<Date of submission: 18 February 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)"

Comments from:

Name of organisation or individual
Institute for Quality and Efficiency in Health Care (IQWiG) Im Mediapark 8 50670 Cologne Germany

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)*
	IQWiG appreciates the opportunity to comment on the Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited".	
	IQWiG would like to summarise its main comments as follows: • New models of dissemination of clinical trial information are currently being discussed. The EU database (and other databases providing comprehensive study information) will have a major role in this new model of medical knowledge generation and transfer. Therefore, the specifications of the database need to meet the requirements of future knowledge generation. This increase in transparency is required for a better contribution of clinical trials and their results to the protection of public health as well as to innovation as laid down in the objectives of the EU Clinical Trial Regulation. • The suggested definition of commercially confidential information does not consider the general ethical requirements for research in humans and the requirements laid down in the EU Clinical Trial Regulation. To meet the basic ethical requirements	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	of research in humans and to allow for clinical trials to improve patient care (which is an overriding public interest) the methods and results of a clinical trial generally cannot be considered commercially confidential.	

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)*
Lines 107 - 112		It is correct that clinical trials are conducted to support applications for marketing authorisation and to expand medical knowledge. However, expansion of medical knowledge cannot be ensured through publication in medical journals as suggested in the present draft proposal. Numerous studies have shown that journal publications often are insufficient in reporting full and unbiased information on clinical trial methods and results. Therefore, new models of dissemination of clinical trial information are being discussed. The EU database (and other databases providing comprehensive study information) will have a major role in this new model of medical knowledge transfer and generation. Therefore, the specifications of the database need to meet the requirements of future knowledge generation. This increase in transparency is required for a better contribution of clinical trials and their results to the protection of public health as well as to innovation as laid down in the objectives of the EU Clinical Trial Regulation. Proposed change (if any): Delete the reference to medical journals and include a section on the role of the EU database in knowledge generation by clinical trials.	
Lines 259 - 272		Given the fact that the authorisation of the vast majority of	

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)*
		drugs in current use is based on clinical trials conducted before the new EU Clinical Trial Regulation (No 536/2014) comes into effect, there is a need to expand the publication of study information also to these older trials. A first step (meeting the objectives of the new EU Clinical Trial Regulation) could be to expand the information on the trial registered according to Directive 2001/20/EC, e.g. by publishing the clinical trial reports available at the regulatory authorities. Proposed change (if any): Describe the need to provide extended information on trials registered according to Directive 2001/20/EC and further steps to achieve this aim.	
Lines 454 - 459		<u>Definition of commercially confidential information</u> From IQWiG's point of view, the suggested definition of commercially confidential information does not consider the general ethical requirements for research in humans and the requirements laid down in the EU Clinical Trial Regulation. To meet the basic ethical requirements of research in humans (e.g. according to the Declaration of Helsinki), methods and results of trials have to be publicly available so that knowledge generation from this research is possible. This requirement defines a public interest that generally overrides economic interests.	

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)*
		In addition, publication of the study results is in the public interest because clinical trials aim to improve patient care. In this context, publication of the full information on study methods is also required to enable the assessment of the validity of study results and thus to reliably inform decision making in health care. This position is supported by the EU Clinical Trial Regulation according to which data from a clinical study report should in general not be considered commercially confidential once a marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed or the application for marketing authorisation has been withdrawn (Recital 68). In conclusion, the methods and results of in a clinical trial generally cannot be considered commercially confidential. This does not become clear from the definition of commercially confidential information provided in the draft proposal. Proposed change (if any): Add the following sentence to the definition: In general study methods and study results cannot be considered commercially confidential information.	
Lines 460 - 479		The draft proposal suggests that the need of non-commercial or academic sponsors to obtain research funding could be a	

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)*
		legitimate economic interest allowing to claim that certain information relating to a trial should be considered commercially confidential. The draft proposal further suggests that information may be classified as commercially confidential because this could be required to obtain future research funds or to publish the research in journals. It seems that this would allow publicly funded research to be considered commercially confidential. This seems inappropriate. Proposed change (if any): Even if the legislation does not distinguish between different sponsor types, the addendum to the functional specifications should not suggest that publicly funded research could be considered commercially confidential.	
Lines 480 - 490		Based on the basic ethical requirements for research in humans and to ensure safe and efficient use of authorised drugs there is a very strong public interest in making available all information on the methods and results of all studies on these drugs. Therefore, the default position should be that for study methods and results there is an overriding public interest requiring publication. Any deviation from this rule requires justification and an independent audit. Proposed change (if any): Clarify the overriding public interest in the publication of study	

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)*
		methods and results.	
Lines 493 - 500		It should not be possible to withhold information on study methods and study results just because there might be bits of commercially confidential information in a given document.	
Lines 349 – 350 Lines 503 - 515 Appendix 2 CT regulation Annex I D		We disagree that study protocols contain commercially confidential information. Clinical trial methodology as laid down in study protocols is a well-known, publicly discussed scientific methodology. Even indication-specific methods (such as treatment protocols, endpoints or analyses) are generally publicly available. Specifically, clinical trials aiming to support marketing authorisation are performed according to publicly available guidelines by health authorities. In general, the methods and results of a clinical trial cannot be considered commercially confidential. To meet the basic ethical requirements of research in humans, methods and results of trials have to be publicly available so that knowledge generation from this research is possible. <u>Time of availability of study protocols</u> A full assessment of study results to support decision making in health care (on the level of an individual patient or on a public health level [e.g. for clinical guideline development or for reimbursement decisions]) requires the availability of detailed information on the planned conduct of the study. Therefore, for this assessment the full study protocol is required.	

