17.02.2015

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”

<EMA/641479/2014>
Date of Document: 20 January 2015

Comments from:

Name of organisation or individual
Network of Coordinating Centres for Clinical Trials, Germany (KKS-Netzwerk)

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).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*

Two key objectives of the Regulation (see 4.4 of the consultation document) are to provide extensive public information on clinical trials and to promote the EU as a location for clinical research.

We agree that a good balance needs to be achieved with regards to the aim to make as much information available to the public as soon as possible and the exceptions foreseen in the Regulation in article 81 (4). Unfortunately, we do not find that the current proposal is meeting the requirements of Regulation 536/2014. The objective of the Regulation, to increase transparency has fallen victim to the intention to protect commercially confident information. The proposal is in a lot of its parts focussed on recital 68 of the regulation, negating more or less recital 67.

It was an important objective of the Regulation that more information should be published in the database than the information already available in clinical trial registries and that in general all information send with the application (all information which is part of the application dossier) should be made available as early as at the time of the decision on the clinical trial. In several proposals of the consultation paper the time point for publication of relevant data/documents such as protocol, patient information sheet, IB, IMPD is suggested to be postponed to more than 10 years after this decision. I our view this cannot be regarded as a reasonable approach and is not substantiated by declaring that this information would be commercially confidential.

To achieve the aim to foster progress in clinical research for the benefit of patients it is important that the information is published at a time where this is still relevant for the scientific community for scientific purposes. The information is needed as early as possible in order to enhance the further development of existing medicines and evidence-based improvement of treatments (see line 112 of the consultation document) and protecting public health and fostering the innovation capacity of Europe (see line 121/122 of the consultation document).

In the consultation paper it is stated that public access is provided amongst others to

> "Acting as a knowledge management resource to foster innovation and stimulate and accelerate further research by building on accumulated knowledge and technical ability. This aims to avoid unnecessary duplication of clinical trials, and repetition of trials that have been terminated due to major safety or efficacy failures, or have demonstrated such failures even is the trial was completed. (line151 – 155)

We do not see how this would work with proposals that postpone information on the clinical trials to more than 10 years after the decision on the clinical trial.

We therefore propose to only make a distinction between non-therapeutic and therapeutic trials and would allow for non-therapeutic trials to publish the full information at the time the summary of the results is posted in the database. For all other trials (therapeutic and prophylactic trials) the information should in general be made public at the time of the decision on the clinical trial. Exemptions from this rule for therapeutic and prophylactic trials would be subject to a

deferral that would have to be substantiated by the sponsor and be assessed by the Member States during the initial assessment of part I of the clinical trial. In our view with a deferral it should only be possible to postpone the time point to no later than the time the summary of results is posted in the database.

Furthermore, in our view it is also especially and equally important that all the information regarding clinical trials carried out with non-authorised medicines, in the early phases of development prior to marketing authorisation, which are never later used in a marketing authorisation as the development is discontinued, is published. For the scientific community it is important to know that ideas / hypothesis which have been followed have not worked out (either for the product, the indication ...) so that a duplication of efforts in the wrong direction can be avoided.

It should be avoided that for the sake of an easy and automated handling of the database key objectives of the Regulation are disregarded.
In case of major disagreements with regard to whether the objectives of the Regulation have been met, these should be resolved by the Member States and the European Commission and maybe the Parliament.

In general the consultation paper would have gained from more clarity and less redundancies.

