EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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
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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 Federation for Early Medicines Development welcomes 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. **Introduction of EUFEMED** EUFEMED was recently founded to create a "European voice" for exploratory medicines development; the Federation currently consists of four associations: AGAH (Germany), AHPPI (UK), BAPU (Belgium) and Club Phase 1 (France). • EUFEMED is a European not for profit Federation of associations involved in early clinical development of new medicines. • Members of the founding societies are all professionally active in exploratory clinical trials in healthy participants, special populations and patients with the target disease which are commonly non-therapeutic and/or non-prophylactic in nature. ➢ Academics ➢ Investigators ➢ Pharma or Biotech companies ➢ Service providers • The Federation's main purpose is to support exploratory medicines development in Europe by :	

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	➢ sharing expertise of its members ➢ organising conferences and training sessions (next: 20-22 May 2015, Brussels) ➢ developing standards to improve European competitiveness **Overview General Comments Section** Support of EMA draft proposal in relation to Phase 1 clinical trials: • Commercial sensitivity • Application of status of marketing authorisation – Our choice of proposal • Publication of Phase 1 clinical trials' registration information • Publication of study and product specific documents: – Our choice of proposal Remaining issues and proposals: • Definition of "Phase 1" • Publication of (lay) summary reports **Support of EMA draft proposal in relation to Phase 1 clinical trials: Commercial sensitivity** – 80: "Phase 1 trials are commercially particularly sensitive […]" – 345: "In the case of Phase I clinical trials in healthy volunteers there is particular sensitivity about	

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	the commercial confidentiality of information on the trial. – 617: “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.” **Support of EMA draft proposal in relation to Application of status of marketing authorisation** We support Proposal 1.3: 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.” Justification: – A significant number of clinical trials conducted by EU Clinical Pharmacology Units investigate new indications, formulations and/or route of administrations. These studies are considered Phase 1 (non-therapeutic) clinical trials. – Sponsors do not wish to disclose information on new indications and/or formulations early, as this may affect patent protection. – If a marketing authorisation has been issued, by at least one Member State for the active substance contained in that product, a wealth of information is available to the public for the active substance concerned.	

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	– For non-therapeutic trials it would be difficult to justify an overriding public interest requiring publication of study specific and product specific documents prior to marketing authorisation for the studied indication, formulation and/or route of administration. – If early disclosure would be required in the EU, it is likely that these trials would be conducted outside the EU. **Support of EMA draft proposal in relation to Phase 1 clinical trials: Clinical trials' registration information** We support that 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". Justification: – Commercially confidential information is protected – The proposed minimal information to be published is not commercially sensitive – The registration of all trials will assure the public that trials are bona-fide and authorised and that further information will be made available **Support of EMA draft proposal in relation to Study and product specific documents** We support Proposal 4: – the distinction between non-therapeutic/therapeutic trials	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	– and the staging of publication accordingly Justification: – The public will be able to access relevant information for all types of trials via the summary reports at predetermined time points – Protocols in particular contain information (as outlined in the draft proposal's section 4.4.1.2), that is likely to be considered commercially confidential beyond the time of summary report publication – For non-therapeutic trials it would be difficult to justify an overriding public interest requiring publication of study specific documents at the time of the summary report being posted – For therapeutic trials on the other hand there may be conceivable benefits of public access to the specified study specific documents at the time of the first summary report being posted (e.g. development of best methods and trial designs) **Remaining issues and proposals: Definition of "Phase 1"** The draft proposal appears to limit the definition of "Phase 1" to trials in healthy volunteers. Our proposed definition of "Phase 1" for the purpose of applying transparency rules: Phase 1 trials are clinical trials • using IMP, device & IMP/device combinations • performed in healthy volunteers and/or patients without therapeutic (or prophylactic) intent.	

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	Justification: – An increasing number of innovative, non-therapeutic/prophylactic early phase (including First Time in Human) studies are conducted in patients with the target disease and/or a combination of healthy volunteers and patients – Our definition of “Phase 1” is in line with current relevant legislation in the UK and Belgium. It would be very disappointing and against the objectives of the EU CTR, if its implementation would use a definition of “Phase 1” which is very out-dated and which would hinder research and innovation in the EU. – During this phase of drug development there is particular sensitivity about the commercial confidentiality of information on the trial – In the draft proposal, the definition of “Phase 1” impacts on the 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 – Most potential benefits of public access to information at the time of decision on a trial are not applicable to non-therapeutic trials, whether in adult healthy volunteers or patients – Publication of details of trials in patients without therapeutic intent may even be misleading as the potential indications mentioned in the protocol may raise unrealistic hope especially in end-stage diseases – The limitation to healthy volunteers will lead to a decrease in innovative non-therapeutic trial designs being conducted in the EU	

