EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3 November 2015

Submission of comments on "External guidance on the procedural aspects related to the submission of clinical reports for the purpose of publication in accordance with EMA policy 0070" (EMA/471266/2015)

Comments from:

Name of organisation or individual
EFPIA – European Federation of Pharmaceutical Industries and Associations VE - Vaccines Europe

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	EFPIA and Vaccines Europe welcome the opportunity to provide comments on the EMA's draft external guidance on procedural aspects related to Policy 0070. Since both companies and the Agency are on a steep "learning curve", we would welcome the opportunity for flexible interactions with EMA to make these requirements workable. In preparing these comments, we have taken into account the information shared and the discussions that have taken place at the stakeholder consultation meetings that EMA has held, as well as EMA's responses to EFPIA's letter of 22 September. Detailed comments and proposals for revisions are included in the section on specific comments, below. In summary, the following major points concerning the content of the draft guidance are noted: <u>Removal of prescriptive guidance</u> We welcome the EMA's confirmation, in its 7 October letter to EFPIA, that "the draft External guidance does not contain prescriptive measures" and that "MAHs/applicants should consider, also with regard to case narratives, the best way on a case-by-case basis, to anonymise the information to be published."	

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	In light of the above, the prescriptive guidance concerning the removal/redaction of case narratives should be deleted, to permit the MAH/applicant to decide upon the best approach for anonymisation. <u>Clarity and consistency</u> On some aspects, there is a lack of clarity (e.g. on removal of patient listings) or there are inconsistencies (e.g. precise scope of Policy 0070) which could lead to a great deal of confusion if they are not addressed. <u>Compliance with eCTD specifications</u> There are several issues with the proposals for use of eCTD that need to be addressed, in order to ensure that submissions of redacted documents do not unnecessarily fail validation under eCTD specifications. <u>Cover letters</u> The cover letters need to be modified, to better reflect what the applicant/MAH is able to affirm and commit to. <u>Anonymisation Report</u> We welcome some of the changes that have been made to simplify the proposed anonymisation report template, following the targeted stakeholder consultation meeting of 7 September. We do, however, believe that there is the possibility for further improvement, to reduce the	

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	potential for duplication of information and further simplify. In addition, we feel that the permanent availability of the published documents in the face of continually evolving and improving re-identification techniques deserves close attention; this aspect requires MAHs/applicants to err on the side of caution in order to durably safeguard patient-level information. <u>CCI justification table</u> The CCI justification table would benefit from some further improvements to the description of the information requested, to avoid unnecessary duplication of information. In addition, companies would appreciate receiving more guidance on how to clearly explain that disclosure of particular information would undermine the economic interest or competitive position of a company. This impact can only be clearly demonstrated after the damage has occurred. We believe that it is important that the precautionary principle is applied in this case to ensure the damage does not occur, as any legal recourse is ineffective after the fact. <u>Interim relief</u> It would be helpful to describe in the guidance the options and the process the MAH has in case of a disagreement with the EMA redaction conclusion, and also to add this in the work-flow in the appendices.	

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	Applicability to Article 58 procedures The draft guidance does not address the publication of redacted/anonymised clinical reports submitted via the Article 58 procedure, for which no EC decision will be issued. The guidance and flowcharts should be revised to provide clarity for this submission type, should the Article 58 procedure fall under the scope of the Policy 0070.	
	In addition to the above points concerning the content of the draft guidance, the following more general points regarding the implementation of Policy 0070 should also be considered: Review of experience and requirements Under Policy 0070, the proposed redaction process will mandate that each applicant submits 2 additional regulatory submission packages for each new product and all variations or extensions containing clinical data. Often, the same team will be managing the regulatory submissions to the Agency as well as other global Regulators. This additional burden within a critical time period during the EU authorization process might have an impact on other marketing authorisation-related activities. In order to measure the full impact of the new requirements, we propose that key metrics are discussed with stakeholders. The initial experience with implementation of Policy 0070 should be reviewed to determine if the	

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	objectives of the disclosure scheme are being met in a balanced manner. The procedures and requirements described in EMA's external guidances supporting Policy 0070 should then be revised if necessary. For example, as suggested in EFPIA's letter of 22 September, an alternative approach to the review of CCI redactions could be considered, with redaction of CCI only be reviewed when there is an Access to Documents request (under EMA's Policy 0043), instead of at the time of submission under policy 0070. <u>Consistency with EU CT Regulation</u> Industry supports the provisions related to disclosure of information on clinical trials under the new EU Clinical Trials Regulation. While EMA Policy 0070 is being implemented, consistent and integrated processes should be developed at the same time for the implementation of the legal provisions regarding the publication of clinical study reports. It is essential for industry that there is close convergence and integration to reduce complexity and allow a comprehensive system that is operable and cost efficient. A simple and easy system can greatly facilitate stakeholder compliance. <u>Implications for other jurisdictions</u> If the Agency has not already done so, we encourage it to actively seek input on the draft guidelines from other key regulatory agencies, to ensure that legal requirements in other jurisdictions and their impacts are	

