EC) No. 1394/2007' (EMA/354785/2010)

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

Stakeholder number	Name of organisation or individual
1	Voisin Consulting Life Sciences
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1. General comments

Stakeholder number	General comment	Outcome
1	The document provides very useful information and is well detailed. We welcome this guideline, and particularly the transparent and clear approach it provides on how the EMA CAT intends to interact with Notified Bodies and on how the Applicant will be involved. The complexity of combined ATMP is well recognised, we therefore concur that this procedure will be helpful to ensure the highest and most appropriate level of expertise is involved for the evaluation of these products for marketing authorization. We also welcome the fact that the review of the data by a Notified Body, when the assessment of the medical device is not provided in the initial Marketing Authorisation Application (MAA), does not intend to delay the MAA assessment, and that the review period is integrated into the MAA review process.	
	We suggest reorganising slightly the guideline to limit redundancies and having a more direct approach by providing details upfront, rather than "little by little". We recommend including "generalities" at the beginning of the document before moving to the description of the procedure itself.	Comment noted. Please see redrafting of the procedural guideline document, sections 4 and 5.
	It would be very helpful to have concrete examples or "case studies". We anticipate this could be done in future versions of the guideline. A few typographical errors will need to be fixed.	Comment noted. As there is not yet any precedents this will be considered for future revision as an update or an Annex to this document. Noted and implemented.
2	**1) Factors to be Considered Before Final Procedural Advice Is Offered** While "Procedural advice on the evaluation of combined ATMP and the consultation of notified bodies in accordance with Article 9 of Regulation (EC) No. 1394/2007" will be useful, it may be premature to	1(a) Please note that Notified Bodies (through NB-MED) and competent authorities for medical devices (through NBOG) have been part of the drafting group of this procedural guideline. Below is the link to the Collaboration group composition

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	issue this advice. Several items need to be addressed before final procedural advice should be issued. a) There is a need to further engage Notified Bodies (NB) in the development of the procedural advice:	http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CAT/people_listing_000086.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac058029021c
	1) It is not clear specifically how a NB would be assessed by a Member State's Competent Authority (e.g., per EN 45000) and designated as competent/ qualified to review devices that act in concert with cellular or tissue products, where knowledge of the biological interactions in the body are paramount, or if the Accreditation Body or Notifying Authority would be the same as currently in place, and if this process would be recognized under the current Mutual Recognition Agreements. There does not appear to be any information about NB designations with respect to combined ATMPs in the NANDO Information System.	(1) Please note that scope of this procedural guidance document is not to designate NBs to be involved in the consultation of combined ATMPs evaluation in the context of Article 9 of Regulation (EC) no1394/2008, but rather to describe the way interaction between EMA/CAT & NBs should be established. It is acknowledged that NANDO does not specifically identified NB designated with respect to combined ATMPs as these products are considered to be medicinal products, hence the wording in section 4.4 of the procedural guidance document which, within the existing framework, does identify the criteria for the best notified body to be dealing with these type of products.
	2) The MDD Essential Requirements are both very broad and yet specific to device characteristics. It is not clear in the advice how a NB would or could restrict its assessment to just the device constituent part of the combined ATMP when its defined Essential Requirements assessment is to include such topics as product design, manufacture, general and specific design, user, and process risks (under ISO 14971), device quality (under ISO 13485), chemical, physical and biological properties, toxicity, biologic compatibility (under ISO 10993), packaging interactions, clinical evaluations, environmental storage considerations, and labelling, including instructions for use. Whether a NB should approach their assessment as a "type examination" or a "quality system" assessment should be clarified.	NANDO is mentioned as a general EU guidance reference as it lists the NBs according to their expertise for medical device assessment and this may be helpful in the Applicant/CAT choice of the NB (see also section 4.4). (2) The focus of NB will be on the device component and the effect of the cellular component directly on the device. The review conducted by the NB should be based on and reported like a design dossier examination. This is already included in section 4.2. Please see redrafting of the procedural guideline document, sections (4.2).
	3) There is no guidance provided on the content or format expectations of a NB's assessment report in the current	(3) Addressed in section 4.2. In time, further guidance may be developed on this.