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	Remaining issues and proposals: Publication of (lay) summary reports The issue: – The draft proposal does not allow for a distinction between development stages of the product (phases of clinical research, therapeutic/non-therapeutic trials) or marketing authorisation status where the publication of summary reports is concerned – It is inconsistent with the spirit of the document and the CTR's definition of Commercially Confidential Information that summary reports should be published in all cases within 12 months after the end of a trial – It is unclear why the draft proposal does not acknowledge that summary reports can "contain extensive detail of a commercially confidential nature" whilst it does acknowledge this e.g. for the subject information sheet and protocol Our proposal: – The same application of commercial confidentiality should apply throughout – If it is decided that the publication of summary reports should be at a fixed point following the end of a trial we propose to set this at a later time when the published information has ceased to be 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)*
293-303		Comment: EUFEMED understands and supports the need for automatic rules to produce consistent and predictable outcomes. This should however not hinder the development of innovative medicines. The system should offer flexibility through a selection of pathways which then lead to specific rules (e.g. different pathways for non-therapeutic and therapeutic trials as already proposed in the draft addendum). Proposed change (if any): To consider addition of alternative pathways e.g. for advanced therapies where a distinction between therapeutic/non-therapeutic may not be clear-cut.	
382-410 Question 1		Comment: We agree with the proposal that principal investigators' CV's, relevant economic interests and institutional affiliations, and the statement of facility suitability are made public, as long as the information is limited to the minimum required and the privacy of the persons concerned is respected. Proposed change (if any): Templates should only include essential information. Templates should be discussed and agreed with relevant stakeholders (in particular investigators) prior to implementation.	
411-416 Question 2		Comment: There should be a mechanism by which the public can confirm the	

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		absence of potential conflicts of interest, independence and impartiality of Member States experts. Proposed change (if any): If personal identifying information of experts will not be published, we suggest that Member States use other means to confirm to the public that they have ensured the absence of potential conflicts of interest, independence and impartiality of Member States experts.	
417-425 Question 3		Comment: The proposal exposes the Investigator to a much higher degree than any other party responsible for a clinical trial (sponsor representatives, Member State experts). The rationale for this is unclear as all parties have equally important responsibilities, especially where doctors' duties are concerned (whether that doctor is an investigator, sponsor representative or Member State expert). Proposed change (if any): We propose that all relevant parties are treated equally in accordance with their responsibilities, where public disclosure of personal/professional details are concerned.	
426-436 Question 4		Comment: We agree with this proposal Proposed change (if any):None	
437-446 Question 5		Comment: We do agree with the proposal that the sponsor should provide contact details (e.g. functional roles) for information on a trial and its scientific aspects. We also agree that the investigator should have an option to provide a contact point for enquiries. However, whether or not contact details are published for natural	

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		persons (such as the investigator) will make little practical difference, as this information is easily accessible, once the name of the natural person is published. Proposed change (if any): We refer back to our comment on Question 3. It appears that the investigator carries a high burden of personal details being disclosed, compared to other responsible parties. We propose that disclosure of personal identifying details is applied equally for all parties who carry medical and/or scientific responsibility for a trial.	
584-609 Question 6		Comment: We support Proposal 1.3: 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.” Justification: – A significant number of clinical trials conducted by EU Clinical Pharmacology Units investigate new indications, formulations and/or route of administrations of medicines that have a marketing authorisation in at least one Member State for the	

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		active substance contained in the IMP. These studies are considered Phase 1 (non-therapeutic) clinical trials. – Sponsors do not wish to disclose information on new indications and/or formulations early, as this may disclose programme strategy and affect patent protection. – If a marketing authorisation has been issued, by at least one Member State for the active substance contained in that product, a wealth of information is available to the public for the active substance concerned. – For non-therapeutic trials it would be difficult to justify an overriding public interest requiring publication of study specific and product specific documents prior to marketing authorisation for the studied indication, formulation and/or route of administration. – If early disclosure would be required in the EU, it is likely that these trials will be conducted outside the EU. This would not only result in the EU losing clinical research to other regions, it would also result in the public having less access to trial information or data than if the study would be	

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		conducted in the EU. Proposed change (if any): N/A	
610-642 Question 7		Comment: We strongly support the EMA's proposal that the IMPD-Q section and the related list of questions, responses and assessment report sections should be considered to be commercially confidential and not be made public for any trial at any time for the reasons stated in lines 638 to 640 in the draft proposal. Proposed change (if any):N/A	
643-654 Question 8		Comment: We agree with the proposal that there should be an option to defer publication of study and product specific documents for trials of products with a marketing authorisation until the time that summary of trial results are published. This is due to the fact that there would be no perceivable public benefit of publishing these documents until summary results also become available. On the other hand the sponsor may have justified economic interests in protection commercially confidential information until that time. Proposed change (if any):N/A	
655-708 Question 9		Comment: We support Proposal 4:	