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)*
		The information provided in the “major study characteristics” according to Draft Appendix 1 is insufficient to understand the study methodology to the extent required for the assessment of study results. Therefore, the full study protocol needs to be available when the summary of study results is published 12 months after the end of the study. Otherwise, the aim of improving transparency by making the study results available as laid down in the EU Clinical Trial Regulation cannot be met. Proposed change (if any): The full study protocol (without redactions) is to be made publicly available together with the study results, i.e. 12 months after the trial. Clinical trial methodology cannot be considered commercially confidential information.	
Question 6 Lines 584-605		Question 6: 4.4.2. How should the status of marketing authorisation of the medicinal product be applied in the context of Article 81(4)(b) of the Regulation? The availability of comprehensive study information (methods and results) is required at the latest when a drug becomes available on the market. At that point in time the drug can be used both within the approved indication (label) or off-label. Therefore, IQWiG supports proposal 1.1 defining marketing authorisation status by the authorisation of the active substance in at least one Member state.	

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)*
		Proposals 1.2 and 1.3 would mean that study information on use in indications that are not yet licensed would not be available, although the drug may already be used in these indications in clinical practice. Another problem with proposals 1.2 and 1.3 is that a clear definition of “indication” in this context is difficult.	
Question 8 Lines 643 - 651		Question 8: Please comment and give a brief rationale for your support or disagreement with this proposal regarding clinical trials on products with a marketing authorisation. From IQWiG’s point of view it is important that for trials on products with a marketing authorisation, the “major characteristics of the trial“ according to Appendix 1 are available at decision on the trial and that the full study protocol and the summary of study results according to Appendix 5 and 6 (without redactions of study methods and results), as well as a clinical study report according to Appendix 7 (without redactions of study methods and results), are available 12 months after the end of the trial. IQWiG disagrees that study methods or results of a trial on a product with a marketing authorisation could be considered commercially confidential (see above). From the text of the guidance it seems that it would be the sponsors’ decision whether any information would be	

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)*
		commercially confidential. Any decisions on commercial confidentiality would need to be justified and independently audited.	
Question 9 Lines 655 - 703		Question 9: Please comment on proposals one, two, three or four regarding clinical trials on products without a marketing authorisation indicating which proposal best meets the requirements and objectives of the Regulation. Please provide a brief rationale for your choice of proposal and explain briefly disagreement with the other proposals. The regulation foresees publication of summary study results 12 months after the end of the trial. This publication is independent of the marketing authorisation status. These results can only be interpreted appropriately if the full study protocol is available. The methodological information available in the “major characteristics of the trial” is insufficient for study assessment. Therefore, the full study protocol should be published together with the study results. Otherwise, the aims of the publication of study results as laid down in the regulation cannot be met. IQWiG therefore does not support the delay of publication of study protocols as outlined in proposal 2, 3 and 4.	
Question 10 Lines 709 - 721		Question 10: Please comment on the proposed time points in paragraphs 6.5.1 and 6.5.2 and indicate whether they meet the requirements and objectives of the Regulation. Please provide a brief rationale for your support or disagreement.	

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)*
		As for question 9 above, it is important to note that the regulation foresees publication of summary study results 12 months after the end of the trial. This publication is independent of the marketing authorisation status. These results can only be interpreted appropriately if the full study protocol is available. The methodological information available in the “major characteristics of the trial” is insufficient for study assessment. Therefore, the full study protocol should be published together with the study results. Otherwise, the aims of the publication of study results as laid down in the regulation cannot be met. Therefore, neither proposal 6.5.1 nor proposal 6.5.2 is appropriate to ensure a sufficient level of transparency.	
Question 18 Lines 859 - 870		Question 18: Please comment on whether these proposals meet the requirements and objectives of the Regulation. From IQWiG’s point of view the proposals do not meet the requirements and objectives of the Regulation. According to the Regulation (Recital 68), 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 or the application for marketing authorisation has been withdrawn.	

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)*
		Therefore, the full clinical study reports without redaction of information on study methods and study results should be published. Redaction of information because it is considered commercially confidential information should not be possible. Any separate guidance on the content and publication of clinical study reports needs to meet these requirements of the Regulation, even if prepared outside the functional specifications for the EU portal and EU database. For this question the current discussion between EMA and the European Ombudsman on the redaction of clinical study reports by AbbVie is of particular concern. The examples of commercially confidential information supported by EMA do not seem sufficiently justified. For example, the fact that results from a secondary endpoint do not alter the overall benefit/risk assessment based on a primary endpoint in regulatory decision making does not mean that there is no public interest in these data. These data can be required for decision making in other contexts, e.g. for individual treatment decisions, clinical guidelines or decisions on reimbursement and pricing.	
Appendix 5 F ADDITIONAL INFORMATION		Comment: There should be an additional field for inclusion of information on study publications Proposed change (if any): Insertion of an additional field	

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)*
General comment on search functionalities		Although the search functionalities of the public user interface are not part of the functional specifications to be audited as set out in Article 82, we would like to include some general comments on them. Comment: The public user interface should include up-to-date search functionalities (as in ClinicalTrials.gov). Proposed change (if any): It should be possible to: - truncate search terms, - implement a search in all or single search fields, - enable a search with synonyms (including the display of relevant synonyms), - enable the use of brackets to structure the search, - use Boolean operators, - save searches, - combine different search lines, - save or copy the search history. Comment: The public user interface should enable different download options (as in ClinicalTrials.gov). Proposed change (if any): It should be possible to export and download: - single hits or all hits retrieved by a search query	

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)*
		- different download options (e.g. study summaries, selected fields or all fields) - different download formats (e.g. XML, plain text, tab-separated values, comma-separated values)	

Please add more rows if needed.