EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Submission of comments on 'Draft proposal for an addendum, on transparency, to the “Functional specifications for the EU portal and EU database to be audited' (EMA/42176/2014)

Comments from:

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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).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The European CRO Federation appreciates the opportunity to submit these comments and observations on the European Medicines Agency's ''Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited' (EMA/42176/2014) issued for public consultation. EUCROF represents members from 16 EU countries: It speaks for 300 member Contract Research Organisations and their over 15,000 employees. EUCROF's aims and objectives are - amongst others - to promote clinical research of high quality in Europe/the European Union, and to represent its members in interactions with regulatory bodies, the pharmaceutical-biotechnology industry and the medical research community. EUCROF support's the EMA and Member States' efforts to balance transparency and availability of information on clinical trials with the aim of fostering research innovation in Europe. We support the EMA's acknowledgement of the particular commercial sensitivities of Phase 1 trials. Furthermore we support the EMA's proposal that information on clinical trials should be made available in stages: *"Thus, the extent of information made public could progressively increase during the development period to the marketing authorisation of a medicine from first in human Phase I trials to post-authorisation Phase IV and low-intervention trials."* **Overview General Comments Section** Our specific comments will be dealing with the EMA's questions. In the general comment section we would like to present our views on two specific points which relate to the proposal in general, rather than the EMA's proposals and questions: • **The definition of what constitutes a "Phase 1" trial** • **The publication of (lay) summary reports**	

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	How should a "Phase 1" trial be defined? We strongly advocate defining a "Phase 1" trial for the purpose of applying transparency rules as follows: **Phase 1 trials** are clinical trials using IMP, device & IMP/device combinations, performed in **healthy volunteers and/or patients without therapeutic (or prophylactic) intent** This is in accordance with Belgian and UK law and the current application of this term within Europe and globally. **Belgian law states in Article 2, 12:** "Phase 1 study: "*study performed on healthy volunteers or on certain types of patients without therapeutic objectives which covers one or more of the following aspects: estimation of initial safety and tolerability, pharmacokinetics, pharmacodynamics, early measurement of drug activity*". **UK law (Statutory Instrument 2004 No. 1031) states under "Interpretation":** *"Phase 1 trial means a clinical trial to study the pharmacology of an investigational medicinal product when administered to humans, where the sponsor and investigator have no knowledge of any evidence that the product has effects likely to be beneficial to the subjects of the trial;"* **21 CFR Part 312.21 states** *"Phase 1 (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies.* *(2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of*	

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	action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. **ICH E8 states:** *"Phase I starts with the initial administration of an investigational new drug to humans. […] Studies in this phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteer subjects or certain types of patients […]."* Rationale: A limitation of "Phase 1" trials to healthy volunteers would be inappropriate for an innovative research environment in the EU. In fact, such a limited definition has not been used in the EU or globally for many years and would be a significant step back, which is against the objectives of the EU CTR. Therapeutic intent is an intent to treat and/or to cure. Prophylactic intent is an intent to prevent disease. If a trial is designed with therapeutic/prophylactic intent (i.e. a Phase II and higher trial), then it is understandably in the interest of all parties that relevant information is shared with the public. Patients can reasonably expect that the product used within the terms of the trial protocol has effects likely to be beneficial to them. Patients will be recruited and consented on that basis. Such expectations should not be raised lightly e.g. for the purpose of recruiting patients into trials, especially when life-threatening diseases or rare chronic diseases are concerned. A first-time-in-human trial in patients (including oncology patients) would only in extremely rare circumstances be designed with therapeutic intent. There are too many uncertainties at that stage of development, even if the trial design was to include methods to gain early evidence of efficacy (such as biomarkers). For a study without therapeutic/prophylactic intent, patients must be recruited and consented on the basis that they cannot expect that the product used within the terms of the trial protocol will have effects likely to be beneficial to them. This is to ensure that no false hopes and unrealistic expectations are raised.	