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	considered, as all published documents will be globally available and usable. It would be equally important for other Regulators to fully understand the implications.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
48-52		Comment: It is agreed repetition is not ideal, but referring to a definition included in other documents may not be helpful, particularly as section 2.2 (types of documents subject to publication in Phase I) as currently written may cause some confusion.. Proposed change (if any): Clearly state the document types that are in scope (see also comment below).	
53-104		Comment: This section is not easy to follow as currently written: the bullets alternate between "are not considered subject to publication" and "considered subject to publication". In addition, not all subsections of Module 5.3 are mentioned: for example, it should be made clear that Module 5.3.7 (case report forms and individual patient listings) is out of scope, consistent with Appendix 16.2 of a CSR being out of scope. Proposed change (if any): Re-write the section so it is a clearer and more comprehensive description of what is and is not considered subject to publication. EMA	

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		could consider presenting the types of documents in a tabular format, similar in format to the one in the *HMA/EMA Guidance on the identification of CCI and PPD within the structure of the MAA*.	
58-59		Comment: The US Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE), if included in the EU MAA dossier, are more likely to be contained in Module 5.3 (under "Reports of Analyses of Data from More than One Study"). The reference to their inclusion in module 2.7 may, therefore, cause confusion. Proposed change (if any): Delete reference to US ISS and ISE in lines 58-59 (lines 65-67 confirm that these documents would be in scope if included in 5.3). Clarify what other "additional documents" (line 58) in 2.7 may be in scope.	
63		Comment: Studies involving human materials are sometimes included in Module 5.3 (e.g. in 5.3.2). These studies are generally *in vitro* and do not involve subjects *per se* and do not directly assess efficacy or safety. It would be helpful for this section to further clarify that such biomaterial studies are out of scope.	

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		Proposed change (if any): "…studies not involving human subjects (including in vitro studies involving human biomaterials) and PSURs/PBRERs. These types of documents are not CSRs and therefore they are not considered subject to publication."	
65-67		Comment: The structure of additional reports in module 5.3 will not necessarily follow the ICH headings of a CSR. It should be confirmed that if a section in an ICH format CSR is not to be prepared for publication, e.g. an appendix defined as out of scope, the same is true for these additional reports. Proposed change (if any): Confirm that the expectations for public disclosure of appendices from reports that do not follow the ICH E3 CSR format are the same as for those reports that do follow ICH E3.	
67-68		Comment: In line with the advice included on Reports of supportive studies not including human subjects and on CTD section 5.3.1.4, it should be clarified that "In vitro-In vivo Correlation Study Reports" (Module 5.3.1.3) are not CSRs and therefore not in scope. Proposed change (if any):	

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		Add "<u>According to ICH M4E, CTD section 5.3.1.3 may include studies used in seeking to correlate *in vitro* data with *in vivo* data. These types of documents are not CSRs and therefore they are not considered subject to publication.</u>"	
79-80		It seems unreasonable to expect additional justification for the redaction of the efficacy data in clinical reports for an indication that has not yet been applied for. If the data are not yet published, then efficacy data should be seen as CCI because the applicant may want to apply for this indication in the future. Proposed change: we suggest to remove the text *"and not to provide as a justification that they have not yet applied for a particular indication"*	
84-86		Comment: The meaning of these lines is not clear. The meaning of 'main period/phase' of a clinical study should be confirmed. We suggest there is additional clarification added here with some examples, including regarding disclosure of interim results from ongoing long-term studies. Publication of data from interim analyses could compromise the integrity of the ongoing study. Redaction of data from interim analyses supported	

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		by a justification that the redaction is protecting the integrity of the study should be permitted. Proposed change (if any): To be added to the end of the paragraph at line 86: "For interim reports of ongoing studies, a rationale for redaction could be based on the impact of disclosure on the integrity of the ongoing study." Include an explanation of what is meant by the 'main period/phase' of a clinical study	
88-90		Comment: Policy 0070 indicates that "clinical summaries (generally submitted in module 2.7)" are in scope. Elsewhere in this procedural guidance (e.g. Table 1 on page 6) it appears that only sections 2.7.1 to 2.7.4 of the Clinical Summary are in scope. The reference in line 87 to "all sections of the clinical reports falling within the scope of the policy" is therefore confusing. Policy 70 and Table 1 in this guidance also indicate that 3 appendices of the CSR are in scope (sample CRF, protocol+amendments, SAP) -	

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		guidance and Policy should be consistent to avoid confusion Proposed change (if any): "In particular, sections 2.7.1-2.7.4 of the clinical summary, all appendixes (as per ICH M4) of the clinical overview and clinical summaries and all sections of the CSRs up to and including section 15, as well as appendices to the CSRs no. 16.1.1 (protocol and protocol amendments), 16.1.2 (sample case report form) and 16.1.9 (documentation of statistical methods) (as per ICH E3), are subject to publication."	
91-99		Comment: CSRs may contain several individual patient data listings, in addition to the Abnormal Laboratory Value Listing in 14.3.4, mentioned by EMA. The mention of only one specific listing may lead to confusion regarding what is or is not in scope of phase 1 of the policy. Proposed change (if any): "However, EMA notes that under ICH E3, the CSRs are expected to contain individual patient data listings even within the body of the report. For example~~In particular~~, these listings may be~~are~~ contained in section 14.3.4 Abnormal Laboratory Value Listing (Per Patient/per Visit),	