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47-53		Comment: We appreciate that it has been tried to strive for the right balance between all the different needs with the proposals set out in the document. Unfortunately, we do not see that this has been achieved. A lot of the proposals which have been put forward do not meet the requirements and objectives of the Regulation. Proposed change (if any): See comments later in the document.	
54-65		Comment: Information on clinical sites is missing here (see line 55-58) Proposed change (if any): Line 54 should read “The minimum information that will be made public for all clinical trials registered in the system will include: … Other information will be made public subject to the applicability of exemptions, i.e. because the information is commercially confident or personal data have to be protected.	
72-78		Comment: We do not agree that the documents mentioned are containing significant commercially confidential information. For a lot of clinical trials at least as early as Phase II sponsors publish	

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		data as soon as possible for the sake of increasing "shareholder value". For clinical trials where NIH funds have been obtained, all data are public from the time of decision.	
79 -84		Comment: Phase II and III trials are not mentioned. We would apply the same rules for those trials as for Phase IV and low-interventional trials, especially as individual deferrals are possible.	
99		Comment: The addendum in section 5 is not final (as is stated in section 5) and subject to this consultation; this should be clearly stated here.	
151-155		Comment: This key objective cannot be achieved with most of the proposals set forth in this document.	
157		Comment: Does it have to read "downloadable from the portal" or would it be "downloadable form the database"	
162		Comment: The legitimate interests of sponsors need to be recognised, but the approach to do this should be reasonable and not undermining the objectives of the Regulation.	

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179-181		Comment: We suggest storing also data in the database which are not defined in the Regulation as they are outside the scope of the Regulation, if they form an integrative part of the set of documents for a given clinical trial. This is i.e. the case for additional approvals requested for the clinical trial in the different MS. Those documents should be part of the database as those would be needed to achieve full transparency about the clinical trial. There is nothing in the Regulation that would conflict with this. Proposed change (if any): Other data/documents required by the Member States (e. g. further approvals) will be included into the database even if not specified in the Regulation and will be part of the specifications to be audited.	
252-254		Comment: Data from paediatric clinical trials conducted in third countries should also be stored in the database. The requirements of the Paediatric Regulation for third country clinical trials are an integrative part of a PIP. Therefore, those trials should be an integrative part of the database as well; As a minimum they should be linked to the database. The data or link should be part of the specifications and of the audit to be conducted.	

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		Proposed change (if any): Data from third country paediatric clinical trials to be included into the database and the specifications to be audited.	
293-303		Comment: We see the need for rules to be established that operate in an automatic way. It will, anyhow, not be possible to work without human judgement and intervention, as deferrals have to be handled, too.	
349-352		Comment: The clinical trial protocol and subject information sheet, the IB and the IMPD safety and efficacy sections should be made public at the time of decision on the clinical trial, not after the end of the clinical trial. We therefore do not understand why EMA does put this under the heading “after the end of the trial” and phrase as if this would not be part of the consultation.	
353		Comment: Even if we agree with the proposal that the IMPD quality section should not be made public at any time, this is still subject to the consultation Proposed change (if any):	

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321, 329, 343		Comment: This is subject to this consultation. Proposed change (if any): Headlines should be deleted	
395-396		We agree that a list of the principal investigators and sites should be publicly available, as this constitutes important information for the clinical trial; everyone should be able to know where and by whom a clinical trial is conducted.	
397-399		Comment: We do not agree that it would be necessary to publish the CVs of the investigators as this also does contain personal information. It is not relevant for the clinical trial in questions, that everybody knows e. g. where the investigator has worked 10 years ago. The qualifications of the (principal) investigators to conduct the clinical trial have been assessed by the Member States and / or Ethics committees and the suitability of the (principal) investigators has been confirmed. We do not see that the regulation requires this information to be made publicly available. For what reason would it be necessary for the public to see all contents of the CV? Furthermore, especially for academic clinical trials this would mean a high bureaucratic burden. Proposed change (if any): The CVs of the investigator contain information that is	

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		exceeding the information needed for the conduct of the clinical trial. The CVs will not be made public	
401-403		Comment: Economic interests and institutional affiliations will be assessed by the MS/Ethics committees. The Approval is based on the judgement. We do not find it necessary to have the detailed information in the public domain, especially as this can change over time; in our view this is not required by the regulation. We therefore propose that this is also not published or only published for the principal investigator at a site. Proposed change (if any): It is not necessary to publish the economic interests and institutional affiliations.	
400, 403		Comment: We appreciate the proposal to develop templates for CVs and information on economic interests and institutional affiliations (even if this information would not be published). This would ensure more harmonisation and comparability between the Member States and increase standardisation. The same standards / rules should be applied for the judgement of the suitability all over the Member States.	