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		– the distinction between non-therapeutic/therapeutic trials – and the staging of publication accordingly Justification: – The public will be able to access relevant information for all types of trials via the summary reports at predetermined time points – Protocols in particular contain information (as outlined in the draft proposal's section 4.4.1.2), that is likely to be considered commercially confidential beyond the time of summary report publication – For non-therapeutic trials it would be difficult to justify an overriding public interest requiring publication of study specific documents at the time of the summary report being posted – For therapeutic trials on the other hand there may be conceivable benefits of public access to the specified study specific documents at the time of the first summary report being posted (e.g. development of best methods and trial designs) – This proposal is best aligned with our view that information should be published when it becomes	

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		relevant to the public (including patients), health professionals and researchers). – It is also best aligned with our definition of Phase 1 trials (i.e. trials in healthy volunteers and patients without therapeutic or prophylactic intent). Proposed change (if any):N/A	
709-725 Question 10		Comment: We agree with the triggers for timing of publication being: – The granting, refusal, or withdrawal of the marketing authorisation application – 10 years after the end of a trial We are concerned about the timelines for publication of (lay summary reports) for the following reasons: The issue: – The draft proposal does not allow for a distinction between development stages of the product (phases of clinical research, therapeutic/non-therapeutic trials) or marketing authorisation status where the publication of summary reports is concerned – It is inconsistent with the spirit of the document and the CTR's definition of Commercially Confidential Information that summary reports should be	

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		published in all cases within 12 months after the end of a trial – It is unclear why the draft proposal does not acknowledge that summary reports can "contain extensive detail of a commercially confidential nature" whilst it does acknowledge this e.g. for the subject information sheet and protocol We refer to a position paper by the European CRO Federation (EUCROF) dated 31 October 2014 which was submitted as part of EUCROF's response to the first consultation on the EU portal (https://www.researchgate.net/publication/272151443_EUCROF_position_paper_public_access_to_early_phase_EU_database_information_31_Oct_2014). This paper states that: *"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."* It goes on to say: *"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*	

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		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." The paper provides a detailed risk/benefit as evidence and proposes that a staged approach to publication of results, depending on the relevance to the patient and commercial sensitivity. Our proposal: – The same application of commercial confidentiality should apply throughout the transparency provisions of the CTR Proposed change (if any): If it is decided that the publication of summary reports should be at a fixed point following the end of a trial (which we support as this is a simple process which can be automated), we propose to set this at a time much later than one year from the end of a Phase 1 study, at a point when the published information has ceased to be commercially confidential.	
726-746 Question 11		Comment: We support that the sponsor will have the possibility "**to opt to have only very minimal public information at the time of**	

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		decision on the trial" and for the "remainder to be made public at the point when the summary of trial results is published". Justification: – Commercially confidential information is protected – The proposed minimal information to be published is not commercially sensitive – The registration of all trials will assure the public that trials are bona-fide and authorised and that further information will be made available We refer to the aforementioned position paper by the European CRO Federation (EUCROF) dated 31 October 2014 which was submitted as part of EUCROF's response to the first consultation on the EU portal (https://www.researchgate.net/publication/272151443_EUCROF_position_paper_public_access_to_early_phase_EU_database_information_31_Oct_2014). 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 clinical trials. An argument can however be made for release of relevant Phase 1 registration information in pre-*	

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		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."* The paper provides a detailed risk/benefit as evidence and proposes that a "limited amount of non-commercially confidential registration information is made publicly accessible via the EU database following clinical trial authorisation and prior to study commencement". The proposed information to be made publicly available is in line with the EMA's proposal which we therefore fully and strongly support. In this context the **definition of the term "Phase 1"** is critical. The draft proposal appears to limit the definition of "Phase 1" to trials in healthy volunteers. It is our view that this definition is not in line with current clinical research practice and will hinder	

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		innovation in the EU. Our proposed definition of “Phase 1” is 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 Justification: – An increasing number of innovative, non-therapeutic/prophylactic early phase (including First Time in Human) studies are conducted in patients with the target disease and/or a combination of healthy volunteers and patients – Our definition of “Phase 1” is in line with current relevant legislation in the UK and Belgium. It would be very disappointing and against the objectives of the EU CTR, if its implementation would use a definition of “Phase 1” which is very out-dated and which would hinder research and innovation in the EU. – During this phase of drug development there is particular sensitivity about the commercial confidentiality of information on the trial	

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		– In the draft proposal, the definition of “Phase 1” impacts on the 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 – Most potential benefits of public access to information at the time of decision on a trial are not applicable to non-therapeutic trials, whether in adult healthy volunteers or patients (see above) – Publication of details of trials in patients without therapeutic intent may even be misleading as the potential indications mentioned in the protocol may raise unrealistic hope especially in end-stage diseases – The limitation to healthy volunteers will lead to a decrease in innovative non-therapeutic trial designs being conducted in the EU. The conduct of innovative, adaptive and complex non-therapeutic Phase 1 studies is one of Europe’s key skills and advantages. It would be a great shame if the CTR would lead to a decline of this type of research in the EU. Proposed change (if any): We propose to change the definition of “Phase 1” to clinical trials	