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	advice and therefore, there is no assurance that similar ATMPs with or without similar device technologies, designs, materials, etc., will receive consistent assessments. The current advice should provide an overview of what is expected in an NB's assessment report for the device part of a combined ATMP. An alternative would be to provide an advice document (or procedure) that explains to notified bodies what content should be provided and how the Essential Requirements of just the device components should be addressed (i.e., assessment limited to the device information).	
	4) The advice should provide information on if and/or how a NB will be included in pre-approval inspection process.	(4) This is one of the points identified in the work programme, and will be further discussed in 2011.
	b) This document does not yet provide sufficient advice to applicants in that the Section 4.3 "further details would be provided..." and Section 4.5 "Further EMA guidance will be available..." are necessary and critical to understanding how Article 9 will be implemented. That advice should be provided before the current advice is finalized. **Alternatively, since there are many considerations in the post-marketing setting, the advice should focus on the pre-approval process and a separate advice document developed to provide post-marketing procedural advice.**	(b) Comment noted. Further guidelines may be developed. - See work programme for 2011 http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CAT/people_listing_000086.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac058029021c - Please see clarification in the guideline document on pre-authorisation activities, post-authorisation activities (Section 2. Scope) - Please see clarification in the guideline document that this document does not address data/dossier requirements. (See redrafting section 4.2.)
	1) While Section 4.5 briefly mentions that CAT/EMA will have the responsibility to oversee adverse event reports and assessment (and that further guidance will be available), the current advice should clarify the role of a notified body in this regard (or this section should be deleted in the current document). For many adverse events, it may be difficult to assess whether an incident is caused by a device	(1) Further separated guidance will be provided in the future. See work programme for 2011 http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2010/12/WC500099531.pdf See previous response regarding amendment to section 4.5 & Scope.

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	characteristic or the ATMP, or both, and the ongoing involvement of the applicant's specific NB may be needed for consultation, possibly requiring an extended relationship with a specific NB. In the current advice or when "further guidance" is issued, the potential for an ongoing role of the NB should be clarified, in concert with MEDDV 2.12-1-6, and explicitly state that CAT/EMA will serve and be competent in the role of an "Authorized Representative" for non-EU registration holders where device-related events of a combined ATMP are implicated.	It should be noted that the adverse incident reporting for medical devices is overseen by competent authorities for medical devices rather than NBs. There is no legal basis for CAT to act as Authorised Representative. Responsibility lies with the marketing authorisation holder of the combined ATMP to report adverse events of their product (which includes a medical device).
	2) **Role of the Applicant and Need for Case-by-case Consultation**	
	a) While the review process describes how CAT will consult with the Notified Body (NB) regarding specific product information in addition to clarification of the NB's MDD Annex 1 assessment of the device portion of the product, the advice should be clarified to ensure that product-specific questions that the NB may not be knowledgeable about be directed to the applicant instead of the NB.	(a) It should be clarified that all questions further to the CAT evaluation will be sent to the Applicant who will liaise with NB as appropriate. (See section 4.1.)
	b) It is suggested that the process should be determined and laid out on case-by-case situation and in close co-operation/consultation between CAT/NB and applicant and agreed-upon prior to the start of the MAA evaluation process. In particular cases, this might be accomplished by including the NB in a pre-submission meeting to have alignment on responsibilities, interactions/co-operation, and timelines.	(b) This may be work which will be considered in the future with experience of assessment of these products.
	c) In our view, the 2-month time period specified for the results of the NB assessment cannot be mandated without explicitly addressing the country-specific regulations under which NBs operate. It is recommended that more general language be utilized to allow negotiation of timelines for these reviews (under a voluntary/competitive system) or they be provided according	(c) The 2 month timeframe is mandated by the Regulation EC. 2007/1394. It is hoped that most assessment results can be provided within this timeline. Potential MAAs for combined ATMPs should involve a suitable NB early in the process, prior to submission, to allow this timeline to be readily met.