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404-408		We agree to the proposal to publish the name of the signatory testifying the suitability of the facility and human resources.	
409-410		**Question 1:** We agree that a list of the principal investigators and sites should be publicly available, as this constitutes important information for the clinical trial; everyone should be able to know where and by whom a clinical trial is conducted. We do not agree that it would be necessary to publish the CVs of the investigators as this also does contain personal information. It is not relevant for the clinical trial in questions, that everybody knows e. g. where the investigator has worked 10 years ago. The qualifications of the investigators to conduct the clinical trial have been assessed by Ethics committees / Member States and the suitability of the investigators has been confirmed. We do not see that the regulation does require this information to be made publicly available. For what reason would it be necessary for the public to see all contents of the CV? Furthermore especially for academic clinical trials this would mean a high bureaucratic burden. With regard to the publication of economic interests, this is also part of the assessment by Ethics Committees / Member States. We do not find it necessary to have this in the public domain, especially as this can change over time; in our view	

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		this is not required by the regulation. We therefore propose that this is also not published or only published for the principal investigator at a site. We agree to the proposal to publish the name of the signatory testifying the suitability of the facility and human resources. We appreciate the proposal to develop templates for CVs and information on economic interests and institutional affiliations (even if this information would not be published). This would ensure more harmonisation and comparability between the Member States. The same standards / rules should be applied for the judgement of the suitability all over the Member States.	
415-416		**Question 2:** We agree with the proposal that names of Member State experts will not be published. To publish those names is not required by the Regulation.	
424-425		**Question 3:** We agree with the proposal, that personal information identifying sponsor staff will not be included in the database and that only information for persons with certain legal roles will be made public. The proposal is in line with the requirements of the Regulation.	
435-436		**Question 4:** We agree with the proposal that personal information	

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		identifying MAH/applicant personnel identified in the clinical study report will be made public. This meets the requirement of the Regulation.	
445-446		**Question 5:** We agree with the proposal made in this section, that – except a sponsor contact point for information on the clinical trial and a sponsor contact point for information on the scientific aspects of the trial no other direct contact details will be made public. This proposal meets the requirements of the regulation. In general we feel that it would be sufficient to provide a contact address and a phone number. The Regulation does not require the publication of names of natural persons (i. e. as this could change during the course of the clinical trial). The proposal to publish only functional roles would therefore in our view meet the requirements and objectives of the Regulation. We also agree that a contact point for trial subjects/ health care providers should be published.	
457-459		Comment: The proposed definition is very broad so that nearly all information regarding clinical trials could fall under this definition and could be considered CCI. We do not think that this would be meeting the requirements of the Regulation. We propose to narrow this to “data or information where disclosure would undermine the legitimate economic interest	

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		of the sponsor". Proposed change (if any): CCI can be considered as meaning any information contained in the data or documents submitted to the database where disclosure would undermine the legitimate economic interest of the sponsor.	
460-466		We agree that the consideration of what might be commercially confidential should be based on the nature of the trial and the status of the medicinal product studied rather than the nature of the sponsor conducting the clinical trial. If the sponsor claims that the information should not be made public, the claim would have to be substantiated. The Member States should assess the claim and decide about whether it is reasonable during the initial assessment of part I of the clinical trial.	
467-479		Comment: These should be regarded as possibly legitimating an economic interest, but not generally. Approval should be needed from the Member States in the assessment for part I.	
493-500		Comment: The proposal, that it would mean too much of an administrative burden to structure the documents in confidential and non-confidential parts would not mean that	

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		the documents should not be made public. Proposed change (if any): Delete the whole passage.	
511-512		Comment: Does not have any context to the text above or below. Proposed change (if any): Delete	
503-515		Comment: We do not agree that the protocol in general contains extensive confidential information, at least for clinical trials conducted from Phase II onwards. It should therefore not be treated as an entity for the purpose of transparency rules.	
516-525		Comment: We do not agree that the subject information sheet in general contains extensive confidential information, at least for clinical trials conducted from Phase II onwards.	
526-534		Comment: We do not agree that the assessment reports contain extensive confidential information. Those should be published at an early time point, i.e. at the time of decision about the clinical trial.	