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	Clearly, trials in patients who do not have the target disease, such as pharmacokinetic studies in patients with renal or hepatic impairment are also included into the current global and our proposed continued definition of "Phase 1" trials in the EU. During early phase drug development there is particular sensitivity about the commercial confidentiality of information on clinical trials. For studies without therapeutic or prophylactic intent, the need to inform the public about the study should be limited to the extent that applies for trials in healthy volunteers. With regards to the draft proposal on transparency, the definition of "Phase 1" impacts on whether or not sponsors will have the possibility to opt to have only very minimal public information at the time of decision on the trial. Potential benefits of public access to information at the time of decision on a trial are not applicable to trials without therapeutic/prophylactic intent, whether in adult healthy volunteers or patients. A limitation of "Phase 1" transparency rules to healthy volunteers would inevitably lead to a decrease in innovative early phase clinical trial designs being conducted in the EU. Innovative, non-therapeutic/prophylactic early phase (including first-time-in human) trials in healthy volunteers *and* patients are the future of early phase research in the EU. It is key to the future of clinical research in Europe that we can continue to perform these trials in patients. Moreover, an increase of such trials being conducted in Europe will lead to faster development of new medicines and thereby faster access to these new treatments for patients. **When should (lay) summary reports be published?** The draft proposal sets the publication time point for (lay) summary reports at 12 months after the end of a trial for all stages of drug development, including Phase 1. Whereas throughout the proposal a staged publication approach in relation to the development of the product (phases of clinical research, therapeutic/non-therapeutic trials) or marketing authorisation status is advocated, this approach is not applied for summary reports. The draft proposal acknowledges that the subject information sheet and protocol can "contain extensive detail of a commercially confidential nature". In relation to summary reports, where the same applies, there is uncertainty	

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	how the EMA envisages the concept of CCI to be applied. In relation to the risks of early publication of summary reports for non-therapeutic/prophylactic (Phase 1) trials, this is a particular issue as Phase 1 studies are usually short and completed within months rather than years. This would lead to very early publication of potentially commercially confidential information. We refer to our position paper dated 31 October 2014 which was also submitted as part of our response to the first consultation on the EU portal (http://www.eucrof.eu/images/EUCROF_Position_Paper_Public_Access_to_Early_Phase_EU_database_information_31_OCT_2014.pdf). Following a detailed risk/benefit assessment, *"with regards to the potential benefits of publicly accessible (lay) summary results of Phase 1 studies, we found that the benefits stated by [ClinicalTrials.gov, the WHO/International Clinical Trials Registry Platform (ICTRP) and the CTR] will not necessarily affect patients or ongoing clinical research at the time. Benefits will become relevant at various time points during drug or drug/device combination development. This may be earlier or later than one year from the end of a trial."* And: *"The potential risks of early publication and disclosure of Phase 1 studies' […] results may outweigh its benefits for patients, health professionals and the public. During early drug development much of this information is considered commercially confidential. Regulation outside Europe does not require publication of Phase 1 studies, except after FDA approval in the US. Sponsors would therefore likely manage perceived risks by performing Phase 1 studies outside Europe. This would have a detrimental effect for European early and late phase clinical research, which would ultimately translate into disadvantages for patients and the public."* **We therefore suggest the following in relation to the publication of summary reports:** (1) If summary reports are to be published 12 months after the end of a trial, then the information provided should be limited to non-CCI. In case of Phase 1 clinical trials, this would further limit the benefits of publication, whilst at the same time increasing the administrative burden of providing redacted/abbreviated	

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	reports. (2) An alternative would be to set an automatic trigger to publish Phase 1 summary reports when the first therapeutic study's summary report for that same IMP (indication, formulation, route of administration) is published.	

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)*
131 - 133		Comment: • The partner registries to the WHO ICTRP are missing in the sentence. • The sentence reads incorrectly. Proposed change: The Regulation requires that all clinical trials used in support of a clinical trial application are publicly registered in a registry which is a primary or partner registry of, or a data provider to, the WHO ICTRP (WHO International Clinical Trials Registry Platform).	
382-410 Question 1		Comment: In accordance with the Data Protection Rules, it is not permitted that names are made public without consent of the person concerned. It would be possible to overcome this by having the investigator sign in the respective investigator – sponsor contract that they are in agreement that their names and sites will be made public by the time of the decision on the authorisation of a clinical trial. Through this information, patients would be able to identify sites which are in proximity to them. This is justified. However, to publish the CV and also the financial interests of the investigator is beyond what should be made public. There is a system in place to decide upon the suitability of investigators and sites and this system should be trusted. CVs and financial interest should not be made	

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		publicly available. Proposed change (if any): CVs and economic interests should not be made public.	
411-416 Question 2		Comment: There should be a mechanism by which the public can confirm the competence and absence of potential conflicts of interest, independence and impartiality of Member States experts. It is e.g. common practice that the names of Ethics Committee members are made public. Proposed change (if any): The names of the MS experts should be made public.	
417-425 Question 3		Comment: It has to be clarified whether the sponsor contact person for an Ex-EEA sponsor (in case there is not legal representative) has to be made public. Proposed change (if any): The sponsor contact person for an Ex EEA sponsor (in case there is no legal representative) should be made public.	
426-436 Question 4		Comment: We agree that it is acceptable to make names of signatories and investigators public at the time when the CSR is made public, i.e. 30 days after MA. However, names of consultants, CRO personnel, etc. should be allowed to be redacted; these persons do not have	