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	to timeframes for NBs mandated by their competent authorities. d) It is not clear in the current advice under what circumstances, if any, CAT/EMA may disregard the NB's assessment regarding combined ATMP effects if a NB should issue a final negative finding beyond considerations of the device effects alone, or where CAT/EMA determines that overall clinical or other data on safety and effectiveness have satisfied CAT/EMA's concerns. This provision is provided for when a NB assesses a medical device with an ancillary drug component and finds for conformity with the MDD even when a Drug Competent Authority has issued a negative assessment on the drug's contribution to safety and effectiveness.	(d) It may be possible to develop further guidance on this with more specific experience of combined ATMP applications.
3	Eucomed welcomes the drafting of such a guideline, however, in addition to the specific comment mentioned below, we would respectfully suggest that the draft does not address two very important issues: 1. Guidance on the determination of whether a product is a "combined product" 2. On which basis the CAT might decide that consultation with a NB is not necessary. Eucomed believes that these two points should either included in the current draft or should be dealt with in a separate guidance in order to help manufacturers in determining the need for a pre-application consultation with a NB.	(1) Comment noted and importance of topic mentioned acknowledged. Discussion initiated at CAT & European Commission level. However, these two points are outside the scope of this procedural guidance document (see section 2). Once further experience, number of precedents available, EMA/CAT may publish further guidance in the future.

2. Specific comments on text

Line numbers	Stakeholder number	Comment and rationale; proposed changes	Outcome
89-92	1	The guideline states that “results of the assessment of the medical device by a notified body (NB) for medical devices shall be included in a Marketing Authorisation Application (MAA) for a combined ATMP”. Please consider being more specific by giving the type of information that should be included: CE mark conclusion, CE mark summary of basis for approval.	The wording of the Legislation is merely reminded in the introduction, for more details on data requirements please refer to section 4.3
97, 102	1	The guideline states that “the EMA/CAT may seek an opinion on the conformity of the device part (…) from a suitable designated NB.” “The Agency may request the relevant notified body” It would be useful to clarify the method to select the “suitable designated NB”: selection criteria, committee/responsible person to designate it, etc. We understood, from section 5.1, that the Applicant would be involved in the selection of the NB as well. Clarification on this process would be valuable. In addition, it would be helpful to clarify who could request this and when (“EMA/CAT” is not clear). Does it mean that further information can be requested by the CHMP at a later stage of the MAA assessment?	See redrafting of section 4.3. It is the responsibility of the CAT to identify the need for NB consultation within the context of Article 9 of Regulation 1394/2007. Noted.

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99-100	1	The guideline states that any interactions with the EMA/CAT and the NB(s) will be done “in conjunction with the Applicant”. We appreciate this opportunity to interact further with the Authority, and we welcome this approach.	
112	1	In this paragraph, it would be helpful to clarify when the procedure described in the guideline does apply. For example, applicability of delivery system should be discussed. Other examples would be helpful.	In a future revision of the procedural guidance document once precedents become available they may be considered.
173	1	It would be helpful to describe the role of the Notified Body at the beginning of the document, instead of addressing it in section 5.1. Consider discussing it in section: “Consultation of a Notified Body”	See redrafting of section 4.
177	1	“…in conjunction with the combined ATMP Applicant.” We recommend mentioning this information once at the beginning of the guideline, and not repeating it if possible in other sections of the document. Cross references may be helpful. In addition, the nature of the interactions could be briefly introduced (meeting, etc.)	Clarification on “Applicant” will be included in new section 4.1. of the document.
188-189	1	We suggest adding a reference to the corresponding section of the document dealing with this point.	Section 5.1 combined in section 4 to avoid duplication of information.