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		as well as elsewhere in the CSR or in Modules 2.5 or 2.7. EMA considers that such listings ~~(contrary to individual patient level information – see below)~~ fall outside the scope of phase 1 of the policy and, therefore, it is acceptable to have them removed from the CSRs prepared for publication at this stage of the implementation. It is not expected that the removal of this data would affect in a significant way the understanding of the findings and data utility of the published clinical report since the clinical relevant findings are revealed in other sections ~~12.4.2.3 Individual Clinically Significant Abnormalities~~of the CSR, which ~~section is~~ are subject to publication."	
100-104		Comment: The provision of prescriptive guidance here – that case narratives should not be removed nor redacted in full – is at odds with EMA's position (as stated in its 7 October letter to EFPIA): i.e. that "the draft External guidance does not contain prescriptive measures" and that "MAHs/applicants should consider, also with regard to case narratives, the best way on a case-by-case basis, to anonymise the information to be published." Rather than explicitly object to or prohibit removal or redaction of case narratives, these lines should be deleted to permit the MAH/applicant to	

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		decide upon the best approach for anonymisation. This is particularly important, as there is a risk of re-identification using narrative information, for example by patients' clinicians (described as "Clinician adversaries" in El Emam, Abdallah, 2015: De-identifying Clinical Trials Data, Applied Clinical Trials) or relatives, which cannot be further mitigated by contractual or system controls, once clinical reports have been made public on a website. A possibility to re-identify a patient with a rare disease needs to be particularly mitigated. Proposed change (if any): Delete lines 100-104.	
110-117		Comment: This section as written could lead to some confusion: there are different numbers of "advance" notifications for MAA and for Variations; and all notifications are referred to as "advance" even though it is possible for the applicant to submit the proposal package prior to the final notification. Proposed change: Harmonize the notification procedure for MAAs and indication extensions. Have one "advance notification" with the validation in both procedures (as already described) and one or two	

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		"reminders" at comparable stages of the procedures (the last being at time of Opinion).	
121		Comment: It should be clarified that the redactions proposal and final redaction submissions are under the same life cycle assembly sequence as the marketing application.	
130		Comment: There is an error in the reference to the Appendix. Proposed change (if any): A workflow for the "Redaction Proposal Version" process is at Appendix ~~5.8~~ 5.7.	
144		Comment: It is unclear what is meant by the sentence "The clinical reports within a module need to be individual." Previously it had been discussed that redacted documents should be provided in the same format as the original documents in the dossier: i.e. if a CSR and appendices were originally one document, that is how the redacted versions should be provided; if the CSR and appendices were in separate documents, then separate redacted documents should be provided.	

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		Proposed Change: "The clinical reports within a module need to be individual. This means that multiple clinical reports should not be merged into a single document. Redacted versions of a single clinical report and its appendices can be a single document if the original report was submitted this way. If a clinical report and its appendices were in separate documents when submitted for review, then this is how they should be submitted in the Redaction proposal and Final Redacted version."	
149-151		Comment: Some of the content of Table 1 should be revised for greater clarity. Similar comments apply also to Table 2. Proposed changes: Module and Section references are mixed and confusing. There is also no "format" mentioned in the table, other than in the heading of the 2nd column. We recommend changing the heading of the 2nd column to 'eCTD Module/Section within eCTD' then just use the numbers in the table e.g. Module 1.0 → 1.0 Module 2.7 – sections 2.7.1 – 2.7.4 → 2.7.1 to 2.7.4	

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		Module 5 0 section 5.3 → 5.3 In the middle of the table, the text should be amended to ""Redaction Proposal Version" of all clinical reports as follows: the "Redaction Proposal Version" is an initial version of the clinical reports intended for publication in which ~~proposal~~ proposed redactions are marked" Table 1 should mention all appendices of the clinical overview and clinical summaries, to be consistent with section 2.2 (see also comment on lines 88-90). If a document intended for publication does not require any redaction of CCI, we propose that this be mentioned in the cover letter of the redaction proposal version, and documents that contain no proposed CCI redaction will only be submitted in the "Final Redacted Document" package. Justification tables should not be required for such documents (see also comment on lines 191-192). The link to the downloadable template for the justification table is currently placed in Section 3.3.1.5, not in Appendix 5.10. Please align	

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		statement with location of the link.	
155-156		Comment: The current eCTD specification allows PDF version 1.4 – 1.7. This guidance should simply refer to the current specification. Alternatively, if there are specific requirements for redacted clinical reports, this should be clearly stated. See also comment on line 365. In addition, other file format requirements are mentioned in section 3.3.3.4 but not here, in section 3.3.1.3: • The PDF format is more specific in section 3.3.3.4. • There is a file size maximum in section 3.3.3.4. • There is no mention of password protection in section 3.3.1.3. To avoid confusion, we propose that the same requirements are included in sections 3.3.1.3 and 3.3.3.4, or that a single format description section that applies to both packages is included. Proposed change (if any): "With regards to PDF formats submitted within the eCTD, the current eCTD specification applies ~~and PDF version 1.7 onwards are currently accepted~~."	

