SUBMISSION OF COMMENTS ON Draft list of fields contained in the 'EudraCT' clinical trials database to be included in the 'EudraPharm' database on medicinal products and made public, in accordance with Article 57(2) of Regulation (EC) No 726/2004

COMMENTS FROM EFPIA - Contact Person Christine-Lise Julou

GENERAL COMMENTS

The R&D based pharmaceutical industry in general and EFPIA in particular recognises that there are important public health benefits associated with making clinical trial information more widely available to healthcare practitioners, patients and the general public. However the proposed list of fields contained in the EudraCT clinical trials database to be included in the EudraPharm database on medicinal products and made public in accordance with Article 57(2) of Regulation (EC) No 726/2004 raises a number of concerns

As indicated in our letter BA/CLJ 63.994 of 28 July 2008 we do not believe that the scope of the guidance document is consistent with the scope of EudraPharm as foreseen in Article 57 of Regulation (EC) No726/2004. The justification for the amendment tabled by Members of the European Parliament to support the introduction and adoption of the second paragraph under Article 57.2 of Regulation 726/2004 confirm that some of proposed requirement are not consistent with the intent of the legislator.

- "*the database 'should contain only details of the research methods employed, but not confidential or personal data such as that incorporated in the database set up under Directive 2001/20, to which the public quite rightly has no access.*
- *ethically dubious publications of trials can be prevented and on the other hands, patients who are seriously ill can obtain information about clinical trials involving the treatment of their diseases more quickly, the can discover whether they meet the criteria for inclusion in the trial and the name of the person or body they much contact….*
- *the publicly accessible data fields should be administered in a manner consistent with the best practice employed by independent organisations , etc. "*

The present public consultation paper raises a number of comments as follows:

1. Many Pharmaceutical companies already make information on ongoing clinical studies publicly available via clinicaltrials.gov[1] or other such databases[2]. By implementing a bespoke and duplicative European system for doing the same thing but from a different route of information (distilled from that provided to the national competent authorities for clinical trial applications), there is a significant risk that discrepancies will exist between the different public databases. These discrepancies will only serve to confuse rather than inform patients.

2. The high level of detail on a protocol included in the draft list means that there will be a greater number of occasions when changes to a clinical trial will result in a need to update the public database. This could result in greater resource being required to maintain the public database and keeping it up to date unless an efficient and elegant IT solution is provided.

3. While the Member States remain unable to agree on whether comparator, standard of care, co-administered or reference products are investigational medicinal products or non-investigational medicinal products, important inconsistencies will occur in the information provided on medicines being used in a trial that is made public from EudraCT.

---

[1] Experience with the information disclosed on other clinical trials sites e.g. *clinicaltrials.gov* in the USA, would indicate that the level of information disclosed in those databases has been found sufficient both by patients who may want to participate in clinical trials and also for physicians who are interested in the trials either on their own behalf or on behalf of their patients. Therefore we would strongly recommend that a similar level of disclosure of information should be made on the EudraPharm website.

[2] A comparison of the WHO-20 data set with the EUDRACT fields identified these discrepancies as examples of the above need for harmonisation:

- EUDRACT uses "Trial Identification" while WHO-20 uses both "Trial Identifying Number" and "Secondary Identifying Numbers" to capture the unique ID numbers assigned to a particular trial.
- EUDRACT uses "Sponsor" while WHO-20 uses both "Primary Sponsor" and "Secondary Sponsor" to name the individuals, organizations, or groups which take responsibility for managing and/or financing a particular trial. EUDRACT does not recognize a "Secondary Sponsor".
- EUDRACT uses "Contact Point" while WHO-20 differentiates between "Contact for Public Queries" from "Contact for Scientific Queries". EUDRACT requires a FAX #, while WHO-20 does not.
- EUDRACT uses "Full Title" while WHO-20 requires both "Public Title" and "Scientific Title".
- EUDRACT requires "Ethics Committee Information" while this not part of WHO-20 at all.
- EUDRACT uses "Medical Condition" (in very much detail) while WHO-20 uses "Health Condition or Problem Studied" in minimal detail.
- EUDRACT uses "IMP" (in very much detail) while WHO-20 uses "Intervention" with generic, chemical, and serial # information only.
- EUDRACT uses a variety of terms to capture the elements of study design, such as "Design", "Objective", "Scope", "Planned Population", etc. while WHO-20 asks for only specific elements including: Key Inclusion and Exclusion Criteria, Study Type, Primary and Secondary Outcomes.
- EUDRACT asks for "Target Sample Size" vs. "Planned # of Subjects to be Included" in WHO. Labels differ but definitions are the same.

4. To address these issues, it is proposed that the public European database displays the necessary administrative fields from EudraCT, but that all protocol-related information for the trial is provided by cross-linking to an existing public database, such as clinicaltrials.gov. This could be readily achieved by including a field in EudraCT for the link to the clinicaltrial.gov or similar database summary to be entered.

5. There is no description on how information on individual studies conducted in multiple Member States will be made available to the public. It is not clear which Annex 1 forms (will be used to transfer information to the EudraPharm website. In every EU member state participating in a multi-country study 2 different Annex 1 forms are generated - one for the Ethics Committee and one for the Competent Authority. In some countries these forms are in the local language. The same clinical trial will be subject to separate applications to each competent authority in participating Member States. Applications might be made in a staggered fashion to different agencies during which time information might have been supplemented or otherwise adjusted to meet differing national requirements. This is likely to affect the following fields: A.1, E.8.3-E.8.6, F.4 and N. How is the EMEA going to keep the public information current if different application forms exist for one trial? We assume that this information will be combined and made available to the public as single entry. This should be confirmed, as making multiple sets of information for the same trial publicly available would be confusing.