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		Proposed change (if any): "Such assessment, when available and submitted as part of the MAA, may facilitate the review of the application and specific consultation with a NB may not be required. **Please also refer to section 5.1**"	

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192-205	3	These paragraphs show that there might be some misunderstanding on the assessment of a device by a Notified Body. If a device is intended to be used with an ATMP and placed on the market, in view of being used *with* an ATMP (for example to hospitals) it must have been evaluated accordingly by the Notified Body in the context of the relevant conformity assessment procedure of Directive 93/42/EEC. Therefore the two paragraphs should be merged since they refer, in fact, to a single situation: the device was not intended initially to be used with an ATMP **Proposed change (if any):** An illustration of the above request from the Agency/CAT to the NB could be the case when the results of the assessment on the device part performed by a NB relates to the use of the device, which is now combined with an ATMP, but in a different intended use. In such case, combining a medical device with an ATMP may have an effect on the original technical, clinical and biological characteristics of the device as a result of the addition of the ATMP. Further opinion on the suitability of the device for the intended use proposed when in combination with an ATMP may be sought from a NB. Also in this case, within the remit of Article 9 of Regulation (EC) No 1394/2007, the EMA/CAT may seek an opinion on the effect of the combination on the device part from a NB	
219-226	2	The notified body should be informed by the EMA or the applicant that its name is mentioned in the application form and that it may be consulted in a near future as part of the review of a combined product. This	This is covered in section 4

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		responsibility should be clarified **Proposed change (if any)**: Following submission of the application form, XXX should inform the NB that it may be consulted as part of the review of the combined product containing the device XXX.	See redrafting of section 4.
225 Section 4.2 Identification of Notified Body	2	To ensure clarity, revise this sentence to simply address the case where assessment by an NB *has not been* included in the MAA and specify the rationale for providing this information. **Proposed change**: This information is required even in the case where NB assessment of the device component has not yet taken place. The NB specified may be consulted in the event that CAT determines that advice on the conformity of medical device is required (see Section 5.1).	
235-236	1	The guideline states that the choice of Notified Bodies will be guided by their expertise. However, we anticipate Notified Bodies have limited experience in the area of combined ATMPs. We suggest clarifying the option when no expertise has been identified within the recognised Notified Bodies.	It is acknowledged that NBs may have limited experience with combined ATMPs. It is up to the combined ATMP applicant to identify the NB in the application form. This NB may be consulted by CAT if necessary.
242-243	1	It would be useful to specify when the guidance referred to in the guideline is expected to be made available and to specify who (which group) is responsible for preparing these documents inside the European	The EMA/CAT & NB collaboration group is coordinating the drafting of further guidance on behalf of CAT. See collaboration group mandate & work plan 2011 & composition. http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CA

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		Medicines Agency.	T/people_listing_000086.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac058029021c
244-247 Section 4.3 Specific Data Requirements	2	The use of the term “if available” in this sentence could be interpreted to imply that you can file your MAA and submit the NB assessment later. *Sponsors need to understand whether this is an option available to them.* The more likely situation is that either the NB has assessed your device and a final report is included, or you decided that no NB review was necessary and it is not included at all (e.g. CE mark available already). **Proposed change**: It is recommended that an introductory statement be added to describe the possible scenarios and clarify whether a pending NB assessment can be submitted after the MAA is filed.	EMA/CAT can only advise applicants to get the medical device part ”of the combined ATMP” assessed by a NB when appropriate and ideally prior to submission. See redrafting of section 4.