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536-552		Comment: One of the key objectives of the Regulation is to increase the knowledge about the clinical trials conducted and to foster innovation. Therefore it would be important that the Investigator Brochure is – with some exceptions – published at an early time point, i.e. at the time of the decision about the clinical trial.	
553-574		Comment: One of the key objectives of the Regulation is to increase the knowledge about the clinical trials conducted and to foster innovation. Therefore it would be important that the safety and efficacy section of the IMPD is – with some exceptions – published at an early time point, i.e. at the time of the decision about the clinical trial. We agree that the Quality section of the IMPD should not be public at all.	
575-583		Comment: We do not agree that the assessment reports contain extensive confidential information. Those should be published at an early time point, i.e. at the time of decision about the clinical trial.	
502-583		Comment: It would be sufficient to list the categories and what falls under the categories. It is superfluous to explain what the documents contain and	

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		why they **might** contain commercially confidential information. It seems as if EMA wants to trigger special answers to the subsequent questions. We do not agree that the protocol, patient information sheet related question, responses and assessment reports, investigators brochure, IMPD and related question, responses and assessment reports automatically contain substantial commercially confident information. (see comments above) Proposed change (if any): Delete all information on the content of the respective documents.	
606-609		**Question 6:** We are of the opinion that **proposal 1.1** (once a marketing authorisation has been issued, by at least one Member State, for the active substance contained in that medicinal product) should be chosen to apply the status “marketing authorisation” as it best meets the requirements and objectives of the Regulation. Otherwise - e. g. in paediatric research, in a lot of oncology research - important information could not be used for the further development of treatments, even if the MAH of the active substance is not interested in developing e.g. a paediatric indication.	

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615-617		In general, it seems to be sensible to apply a graduaded approach.	
630-635		Comment: It is not clear, why this paragraph is included in the general considerations. What is the proposal? Clinical trials like this are especially important and the information should be available as soon as possible. 630- 634: what is the proposal??? / For what reason is this mentioned here? Information on clinical trials carried out on non-authorised medicines in the early phases of development prior to marketing authorisation , which are never later used in a marketing authorisation e. g. as the developments of the medicines is discontinued is very important for the future clinical research. It would be very important to know, which scientific questions /Hypothesis did not work out, when tested, to avoid duplication of efforts and unnecessary involvement of subjects in clinical trials. Proposed change (if any): Delete	
641-642		**Question 7:** We agree that the IMPD-Q section can be regarded as confidential throughout the lifetime of the product.	

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648-651		Comment: It should be stated, that the decision on a deferral is by the Member States. Proposed change (if any): Add a sentence on who decides about a deferral.	
654		It should read “with a marketing authorisation”.	
652-654		**Question 8:** We agree with the proposal that the information will be made public at the time of the decision of the clinical trial for clinical trials on products with a marketing authorisation. Any deferrals should be substantiated and agreed by the Member States. In general the respective documents would not contain economically important information but information on hypothesis of alternative treatment options, comparison of treatment options etc. which would be of interest for other researchers too. Proposed change (if any): It should be added that Member States decide on a deferral.	
659		Comment: It is stated that only one of the proposals will be selected for inclusion in the final rules. What, if a proposal five would be the best choice. Is this not regarded as a possibility?	