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		any legal responsibility and therefore do not need to appear in the public domain. Proposed change (if any): N/A	
437-446 Question 5		Comment: EUCROF agrees to the proposed rules. Proposed change (if any): N/A	
584-609 Question 6		Comment: EUCROF believes that proposal 1.3 meets best the requirements and objectives of the Regulation. Commercially confidential information should be considered taking into account, in particular, the status of the marketing authorisation using the following concept: “Once a marketing authorisation has been issued, by at least one Member State, for a medicinal product **using that active substance** and **for the indication** and **formulation / route of administration under study**.” Rationale: EU Clinical Pharmacology Units are frequently involved in clinical trials investigating new formulations and/or routes of administrations of medicines and/or trials in new indications of	

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		active substances with marketing authorisations in at least one MS. These trials usually have no therapeutic/prophylactic intent (Phase 1). At an early stage of formulation/route of administration or new indication development, sponsors can – for commercial reasons – not disclose information to the public as this would disclose programme strategy and affect patent protection. In our view there is no plausible overriding public interest in disclosing information publicly for these studies prior to the timelines stipulated in option 1.3. (a) If a marketing authorisation has been issued for the active substance, a significant amount of information on the active substance is available in the public domain. (b) There is no risk of duplication of research (any different, new formulation, route of administration or indication will require new, specific trials). (c) If a trial is negative (e.g. unfavourable pharmacokinetics and/or tolerability of a new formulation or route of administration), then this is of importance to the manufacturer who may wish to test a different formulation or route of administration, but not to the public. (d) For studies without therapeutic/prophylactic intent, there is no overriding need of the public to know that these studies	

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		are ongoing. Once studies reach the stage of therapeutic intent, there may be potential benefit, but not before. Public disclosure would first and foremost serve the manufacturers' competitors. If early disclosure of information would be required in the EU, it is certain that many of these trials would be conducted outside the EU. Proposed change (if any): We wonder why dosage changes are not mentioned in this context. Should this scenario be included in the definition: "Once a marketing authorisation has been issued, by at least one Member State, for a medicinal product **using that active substance** and **for the indication** and **formulation / dose / route of administration under study"**	
610-642 Question 7		Comment: EUCROF agrees that the IMPD-Q section should be considered as CCI and therefore should never be made public. Proposed change (if any): N/A	
643-654 Question 8		Comment: This question should probably read "[…] *with* a marketing authorisation" EUCROF agrees with the proposal to offer the possibility to defer the	

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		publication of study specific and product specific information until the time that the summary of results is loaded into the database and made public, as there might be intellectual property in trial documents which relates to new approaches in relation to endpoints and/or procedures. There would be no credible public benefit of publishing these documents until summary results also become available. Proposed change (if any): N/A	
655-708 Question 9		Comment: EUCROF favours **Proposal 3**, because it is most in line with our view that information should be made public at the point of plausible overriding public interest in that information. We do support the distinction between trials without and with therapeutic/prophylactic intent, and would for that reason have liked to give our support to Proposal 4 (which uses that same distinction). However, we cannot support the automatic release of the study protocol and subject information sheet for therapeutic studies (including early Phase II studies) into the public domain at the time when first summary results are posted. Study protocols and subject information sheets are characterised by the detailed description of methods, techniques and advanced designs. This information is likely to be considered commercially confidential well beyond the time of summary report publication for Phase II trials.	

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As a result we support **Proposal 3** which in our understanding can be applied in conjunction with our proposed definition of Phase I trials as follows:

Document	Publication via EU Portal
All documents	Voluntary publication by the sponsor should be permitted
Study specific documents - **Protocol synopsis**- *"as set out in the clinical trial application form – being in effect a structured synopsis of the clinical trial protocol"* (draft proposal lines 322 - 323)	Phase I trials (without therapeutic/prophylactic intent) - Time of first summary results being posted
	Phase II and III trials (with therapeutic/prophylactic intent) – At the time of decision on the trial
Study specific documents - **Subject information sheet**	Phase I and II trials - Time of MA or 9 years after first summary results posted
	Phase III trials - Time of first summary results being posted
	Note: For Phase II and III trials (with therapeutic / prophylactic intent) – Patients and other interested parties can approach sponsor and/or investigator to