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270-274 Section 4.4 Access by the EMA/CAT to data concerning the medical device component and confidentiality	2	This statement includes the words “after the marketing authorisation has been granted”. However, the document primarily addresses the initial approval process. **Proposed change**: Remove reference to post-marketing setting from this section. *See general comments for recommendation to issue a separate procedural advice document addressing the post-marketing setting.*	Comment noted & implemented. Section removed.
277-280	1	It might be relevant to describe and discuss the potential of data owned by a third manufacturer. In this specific case, the Applicant may not be able to provide the requested documentation because of confidentiality/proprietary issues restricting the third manufacturer. Information on how the EMA/CAT/NB intends to deal with this situation would be valuable (consider discussing the potential to provide the equivalent of “master file” – i.e. that the manufacturer could send “proprietary” information to the EMA directly.	Dossier must contain all relevant data and it is the responsibility of the Applicant to make sure the dossier is complete in accordance with legal basis chosen. See new section 4.1. It should also be noted that master files can only be submitted for active substances http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002814.pdf
277-280	2	In case of confidential data, the device manufacturer may only agree to provide an answer directly to the EMA/CAT without disclosing the data to the applicant/MAH **Proposed change (if any)**: In case of confidential data, the device manufacturer is allowed to provide the	See above together with further clarifications provided in section 4.5.

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		requested data directly to the EMA/CAT.	
299-302	2	With regards to data pertaining to the medical device, the information published in the EPAR should be agreed upon by the Applicant. **Proposed change (if any):** replace "consultation prior to" with "an agreement with the Applicant prior to".	EMA procedure for EPAR drafting allows for the applicant to make comments on the information that will be made public. (link to EPAR GL publication) http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000433.jsp&murl=&mid
304 Section 4.5 Post-marketing	2	*See general comments for recommendation to issue a separate procedural advice document addressing the post-marketing setting.* 1) Recommendations on how to assess changes to the device portion of a combination product are described in section 4.4 (lines 289-294) instead of this, more logical, section. 2) Reference to EC No. 1234/2008 (variation regulation) is missing. **Proposed changes**: *If separate procedural advice to be provided, specify this in this section.* 1) Move information in lines 289-294 (concerning how to assess changes to the device portion of a combination product) to Section 4.5., 2) Add reference to EC No. 1234/2008 (variation regulation).	See end of section 2.

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324-327: 333-335 5.1 Reasons for EMA to consult a Notify Body	2	This section suggests that CAT may request additional "information" about the device, specifics about its intended use, and potential interactions between the ATMP(s) and the medical device(s) from the NB. However, the applicant would be the expert regarding such information and the NB consultation should be restricted to clarifications only about its assessment. CAT should allow for a request to be made to either the NB or the applicant, or both, regarding device specific information it needs and assess the relevant information from the appropriate responder(s). **Proposed changes**: Suggest revising lines 325-326 to "... but the CAT requires additional information **regarding the NB's assessment** or has additional queries regarding the medical device(s) **and the NB's assessment**. **Requests for technical, safety or performance information related to the medical device(s) may be directed to the applicant**. Suggest revising line 333 to" ... information and confirmation **regarding the NB's assessment** that the medical device(s) can be used..." Suggest revising line 335 to: "...potential interactions **assessed by the NB** between the ATMP(s) and..."	The applicant would generally be expected to provide information and data based on their expert assessment of these aspects of the combined ATMP as part of the original application or, if not, during the assessment process. However, the NB may be consulted on these aspects from the perspective of the medical device part to ensure that the combination does not have a negative impact on the medical device part such that it no longer conforms to the Essential Requirements of the relevant device Directive.
341	1	Again, it would be useful to specify when the guidelines referred to are expected to be made available and to	In accordance with EMA/CAT & NB collaboration group mandate & work program 2011 this will be developed in the future.