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		Include requirements regarding file size and password protection, or explain why they differ from the "Final Redacted Document" package.	
159-160		Comment: The specific method of labelling proposed CCI redactions should be left to the MAH/applicant (e.g. labels inserted as annotations/comments, as part of the 'redaction properties' as "overlay text" or as colour coding with a legend to explain the colour code), in order to accommodate the redaction tool selected by the company. Proposed changes: Add: "<u>The method of labelling proposed CCI redactions is the choice of the MAH/applicant (e.g. labels inserted as annotations/comments, as part of the 'redaction properties' as "overlay text" or as colour coding with a legend to explain the colour code).</u>"	
164-166		Comment: It is not clear what is being "tracked", nor how this should be done (for example, Adobe Pro is the standard tool for redaction but does not offer tracked changes). The feedback on proposed CCI redactions will be included in the justification table not the clinical report. We welcome the statement that the choice of the redaction tool is a	

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		decision to be taken by each applicant/MAH. Most companies will have already selected their tool in order to prepare for these activities and to meet the PhRMA and EFPIA Principles of Responsible Clinical Data Sharing. MAHs should not need to adapt their selected tools to meet the requirements of the Policy. Proposed change (if any): Delete "and clearly tracked"	
171-175		Comment: Lines 159-160 indicate that only CCI redactions should be labelled. Clinical study reports will include much more PPD than CCI. As the EMA will not review proposed PPD redactions, and as it will be obvious that unlabelled redactions are PPD, it would be onerous and unnecessary to also require the labelling of PPD redactions. In addition, in cases where techniques of anonymization and generalization, rather than redaction, have been employed, labelling as "PPD" could be even more challenging (as the new anonymised version of the report would need to be compared with the original version, introducing the possibility of errors) and would undermine the "blending in" that such techniques attempt to achieve.	

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		Proposed change (if any): "EMA will only assess the proposed CCI redactions and not the PPD redactions/anonymisations. It is important that in the redaction proposal version of the submitted clinical reports the applicant/MAH clearly indicates the nature of each proposed CCI redaction ~~(CCI/PPD)~~. Therefore, all pieces of information proposed for CCI redaction should have a label, clearly ~~stating~~ indicating that~~if~~ the proposed redaction is requested on CCI ~~or PPD~~ grounds."	
183-184, 188		Comment: The cover letter templates in Appendix 5.4 and 5.5 do not include an interactive table, and the link on line 183 points to version 2 of a formatted table template which does not include the information shown in the illustrations in the guidance. Proposed change (if any): If the applicant is expected to include a table template in addition to the cover letter in Appendix 5.4 or 5.5, this should be clearly stated and a link to the correct table provided.	
186-188		Comment: The declaration in the illustration below line 188 refers only to the clinical reports, and not to the cover letter. The sentence "In addition to uploading the cover letter applicants/ MAHs must confirm , in	

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		the interactive table that the cover letter including the declaration has been uploaded" is, therefore, confusing. Proposed change (if any): Revise either the sentence on lines 186-187 or the illustration below, for consistency.	
191-192		Comment: As written, it appears that a justification table must be provided for each clinical report, even if there are no CCI redactions in a report. A justification table should only be required if CCI redactions are proposed. Proposed change (if any): "For the redaction proposal version of each of the clinical reports in which CCI redactions are proposed, applicants/MAHs must complete a justification table in Word format."	
198-201		Comment: The request for 4 individual justification tables for each CSR (1 for the body of the report and one for each of the three annexes) seems very cumbersome. As the justification table must clearly reference the location of the proposed redactions, it ought to be acceptable for the applicant/MAH to provide a justification table for each	

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		CSR if they wish, regardless of whether the CSR and its appendices are provided as a single document or as separate documents. Proposed change (if any): "~~For a CSR in Module 5 the applicant/MAH should submit a completed justification table for the body of the study report and three separate justification tables for the three Annexes (16.1.1, 16.1.2, 16.1.9). In this case it will mean the submission of four completed justification tables in total for one CSR.~~"	
202-209		Comment: The guidance concerning folders for the justification table is unclear. We assume that the sequence folder number (e.g. 0000) and "Working-documents" should both be in the root folder. Proposed change (if any): Include a screenshot to illustrate the folder structure for clarity.	
212, 358, 375		Comment: The use of the term "uploaded" should be avoided in respect of inclusion of documents in eCTD. Proposed change (if any): "~~uploaded~~ <u>included</u>"	

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213, 391		Comment: We note that from April 2016 the eCTD specification will include new submission types specifically for these redacted clinical reports (clin-data-pub-rp = Clinical data for publication – Redacted Proposal; clin-data-pub-fv = Clinical data for publication – Final Version), and that "Supplemental Information" should no longer be used. It would be helpful to include this in the guidance, in addition to the workaround, until v3.0 can be submitted by applicants. Proposed change (if any): Include reference to revised submission types applicable from April 2016.	
216-218		The requirement to submit separate redaction packages where multiple duplicate applications have been submitted for the same medicinal product will create additional demands on resources with no benefit to those interested in viewing and using the reports. If the clinical documents are the same then it is not necessary to prepare a new Redaction Proposal Document, and a declaration from the MAH/applicant that the clinical reports in the applications are identical should suffice. When the clinical reports for one of the applications are published, EMA could include a cross-reference to those reports for the duplicate	

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		applications. Proposed change (if any): "Those applicants/MAHs submitting multiple applications for the same medicinal product under different invented names are also required to provide a new sequence for the "Redaction Proposal Document" package for all of the products, unless the reports are identical (with the exception of references to the product names). In the latter case, the MAH/applicant should provide a declaration that the clinical reports in the applications are identical, and the EMA will ensure appropriate cross-referencing when the reports are published."	
219-269		Comment: These entire sections seem out of place as they apply to both the proposed redaction and final redaction submissions. Proposed change (if any): Suggest that sections 3.3.1.7 and 3.3.1.8 are moved to the beginning of section 3.3.	
231 and 232 246 and 247 266		Comment: The proposed naming convention includes the addition of an indicator of "pivotal" or "supplementary" in describing the CSR. This is not a designation used in the eCTD format, and it is not clear why this is	