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		Phase 1 trials are clinical trials • using IMP, device & IMP/device combinations • performed in healthy volunteers and/or patients without therapeutic (or prophylactic) intent.	
747-752 Question 12		Comment: We agree that this proposal meets the requirements and objectives of the regulation. Proposed change (if any):None	
753-760 Question 13		Comment: Proposed change (if any):None	
763-796 Question 14		Comment: EUFEMED is of the view that the publication of inspection reports should have a defined purpose. Only findings that are of relevance to the public should be made publicly available. In case of inspections of early phase clinical research units, national inspection schemes differ widely. Some EU countries have voluntary, non-study-specific inspection schemes (such as the MHRA's Phase 1 accreditation scheme). During these voluntary inspections usually a number of studies will be inspected by the CA in accordance with the relevant schemes' requirements. Full publication of the inspection reports (including minor findings and recommendations) would disclose a large amount of commercially confidential	

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		information (such as methods and procedures) that is of no relevance to the public and may be difficult for the public to put into context. On the other hand, this information could be of commercial interest to the units' competitors. This could potentially disadvantage early phase units who voluntarily participate in inspection schemes and/or who are located in countries with more stringent inspection schemes. Proposed change (if any): Voluntary inspection schemes should allow for voluntary publication with options to redact all information that should not be disclosed. In regard to for-cause and scheduled mandatory inspections we propose to publish only findings that are of relevance to the public (e.g. critical findings). Furthermore, there should be a clear definition of the time point at which the inspections reports are published. This should never be before the inspected party had an opportunity to respond to findings, which may change their classification. We propose that the EMA establishes an arbitration process for disputed findings. Arbitration should take place prior to publication.	
797-802 Question 15		Comment: Proposed change (if any):None	

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803-843 Question 16		Comment: Proposed change (if any):None	
844-858 Question 17		Comment: In early phase clinical trials (e.g. First-in-Human trials), it is not unusual that the benefit-risk balance of a trial changes during the conduct of a trial. This is due to the exploratory nature of these trials. The design of trials (i.e. study protocol), and in particular the use of adaptive trial design, accommodate this by requiring continuous evaluation of evolving data and consecutive adaptation of studies to minimise risk. In many cases, non-substantial modifications of the trial can thereby avoid changes of the benefit-risk balance. For some early phase trials the benefit-risk balance may change in such way that a substantial modification of the trial becomes necessary to manage the risk. This would require MS approval before the study can proceed further. Such a substantial modification may be non-urgent or an urgent safety measure/substantial modification. Study Participants will always be updated of any changes in benefit-risk balance as this is a GCP requirement and forms part of all subject information sheets.	

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		Publication at the time of reporting could hinder Competent Authorities, sponsors and investigators in investigating and dealing with these events using established and safe mechanisms. It could also hinder continued conduct of a trial (following the necessary authorisations). The requirement for early publication could become a barrier to reporting unexpected events or introducing urgent safety measures. As a result unexpected events may be under-reported and necessary safety measures may not be taken to avoid publication. This would have a negative impact on participant safety. Moreover, there will be no benefit to the public, as all necessary information will be routinely made available to (prospective) study participants. Proposed change (if any): It is our firm opinion that in case of Phase 1/non-therapeutic studies, information on non-serious unexpected events (in compliance with Article 53) and urgent safety measures should not be made public at the time they are reported. Established mechanisms of reporting and modifications of trial design and conduct should be used to deal with these issues in early phase research.	
859-872 Question 18		Comment: Proposed change (if any):None	

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894-898 Question 19		Comment: We agree with the concept of text being added to Table 2, Section 4.3 as an addendum, the content of which will depend on the outcome of the final consultation. We also agree with the concept of the application form containing a set of questions which will then trigger select pathways of publication. We note that the proposal states that protocol synopsis and protocol should be separate and have different publication rules applied to each. Although the draft proposal currently does not seem to use this facility in any of its proposals, we believe that this separation would facilitate the implementation of e.g. Proposal 4 (Table 1) which proposes an earlier publication of study specific documents than Proposals 2 and 3. If, for studies with therapeutic intent, publication at the time when first summary results are posted would be limited to the protocol synopsis (and the full protocol be published at MA or 9 years after first summary results are posted), we believe this would serve all parties very well. Proposed change (if any): We propose to update the definition of study specific documents in section 4.4.1.2a and Table 1 accordingly, distinguishing between protocol synopsis and protocol publication pathways as outlined above.	

Please add more rows if needed.