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		specify which group is responsible for preparing these documents inside the European Medicines Agency.	http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CAT/people_listing_000086.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac058029021c&jsenabled=true

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349 5.1 Reasons to consult NB	2	In our view the 2 month time period specified cannot be mandated. The NB could have many assignments and this could jeopardize the procedure. **Proposed change:** *See general comments regarding NB consultation and case-by-case consideration*	
367-372	2	The purpose of the consultation at day 1 should be clarified and the process further detailed as done for the following sections (5.2.2, 5.2.3, 5.2.4).	
370	1	We suggest defining "the Committee" referring to in this paragraph. Do we refer to the CHMP, the CAT, or another Committee?	"Committee" This will be changed to CAT.
382 5.2.3 Identification of Need to Consult a Notified Body at Day 80	2	The advice states that: CAT (may) decide on the need for further consultation of a NB and the need to identify a different NB in conjunction with the Applicant together with the List of Questions (LoQ) to be addressed by a NB." The need for a second consultation with a second NB should be clarified normally in the current advice (e.g., a separation of question topics so that conflicting NB opinions are not rendered), and this should be explicitly agreed to or requested by the applicant, or should not be allowed in the current advice. **Proposed change**: "CAT (may) decide on the need for further consultation of a NB **in conjunction with the Applicant and/or, with the explicit agreement of the applicant, the need to identify a different NB,**	The consultation of a second notified body is suggested as a possibility upon CAT needs/requests. If felt to be needed, such consultation would be with full visibility (mentioned in AR/EPAR) and with the consultation with the applicant. This will be further clarified in section 5.2.3.

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		where either may be provided with the List …"	
396-397	2	The additional questions should be qualified as being critical for the assessment of the combined ATMP, to avoid any unnecessary delay in the procedure at this stage **Proposed change (if any):** clearly establish that only questions considered critical - e.g. pertaining to safety - should be considered at this stage	This possible late stage consultation with Notified Bodies is suggested as an exceptional possibility in line with EMA centralised medicinal products evaluation practice. It is foreseen that it should be initiated only in case critical outstanding issues related to the Device component of the combined ATMP are outstanding/remain to allow the applicant/NB to provide further clarification prior to CAT/CHMP adopts if final (draft) opinion. Addressed also in section 1.

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410 5.2.5 Consultation with the NB at Day 170	2	1) Clarify under what circumstances, if any, CAT/EMA may disregard the NB's assessment (*see general comments for background*), 2) The advice should provide information on if and/or how a NB will be included in pre-approval inspection process.	(1) This is not possible to define at this time but it may be possible to provide some general guidance when specific assessment experience with combined ATMPs has been gained. (2) This is not described within the ATMP Regulation. This will have to be further discussed within EMA/CAT-NB Collaboration Group and is part of its 2011 WP topics. Once available, further clarifications will be provided.
439 5.3.1 Pre-submission meeting at EMA	2	Additional information regarding the medical device should be directed to the Applicant rather than the NB. **Proposed change:** Suggest revising line 439 to: "... found necessary to consult a NB to get additional information regarding **its assessment** of the medical device."	Correspondence with NB is directed through the applicant in the vast majority of circumstances. In certain instances, for the sake of expediency the NB may be contacted directly but this will be will full visibility of the applicant.
452-453 and 470-471	2	The applicant should be given the opportunity to add questions to the CAT questions. **Proposed change (if any):** Add the opportunity given to Applicants to complete CAT questions with its own questions to NB	This is not the purpose of the consultation described in Article 9 of Regulation 1394/2007. The applicant should conduct all correspondence directly with the notified body or other party e.g. medical device manufacturer and should make sure all contractual agreements to do so should be in place prior to the submission of the combined ATMP Marketing Authorisation Application by the Applicant to the EMA.
540 References	2	1) Reference to 2007/47/EC is missing (amendment of MDD 83/42/EEC and 90/385/EEC). 2) If applicable (see comment on line 304), add reference to 2004/23/EC **Proposed changes**: Add reference to 2007/47/EC and 2004/23/EC	The reference to Directive 93/42/EEC and 90/385/EEC with "as amended" added will encompass all amendments of this Directive, including those done by Directive 2007/47/EC. "As amended" will be added to the reference of Directive 2001/83/EC.