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		expected here. Proposed change (if any): Please define what is meant by "pivotal" and "supplementary" and explain the relevance of the designation in respect of Policy 0070.	
241-250		Comment: The character "." cannot be used in eCTD filenames. Proposed change (if any): Delete "." from the filenames listed in these lines.	
246-250		Comment: It should be clarified what file names should be used for documents in Module 5.3 that are only considered CSRs for the purposes of Policy 0070 (e.g. reports of analyses of data from more than one study), and which do not have a study report number. Proposed change: Please provide naming conventions for file names of reports of analyses of data from more than one study or add a statement that MAHs/applicants may define other file names as needed.	
246-250		Comment: There is a 180 character path limit in the eCTD and a single	

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		filename limit of 64 characters. These names could cause eCTD validation failures if the path or filename length is exceeded. This limit includes the extension (.pdf), so in reality the name can be only 60 characters. The filename length will depend on the name of the study report. "module-5.3.x.x-study-report number-appendix-16.1.1-protocol" is 60 characters, or 53 characters with removal of "." (see comment above). Therefore, it might be advisable to remove the module number or reduce 'module' to 'm' (m53xx-study-report number-appendix-1611-protocol.pdf). Even then, some applicants might have issues if they have very long study report names. Proposed change (if any): Consider shortening the length of the fixed elements of the proposed filenames.	
270-288, 393-411		Comment: These sections describe the usual eCTD submission and technical validation processes, so the detail is unnecessary. Proposed change (if any): Replace with a reference to the usual eCTD submission and technical validation processes.	

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		If these sections remain, note that the words "hard media" (lines 284 and 407) should be deleted as there is no eCTD hard media.	
311-312		Comment: A justification Table should not fail validation based solely on the reason that some columns/rows are incomplete. Some redactions for CCI may not be referenced in Annex 3 of Policy 70, thus completion of Column 4 in the justification table for those redactions will not be possible. Since no guidance is provided on how to complete the justification table it is inappropriate to reject a submission if the applicant has not understood what is expected. See also comments on line 725. Proposed change (if any): ~~All the proposed redactions are reflected in the justification table, but some columns/rows are incomplete.~~	
313		Comment: If the justification for CCI is the same then it ought to be possible to repeat the justification. Use of the same justification cannot be a reason to reject a submission. Proposed change (if any): "~~The same~~ Unspecific ~~copy/paste~~ justifications are ~~is~~ used throughout	

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		the entire justification table."	
324-330		Comment: It would be helpful if the EMA provided guidance in this document about their planned communication to the company as to what is unclear or needs further justification during the redaction consultation process, as well as greater clarity on when in the assessment period the applicant should expect to hear from EMA if there are any queries. The timing for the process is short and at a critical stage for project teams within companies. It is therefore extremely important that EMA communications are clear, detailed and timely. If the EMA asks for amendment to several justification tables (there could be 50 or more for some applications) then a response in 5-7 days may be a challenge. It would be helpful to have EMA send issues as they arise – i.e. send individual justification tables for clarification to the company as required rather than batching them or sending in one lot. Companies will require sufficient time in the assessment stage for CCI to be able to adequately address any issues raised. Simplification of the justification tables and more guidance on their completion would be helpful in this respect. See also comments on line 725.	

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		Proposed change (if any): It is proposed that additional text be added to address the above in the guidance	
340-342		Comment: The requirement for the applicant/MAH to provide written agreement to the redaction conclusion within 4 days of the issuance of the EMA redaction conclusion cannot be met where an applicant/MAH does not agree with the EMA redaction conclusion in its entirety, and wishes to apply for interim relief. Preparing the final redacted version package within 20 days could be a challenge, particularly if the EMA does not agree with the all the proposed redactions. The possibility of applying for interim relief is not mentioned until section 3.4. For clarity, the possibility should also be reflected in 3.3.3.1. It would also be helpful if, as the documents were reviewed, there was some feedback to help the MAH prepare accordingly. We propose that the process should be that within 30 days of the issuance of the EMA redaction conclusion, the applicant/MAH should	

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		either provide the final redacted document package or a partial final redacted document package along with informing the Agency that the Applicant/MAH is seeking interim relief. Proposed change (if any): "~~Within 4 days following the issuance of the EMA redaction conclusion, applicants/MAHs must provide their written agreement to the redaction conclusion.~~ The "Final Redacted Document" package, must ~~then~~ be provided ≤ ~~20~~ 30 days following the issuance of the EMA redaction conclusion ~~this agreement~~. In the case of disagreement with that conclusion, applicants must provide a partial package, and indicate that they intend to apply for interim relief (see section 3.4)."	
343		Comment: There is an error in the reference to the Appendix. Proposed change (if any): A workflow of the "Final Redacted Version" process is at Appendix ~~5.9~~ 5.8.	
350		Comment: The use of "uploaded at the same time" is not helpful. We assume it is meant that these documents must be included in the same eCTD sequence.	