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	obtain a subject information sheet at the time of decision on a trial. Contact details and study synopsis are available via EU portal at that time.
Study specific documents - **Protocol**	Phase I and II trials - Time of MA or 9 years after first summary results posted
	Phase III - Time of first summary results being posted
Product specific documents **– IMPD S** and **E** sections and **investigator brochure**	Time of MA or 9 years after first summary results posted

We believe that, if applied as tabled above, the public will be able to access relevant information for all types of trials at suitable, predetermined time points via the EU portal. Any supplementary information can, if required, be requested by patients, carers, health professionals etc. using the normal pathways of obtaining confidential information. In the case of obtaining a subject information sheet, this can be done by a simple call to the investigator, which does not require any effort over and above what patients would normally do. At the same time, there will be a barrier for competitors to access confidential information.

We therefore believe that this proposal achieves a suitable balance

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		between publication of relevant information and legitimate commercial interests of sponsors and researchers involved in a trial that is being published.	
709-725 Question 10		Comment: EUCROF agrees with the EMA proposal. Proposed change (if any):	
726-746 Question 11		Comment: We strongly support that, for Phase 1 trials (i.e. trials without therapeutic or prophylactic intent) the sponsor will have the possibility "**to opt to have only very minimal public information at the time of decision on the trial" and for the "remainder to be made public at the point when the summary of trial results is published"**. Rationale: We refer to our position paper (http://www.eucrof.eu/images/EUCROF_Position_Paper_Public_Access_to_Early_Phase_EU_database_information_31_OCT_2014.pdf). This paper states that *"Following a detailed review of the potential benefits of publicly accessible registration of trials stated by ClinicalTrials.gov, the WHO/International Clinical Trials Registry Platform (ICTRP) and the CTR we found that most are not applicable to Phase 1 non-therapeutic, non-paediatric, non-publicly funded*	

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		clinical trials. An argument can however be made for release of relevant Phase 1 registration information in pre-determined stages and on a need-to-know basis." It goes on to say that "*the potential risks of early publication and disclosure of Phase 1 studies' registration information […] may outweigh its benefits for patients, health professionals and the public. During early drug development much of this information is considered commercially confidential. Regulation outside Europe does not require publication of Phase 1 studies, except after FDA approval in the US. Sponsors would therefore likely manage perceived risks by performing Phase 1 studies outside Europe. This would have a detrimental effect for European early and late phase clinical research, which would ultimately translate into disadvantages for patients and the public."* We support publicly accessible registration of all trials, with a minimal amount for Phase 1 trials being published initially as proposed by the EMA. This will assure the public that trials are bona-fide and authorised, and that further information will be made available when it becomes relevant and at a predetermined time. At the same time, the option to "have only very minimal public information at the time of decision on the trial" and for the "remainder to be made public at the point when the summary of trial results is published" will protect legitimate commercial interests of the sponsors and the interests of researchers involved in early phase clinical trials.	

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747-752 Question 12		Comment: EUCROF agrees with the EMA proposal. Proposed change (if any): N/A	
753-760 Question 13		Comment: Proposed change (if any):	
763-796 Question 14		Comment: This comment also applies for Article 53.2 of the CTR (inspection reports of third country authorities). EUCROF does not agree with the unrestricted publication of inspection reports. The publication of inspection reports should have a defined purpose. Only findings that are of relevance to the public should be made publicly available. With regards to the inspection of CROs, there is no unified European system in place to inspect all CROs fairly, equally and in regular intervals using the same methodology and standards. For reasons beyond CROs' influence, one CRO might be inspected and findings would be publicly available, whilst a competitor may not be inspected and therefore no report would be available. CROs are highly competitive service providers. Sponsors will use all publicly available information in their CRO selection process. A CRO for	

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		which nothing is published - because it was not inspected - might have an unfair commercial advantage or disadvantage (depending on the circumstances) in attracting business over one which was inspected. Publication of inspection reports within the current inspection systems will inevitably lead to unfair commercial advantages afforded to individual CROs and unintended commercial damages to others. This could have legal implications. Until a standardised and harmonised inspection system and process is available in the EU which includes all CROs, the approach of publishing inspection reports for CROs is considered unfair by EUCROF. In case of inspections of early phase clinical research units, the same applies. National inspection schemes differ widely. Some EU countries conduct regular mandatory GCP/GMP inspections to very strict standards, others do not. During early phase inspections usually a number of studies will be inspected by the CA. Some countries have national voluntary, non-study-specific inspection schemes (such as the MHRA's Phase 1 accreditation scheme) which may be run in conjunction with mandatory inspection schemes. The requirements of the national voluntary schemes exceed those of mandatory schemes and may focus on certain specific areas (e.g. the units' capability to conduct trials of potentially higher risk). Publication of inspection reports could potentially disadvantage early phase units who voluntarily participate in demanding	