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660-662		In general we feel that this proposal best meets the purpose of the Regulation. We would only make an exception for non-therapeutic trials (Phase I): for Phase I trials the information should only be published at the time the summary of results has to be submitted to the database. This should be added. For the IMPD-Q section we agree that this information does not have to be made public.	
663-665		We do not agree with this proposal and do not think this meets the objectives of the Regulation. It is far too late from a scientific point of view to make the protocol and all other information available at the time of granting, refusal or withdrawal of the MAA or nine years after the first summary of results is published (this would be from 10 years and longer after the decision about the trial). In most cases the information would be of no scientific value for the scientific community any longer. There is no justification for this proposal in the Regulation and this would not lead to more transparency compared to the current situation.	
666-681		We do not agree with this proposal and again we do not think this meets the objectives of the Regulation. We would not put Phase I and II together as this is different points in the development and different sensibility of data. With regards to the time of publication for Phase I and II see comment for proposal two. For Phase III trials we find it too late if the information is published at the time of posting the summary of results which could be several years after the decision on the	

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		clinical trial. We also see no difference between study and product specific information, except for the quality section of the IMPD.	
682-702		To take a differential approach, which differentiates between non-therapeutic and therapeutic clinical trials is appreciated, but again the time points are not serving the purpose and objectives of the Regulation. For non-therapeutic trials the information should be publicly available at the time the summary of results is posted. For all other clinical trials the information should be posted at the time of decision on the clinical trial.	
704-708		**Question 9:** In general, the publication of the information in the application dossier should be at a point of time where the publication is still relevant for the scientific community, as is foreseen by the regulation (at the time of decision on the clinical trial). Most of the proposals make the exemptions to a general rule and can therefore not be supported. Therefore, in our view **proposal one** best meets the requirements and objectives of the Regulation. But we would suggest including a differential approach with regard to non-therapeutic and therapeutic and prophylactic trials. For non-therapeutic trials, the time point for publication of other than the minimal information (see 4.2) the data (study specific and product specific) in the database is postponed to the time the summary of results is included in the database. So we basically suggest a proposal five.	

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		With regard to Proposal Two, Three and Four, we do not find that the time points suggested for publication of data/ documents meet the requirements and objectives of the Regulation. With regard to Proposal Three we additionally do not find it useful to differentiate between Phase I/II and Phase III.	
722-725		**Question 10:** We totally disagree with both proposed time points time points (paragraph 6.5.1 and 6.5.2) as they do not meet the requirements and objectives of the Regulation (see Recital 67 and 68 below). In the Regulation it is proposed that by default all information should be made public at the time of the decision on the trial. With time points like the ones suggested, the information published is no longer of any value for the scientific community. We want to draw the attention again to the Regulation which states that in general information will be made public at the time of decision on the trial. When looking at recital 67 and 68 another approach would only be an exemption. *(67)In order to ensure a sufficient level of transparency in the clinical trials, the EU database should contain all relevant information as regards the clinical trial submitted through the EU portal. The EU database should be publicly accessible and data should be presented in an easily searchable format, with*	

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		related data and documents linked together by the EU trial number and with hyperlinks, for example linking together the summary, the layperson's summary, the protocol and the clinical study report of one clinical trial, as well as linking to data from other clinical trials which used the same investigational medicinal product. … The information in the EU database should be public, unless specific reasons require that a piece of information should not be published, in order to protect the right of the individual to private life and the right to the protection of personal data, recognised by Articles 7 and 8 of the Charter. Publicly available information contained in the EU database should contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors. *(68)For the purposes of this Regulation, in general the data included in a clinical study report should not be considered commercially confidential once a marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, the application for marketing authorisation has been withdrawn. In addition, the main characteristics of a clinical trial, the conclusion on Part I of the assessment report for the authorisation of a clinical trial, the decision on the authorisation of a clinical trial, the substantial modification of a clinical trial, and the clinical trial results including reasons for temporary halt and early termination, in general, should not be considered confidential.*	