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		Proposed change (if any): "which must be ~~uploaded at the same time~~ included in the same eCTD sequence."	
351-353		Comment: Some of the content of Table 2 should be revised for greater clarity. Proposed changes: Module and Section references are mixed and confusing. There is also no "format" mentioned in the table, other than in the heading of the 2nd column. We recommend changing the heading of the 2nd column to 'eCTD Module/Section within eCTD' then just use the numbers in the table e.g. Module 1.0 → 1.0 Module 2.7 – sections 2.7.1 – 2.7.4 → 2.7.1 to 2.7.4 Module 5 0 section 5.3 → 5.3 Table 2 should mention all appendices of the clinical overview and clinical summaries, to be consistent with section 2.2 (see also comment on lines 88-90).	
358-359		Comment: Table 2 indicates that the anonymisation report is to be	

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		placed in Module 1.9. If this is the case, the filename format of "anonymization report, product name.pdf" will generate an error, as it does not meet the eCTD specification: "," is not permitted in eCTD filenames, and the specification for Module 1.9 requires a filename in the format "clinicaltrials-VAR.EXT". Proposed change (if any): One option would be to use the filename "clinicaltrials-anonymisation report.pdf", to match the filename permitted in the specification.	
365		Comment: The current eCTD specification allows PDF version 1.4 – 1.7. This guidance should simply refer to the current specification. Alternatively, if there are specific requirements for redacted clinical reports, this should be clearly stated. See also comment on lines 155-156.	
366		Comment: If the guidance retains the requirement that files should not exceed 100MB each, then it should be clear how, in the event a document exceeds 100 MB, a company should address this (e.g. split the document and refer to them as "part a " and "part b"), and account for this within the suggested naming conventions sections.	

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		A new ICH agreement is that there will be a 500MB limit for documents. The guidance should therefore reflect this new limit of 500MB to future proof this requirement.	
371-372		Comment: "Redaction codes" appears to be the wrong terminology – the EMA uses redaction codes in the justification tables to indicate its assessment of proposed CCI redactions. We assume that these lines are referring to redaction "labels", as referred to in lines 159 and 174. See also our earlier comments regarding the format of these labels. Lines 159-160 indicate that only CCI redactions should be labelled. In line with our comments on lines 171-175, it should not be necessary to label PPD redactions. Proposed change (if any): "Any (agreed) CCI redaction ~~codes~~ labels (e.g. CCI ~~& PPD~~) should be visible and irremovable together with the final redacted text."	
388-390		Comment: See comment on lines 216-218. Proposed change (if any): "Those applicants/MAHs submitting multiple applications for the same	

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		medicinal product under different invented names are also required to provide a new sequence for the "Final Redacted Document" package for all of the products, unless the reports are identical (with the exception of references to the product names). In the latter case, the MAH/applicant should provide a declaration that the clinical reports in the applications are identical, and the EMA will ensure appropriate cross-referencing when the reports are published."	
391-392		Comment: The eCTD operator "new" applies at document level within eCTD, not to the whole eCTD. It would be odd to use "new": "replace" would be more logical, otherwise the "current view" in eCTD viewers will forever have 3 copies of each report (original, proposals, final), and there is a risk that the wrong CSR sequence will be published. Proposed change (if any): "(using eCTD operator '~~new~~ replace')"	
414		Comment: It is not clear what the watermark will stipulate or include (e.g., the content not be used for submission or inappropriately or refer to appropriate uses at another location) Proposed change: Provide example of watermark in an appendix	

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415-420		Comment: The draft guidance details the timelines for publication of redacted/anonymised clinical reports in the frame of MAAs, line extension applications and extension of indication applications, for which either an EC decision is issued or which are withdrawn. It does not address the publication of redacted/anonymised clinical reports submitted via the Article 58 procedure, for which no EC decision will be issued. The guidance and flowcharts should be revised to provide clarity for the latter submission type should the Article 58 procedure fall under the scope of the Policy 0070. Proposed change: Add text to clarify the timelines for publication of redacted/anonymised clinical reports submitted via the Article 58 procedure.	
434-436		Comment: If the MAH does not submit a complete redaction proposal document – i.e. some clinical reports are missing – it is assumed EMA will flag this during the validation/review process. Also on this point, section 2 outlines some documents other than standard reports that could fall into scope – for some applications this can get quite complex and it is suggested that in these cases EMA	

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		provide some specific guidance/clarification to MAHs. Otherwise, statements of non-compliance could be posted by EMA when the applicant had no intent to be non-compliant. During the last EMA stakeholder meeting the industry group did raise the matter of applicant specific meetings to discuss individual applications if there was a need – particularly for the first few applications when the policy comes into scope. It is felt this is another example of where specific guidance would be helpful.	
458-459		Comment: Data transformations will not take place in the anonymisation process in all cases, so it is not appropriate to give the impression here that they are expected. Proposed change (if any): "...the methodology used, ~~the rationale for data transformations/redactions required for the adequate anonymisation of the data~~ and the impact on data utility."	
474-481		Comment: As this paragraph references the WP29 opinion on anonymisation techniques we propose to add the WP29's "contextual elements" aspect to section 1.1 to emphasise the risks inherent in public	

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		and permanent data/document release. The need for more stringent anonymisation of publically shared data is also emphasised by El Emam, Rodgers and Malin (Anonymising and sharing individual patient data, 2015, BMJ;350:h1139) Proposed change: Please add the following text: "The applied anonymisation techniques (including redaction) should take into account the permanent and public release of clinical documents. In particular, evolving data mining techniques and linkage options should be considered as well as a much higher risk of re-identification attacks than in restricted and contractually controlled environments."	
480		Comment: We acknowledge the options proposed to establish if the data is anonymised. Depending on the nature of individual studies and clinical reports, applicants may choose to apply one option to some reports in a submission, and the other option to the remaining reports. For example, for large multicenter studies the 3 criteria could be fulfilled, but a risk assessment might be applied to smaller studies. It should be made clear that the MAH/applicant may choose one option for each document: the Anonymisation Report should not be limiting or	