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		inspection schemes and/or who are located in countries with more stringent inspection schemes. In all cases, full publication of the inspection reports (including minor findings and recommendations) would disclose a large amount of commercially confidential information that is of no relevance to the public. Indeed, it may be difficult for the public to put the information into context. For ongoing trials, the availability of inspection findings to the public (trial participants), who might not have the expertise to judge the findings appropriately, might lead to an overreaction. As a consequence, participants might leave the trial prematurely. This could be to their disadvantage. The information contained in detailed inspection reports will be of high commercial interest to CROs' and early phase clinical research units' competitors. Proposed change (if any): (1) National inspection schemes (both voluntary and mandatory) should not be reported via the EU portal. (2) For inspections within the EU framework we propose the following: • The fact that an inspection took place should be made public • Only findings that are of relevance to the public (e.g. established critical safety findings) should be	

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		published via the EU portal • Findings should never be published before an inspection has been fully closed out and all findings, responses and outcomes have been agreed • A European arbitration process should be in place in case of disputed findings. Arbitration should always take place prior to publication	
797-802 Question 15		Comment: EUCROF agrees with the EMA proposal Proposed change (if any):	
803-843 Question 16		Comment: EUCROF agrees with the EMA proposal, however with the limitations made under Question 14 for inspection reports. Proposed change (if any):	
844-858 Question 17		Comment: We request that a distinction be made between Phase I/II trials and later phase studies with regard to risk management and the publication of *"unexpected events which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions […]"* and *"urgent safety measures […] where an unexpected event is likely to seriously affect the benefit-*	

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		risk balance […]" (Art 53.1 and 54 CTR). Early phase trials are well contained, with small numbers of participants and investigators; in the case of Phase I trials, there is usually just one investigator. Due to the exploratory nature of these trials, continuous and contemporaneous risk evaluation is an essential process, in particular during First-time-in-Human and consecutive Phase I trials. It is common during exploratory studies that unexpected events occur which may (seriously) affect the benefit-risk balance of a trial. If an unexpected event occurs, changes to the benefit-risk balance can sometimes be avoided by using innovative trial designs, such as adaptive trial design. Adaptive trial design manages risk through modification of trial conduct by way of non-substantial amendment (modification). If the benefit-risk balance of a trial cannot be maintained by non-substantial amendment (modification) then a study can - under current regulation - not proceed further until a substantial amendment (modification) to the trial protocol and subject information sheet/Informed Consent has been approved by the CA and Ethics Committee. In situations where urgent safety measures are required to protect the safety trial participants who are enrolled in an ongoing trial,	

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		these measures can be taken prior to approval of a substantial amendment (modification). Nevertheless, other than those urgent safety measures, the trial cannot proceed further until a substantial amendment (modification) has been approved by the CA and Ethics Committee. This tried and tested process ensures that all parties (CA, Ethics Committee, trial participants, sponsor and investigator) involved in early phase studies are fully aware of any changes in benefit-risk balance and agree with the risk management prior to proceeding further. We do not believe that publication of unexpected events and/or urgent safety measures at the time of reporting would add benefit to the established process for Phase I and II studies. On the contrary, the requirements may bring about under-reporting and failure to undertake necessary safety measures. It may hinder the investigation of the events. Publication may have an unwarranted, negative impact on participant recruitment and study conduct. Proposed change (if any): In case of Phase I and II studies, information on unexpected events which may (seriously) affect the benefit-risk balance of a trial should not be made public at the time they are reported. The authorised application of (non-) substantial modifications of the trial and the use of urgent safety measures, where necessary, are	

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		established and successful mechanism to deal with these events.	
859-872 Question 18		Comment: EUCROF agrees with the EMA proposal Proposed change (if any):	
894-898 Question 19		Comment: We agree with relevant text being added to Table 2, Section 4.3 as an addendum, depending on the outcome of the final consultation. We also agree with the principle that the application form will contain a set of questions which will then trigger select pathways of publication. Proposed change (if any): TBC	

Please add more rows if needed.