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		Even if in general the data / documents should be published at the time of the decision on the clinical, there is still the possibility for a sponsor to ask for a deferral. But even if a deferral is accepted, it would not serve transparency and medical progress if by general rule publication would be postponed to a time point, where the data are no longer needed. Where is the justification to postpone the time point for more than eleven years, to a time where the information in most cases is no longer relevant for the scientific community?	
745-746		**Question 11:** We agree with the proposal, as these are non-therapeutic trials, where pharmacokinetics and pharmacodynamics in healthy volunteers are to be investigated. Phase I trials are very early development. There is not yet proof that the products works in patients, so it is justifiable to postpone the time point for the publication of the full information and reduce the amount of minimal information which is made public at the time of decision on the clinical trial. There is no need to publish a lot of data for those trials at the time of the decision on the clinical trial as it is still not known whether the product is of any therapeutic value. We also agree that this is commercially confidential information.	

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751-752		**Question 12:** We agree that information on payment arrangements between sponsor and investigators should not be published, especially as most people will not be able to judge the reasonability of the payments.	
761-762		**Question 13:** We agree that the proposal meets the requirements and objectives of the Regulation, the draft assessment reports do not have to be made public.	
795-796		**Question 14:** The proposals meet the requirements and objectives of the Regulation. There is no need to have more than the redacted final inspection report publicly available.	
801-802		**Question 15:** We agree with the proposal.	
804-841		Comment: It is not clear to us, which data will be made public and what needs to be in the notice to substantiate that a serious breach has occurred. A standardised approach and hard criteria are needed, so that every MS is judging serious breaches on the same agreed principles.	

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842-843		**Question 16:** In general, we agree with the proposals. We agree that information on serious breaches should not be made public until those have been investigated in more detail and the breach is confirmed. Still more detailed information / definition is needed on what a serious breach means, e. g. to reach a harmonised approach of the different MS when substantiating whether a serious breach has occurred. It is very important that all MS have the same approach and evaluate a notice of a potential serious breach in the same way. The criteria for a serious breach need to be standardised. Confirmed fraud (e. g. manipulation of data base) should be published with the according details. We would find it helpful if it would be made more clear which data will be published and what information will be included in a redacted version. What would have to be included in a description / notice of a serious breach?	
857-858		**Question 17:** We agree with the proposal. Unexpected events and urgent safety measures should be published at the time of reporting; this meets the requirements and objectives of the Regulation.	
871-872		**Question 18:** We agree that the proposal meets the requirements and objectives of the regulation.	

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890-892		Comment: Proposed change (if any): Should read “Any type of document/data that fall under the grounds for exception described in Article 81 (4) of the Regulation and detailed in the above mentioned section will not be made…	
895		Comment: Items 5+6: It is irrelevant for the application of the transparency rules whether the clinical trial is carried out for commercial purposes. The only trigger for a possible exception is that commercially confident information needs to be protected. Commercial purpose and commercially confident information cannot be equated. Item 6: The question is strange as it seems the sponsor (if the sponsor has to answer the questions) can decide at which time point the information should be published. Who will be answering the questions / items at the end of the addendum? If the sponsor is answering those, the Member States have to assess whether the answers are correct.	

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)*
896-898		**Question 19:** The proposed addendum will have to be adjusted according to the outcome of the consultation. Therefore, at this time it cannot be said whether it meets the requirements and objectives of the Regulation. The current wording of the proposed addendum (line 876-895, including table 2, section 4.3) to the functional specifications does not meet the requirements and objectives of the Regulation as it does currently not reflect (and cannot at this stage reflect) the result of the consultation. In our view question 3 and question 4 of the addendum should be deleted. Question 5 and 6 would have to be rephrased as for the application of exemptions it is not relevant whether the trial is conducted for commercial purposes, it is only relevant whether – on the grounds of the Regulation and the detailed exemptions- the information meets the criterion of “CCI”. Question 6 as currently worded is not meeting the requirements of the Regulation.	

Please add more rows if needed.