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		inflexible. Proposed change (if any): "Only one of the options should be followed <u>for each report</u>,…"	
482-497		Comment: The message of the introductory sentence conflicts with the way the 3 criteria a, b, and c are phrased. If the MAH/applicant should clarify that the 3 criteria have been fulfilled, the criteria need to state the contrary of what they do now, e.g. "a. **No** possibility to single out an individual", "b. **No** possibility to link records…", "c. Information can**not** be inferred…". Proposed change: Please either rephrase the heading and introductory statement of this section or the wording of the 3 criteria (including the detailed descriptions).	
521-548		Comment: There is the potential for duplication of information in section 2 "Identification of data variables", particularly on "de-identification" (lines 541-548), with the description of the anonymisation methodology in section 1. We suggest that the information requested in section 2 be presented under section 1 only.	

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		In addition, the MAH is required to provide a clear definition of each variable. This does not seem necessary for many of the variables such as age, date of event, etc, for which the name of the variable should be sufficient. Instead of requesting a list of all direct and indirect identifiers with definitions, a more general description of possible identifiers should be provided. Proposed change (if any): "~~List~~ Describe direct and quasi identifiers in the clinical reports[2] ~~and provide a clear definition of each variable~~" Move information requested in section 2 to section 1.	
550-551		Comment: The wording of this sentence could suggest that the ultimate goal is high data utility with "only" an acceptably low risk of re-identification. Protection of trial participants' identity must be the overarching aspect when publically releasing clinical trial data, and – as is stated in section 4.1 of Policy 0070 - "a guarded approach to the sharing of patient-level data" should be taken. This is of particular importance considering the potential impact that successful re-	

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		identification attacks may have on the public's and trial participants' trust in research, industry and regulators. We propose to amend this sentence to emphasise the importance of privacy protection. Proposed change: "~~A balance must be reached in order to obtain an acceptably low risk of re-identification and high utility data~~ Although a high-level of data utility is of interest in enabling the objectives of Policy 0070, the protection of personal data is of paramount importance."	
553		Comment: In the given context of public and permanent data release, more stringent anonymisation techniques will have to be applied than in contractual relationships, which may have an impact on data utility. Researchers may therefore be interested in more guidance on how they can obtain further information. If needed for additional research, access to the anonymised individual patient level data could be requested from the MAH directly with appropriate controls in place to protect the privacy of patients in the trials. Proposed change: Please add the following text: "The MAH may include direction to how	

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		further information about the data can be obtained. For example, the MAH may indicate how researchers can request access to IPD from the trial(s) to conduct further research.”	
554-557		Comment: It appears the purpose of the conclusion is to restate what is stated already in 1.1.1 or 1.1.2 and therefore the inclusion of section 4 of the anonymisation template seems redundant. Proposed change (if any): Delete lines 554-557.	
597, 650, 708		Comment: Applicants are unable to see the EURS, so cannot assert to documents’ locations in that system. Proposed change (if any): “…with their respective locations in ~~EURS~~ the eCTD.”	
604-605		Comment: Clinical documents potentially submitted with responses at D120 and/or D180 are not explicitly mentioned in this guidance. Their inclusion or exclusion from the scope of the Policy 0070 publication process should be explicitly clarified in the guidance.	
610-612,		Comment: The cover letter templates require that the MAH/applicant	

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663-666		declares that redactions and anonymisation shall fully reflect the provisions and requirements of Policy 0070 and "related guidance documents", which we assume refers to the "external guidance" from EMA. The anonymisation guidance (appropriately) is not intended to be prescriptive (i.e. follow these clearly defined steps), but nor is it truly laissez-faire (i.e. do what you think is appropriate). The Policy and the guidance on redaction of CCI are not comprehensive in their descriptions of what is or is not CCI. It is, therefore, inappropriate to require companies to affirm that what they have done follows the EMA's guidance. Companies should only be required to make assertions in the submission that they know can be asserted as fact, and that are not subjective. As the anonymisation report should factually lay out what the applicant/MAH has done, the applicant/MAH should affirm that they have anonymised in accordance with the anonymisation report. As the CCI redactions will have been discussed by the company and EMA, the applicant/MAH should affirm that the redactions will conform to the agreed outcome of those discussions.	

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		In addition, in order to ensure consistency between the 2 template cover letters for the "Redaction Proposal Document" package, the wording has to be slightly revised in lines 609-612, to include "any intervention needed to ensure". Proposed change (if any): ""…with the exception of (i) omission of documents, or elements thereof, falling out of the scope of POLICY/0070; and (ii) proposed redactions ~~to~~ and any intervention needed to ensure anonymisation of the Clinical Reports Documentation. These redactions of commercially confidential information shall conform with the agreed outcome of the redaction consultation with EMA and any intervention needed to ensure anonymisation shall be conducted in accordance with the Anonymisation Report to be provided by [COMPANY] ~~fully reflect the provisions and requirements of this POLICY/0070 and [REFERENCE TO THE RELATED GUIDANCE DOCUMENT(S)]~~."	
620-622, 674-676		Comment: At the time of submission of the "Redaction Proposal Document" package, it will not be possible for the applicant/MAH to declare that the "Subsequent Submissions" and "Final Submission" "do" not contain additional redactions as those submissions will not yet have	

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		been made. In addition, since the Agency will not check proposals for PPD redactions, the Agency is not in a position to explicitly agree in writing to all individual redactions. Therefore, the current statement in the cover letter does not hold true. Proposed change (if any): Delete lines 620-622 and 674-676.	
715-716		Comment: It is reassuring that EMA will notify applicants when their clinical data is published. However this appears to be the first mention of this. It would be helpful if this was also reflected in the procedural guidance as well as the work flow diagrams in the appendix to the guidance.	
718-722		Comment: process flowcharts in Appendices 5.7 and 5.8 are incomplete. They don't describe the end to end process and are not adding any important additional information to what is shown in Appendices 5.9 and 5.11. To the contrary, starting the consultation process, as per Appendix 5.7, with a submission of the redaction proposal after CHMP Opinion is inconsistent with text and appendices 5.9 and 5.11	

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		Proposed change: Remove appendices 5.7 and 5.8 and add more details to appendices 5.9 and 5.11, i.e. • in 5.9: timelines for indication extension and timelines for publication after EC decision; • in 5.11, mention interim relief process • in 5.9 and 5.11, align timelines with the guidance text (see also earlier comments, particularly lines 340-342) and in both appendices	
724		Comment: Provide clarity on the timeline on the bottom of the workflow. There is no complete timeline presented, the last bar in the "Publish" section has no days associated, and some days are "days" while others are "calendar days". Proposed Change: Provide a complete timeline for the entire workflow and clarify "calendar days" as appropriate (e.g., Redaction Consultation sections only states "50 Days" whereas other sections state "Calendar Days")	
724		Comment: As the redaction consultation steps concern information that	

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		is or may be commercially confidential, all communications between the applicant/MAH and EMA must be secure. Eudralink should therefore be used in all cases to ensure confidentiality. Proposed change (if any): Replace references to "Email" in workflow with "Eudralink".	
725		Comment: The justification table requests either reference to Annex 3 of the Policy or an explanation of how the proposed redacted text falls under the sections in Annex 3. Policy 0070 clearly indicates that information that is not described in Annex 3 may be CCI if appropriately justified (see Policy section 4.2.2.1). It is possible, therefore, that some information proposed for redaction will not "fall under" Annex 3. Column 4 (which requests specific reference to Annex 3) may not be relevant in all cases and adds an unnecessary complexity to completing the justification table. We believe that it is the company's justification for redaction (not this arbitrary classification), which is of most importance. In addition, in cases where the information is not clearly included in Annex 3, duplication of information in columns 4 and 5 of the table should be avoided.	

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		Proposed change (if any): Remove column 4 from the justification table. If column 4 remains, revise its header: "Applicant/MAH to reference the section(s) of the Annex 3 of Policy 0070 on which the redaction is based. (If not ~~straightforward~~ obvious please briefly explain how ~~the proposed redacted text falls under~~ this/these particular section(s) of Policy 0070 ~~and~~ is/are relevant for the text that is proposed to be redacted. If information proposed for redaction is not included in the examples in Annex 3, state "Not applicable" and provide a full justification in the following column."	
725		Comment: It would be helpful to companies if the EMA could provide some examples to illustrate the information and level of detail that is expected in column 5 of the justification table. Proposed change (if any): At the end of these comments, EFPIA has proposed some examples that EMA could consider for inclusion.	
729-730		Comment: In the redaction consultation process flowchart, the	

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		explanation for the validation step of the justification table is misleading. As stated in lines 314-316, the Agency will not assess the content of the justifications in this step but only the more practical aspects. Proposed change: Please delete the text in parentheses, i.e. "~~(meaningful or not, was the guidance followed)~~".	
729		Comment: The timeline in this flowchart (total 47 days) does not match the timeline for the redaction consultation in Appendix 5.9. Proposed change (if any): Please confirm the correct timeline and amend appendices to be consistent.	

Please add more rows if needed

Examples of justifications for redaction of CCI

The following are fictitious examples of potential CCI. Perhaps the EMA can use these to complete the justification form as an example.

Example 1
Text with proposed redactions: "The Company has discussed the development plan with the FDA and suggested the enrolment criteria be broadened to include patients with sickle cell anaemia. An analysis of the total population, plus patients with and without sickle cell anaemia will be necessary. The protocols were amended accordingly."

Justification: "The FDA" should be redacted. Product X is currently under review in the USA and the information that the analyses conducted will be acceptable to the FDA is not in the public domain. This information would be of benefit to competitors.

Example 2
Text with proposed redactions: The blood samples were analysed for product X using an HPLC assay using a column with a filter size of 2.3 micron.

Justification: "With a filter size of 2.3 micron" should be redacted. The size of the filter and the fact that a filter was used in the analytical method is novel technology and release of this information would give competitors significant help in developing an assay for a molecule in the same class.

Example 3
Text with proposed redactions: Patients were asked to rate their pain and emotional status using the Newton scale. The Newton scale is described in the attachment. The attachment to be redacted.

Justification: The Newton scale is copyrighted and the Company has paid a royalty to Newton to use their scale and technology. The Company contract with Newton allows details to be shared with regulatory authorities but not with 3rd parties.