6. When submitting a patent application on, for example new indications/combinations/formulations, etc, the innovative pharmaceutical companies are required to support the application with clinical data. Increasing the extent of disclosure related to sensitive information that a company has to disclose impacts significantly patentability since the applications must be made earlier and subsequently with little or no supporting clinical data, a 'catch-22' position. In short, the negative impact on intellectual property is significant unless there is a possibility to delay disclosure of sensitive information until the prompt approval of any patent applications.

7. As mentioned in our letter dated 28th July 2008, there is concern that the database which was established to provide information on medicinal products authorised in the Community (EudraPharm) is now being used to provide information on unauthorised products. Proprietary information may be included in documents shared with the competent authorities, but companies would not be willing to share that information with the public and their competitors. Furthermore, the intended audience for the public information needs to be defined because it is imperative to make sure that the information contained in this public database is useful to the intended users. Different language/terminology would need to be used depending on whether it is for the lay public or scientific members of the community (Consider terminology consistent with that already used for other disclosure activities in the same area should be preferred)

8. The information being requested for disclosure is in excess of what is being required by legislation in other jurisdictions, particularly the US.

There is concern that even with the same NCT numbers, the lay public will view the two different records as two different trials. Duplication of trial information in different formats and varying degrees of detail is not in the public's best interest

9. With regard to the provision and publication of results, the ICH-E3 synopsis template should be used and only the information included in the template should be required. Companies already have to provide this type of information to be compliant with other legislative requirements (e.g. the US State of Maine legislation). Sponsors will also soon be required to provide data tables to be compliant with US Federal legislation. It is becoming an undue burden to provide essentially the same results in different formats, with varying degrees of detail in different websites throughout the world. Efforts should be made to harmonise the clinical trial registration and results requirements. Ideally, the public should be able to locate clinical trial information for all applicable trials in one location (regardless of where the website is located and where the "public" is located).

The above-mentioned comments are considered to be critically important. Additional comments concerning specific fields are listed

A Trial identification		
Field number	**Comment and Rationale**	**Proposed change (if applicable)**
A.1	There is no information on how information on individual studies conducted in multiple Member States will be made available to the public. The same clinical trial will be subject to separate applications to each competent authority in participating Member States. We assume, however, that this information will be combined and made available to the public as single entry. This should be confirmed, as making multiple sets of information for the same trial publicly available would be confusing.	
A.6	The clinicaltrials.gov and US NCT numbers are essentially	Delete clinicaltrials.gov from the list of additional international

	the same thing. Clinicaltrials.gov provides the US NCT Number when the trial is registered on their system.	study identifiers.
A.6	It would be helpful to indicate that this information should be provided 'if available' since this may not be the case at the time the CT application is made	Additional international study identifiers (e.g. WHO, ISRCTN, US NCT Number1), <u>if available</u>.

B Identification of the sponsor		
Topic name	**Comment and Rationale**	**Proposed change (if applicable)**
B.4	**Source(s) of Monetary or Material Support: Commercial Non-commercial** The name and country of the sponsor will be made public and therefore we do not believe that publication of this additional information supports the intent of transparency around clinical trials in the interest of public health.	Consider deleting
B.5	If a call-centre is used as a point of contact, it should not be necessary to also include an address, fax, and email. The establishment of a single general point of contact for a sponsor or even for an individual clinical trial is likely to be highly problematic, due to, for example, privacy issues, availability of toll free phone numbers, different national requirements and the ability to support different languages. It should be possible to include different contact points to facilitate the handling of queries from different countries or in different languages.	Allow for the entry of either: Address AND/OR phone number AND/OR Fax AND/OR E-mail, but not all 4 items. Confirm that information on multiple contact points for a single study can be accommodated.

D Information on each Investigational Medicinal Product (IMP)		
Topic name	**Comment and Rationale**	**Proposed change (if applicable)**
	Description of the IMP	
D.3.9	This data field should not be accessible to the public. For an ongoing clinical trial this information is not adding value to the public information. On the contrary it may induce the lay public to use approved drugs off-label based on perceived EMEA sanctioning of specific dosing for an (investigational) indication or patient population. For EMEA and NCAs the field is useful.	
D.3.10 to D.6.6 - Description of the IMP	Detailed information on the IMP is not of value to the public and is confidential to the sponsor The amount and level of detail in Fields D3.10 to D.6.6 is very high. As such public availability of this information may be detrimental to the patentability of inventions associated with e.g. the concerned vaccine. Patentability according to Article 54 and 56 of the European Patent Convention (EPC) is based on information not publicly available prior to the submission of patent applications. Also, the availability of clinical data is necessary to support patentability (Articles 56 and 83 of the EPC) which prevents innovative pharmaceutical companies to apply for patents early in the development. Hence, public availability of this information as early as phase 1 could prevent the pharmaceutical industry or any other innovator to obtain the patents necessary to protect their innovations Further more detail on the type of product, origin of cells,	Recommend not including such detailed information (detail on the type of product, origin of cells, type of cells, genes of interest, etc) for public disclosure on EudraPharm.

	type of cells, genes of interest, etc is not of primary interest to the persons who are seeking information on paediatric trials they may be interested to participate in or the lay public. However competitors may find such information quite useful.	

E General information on the trial		
Topic name	**Comment and Rationale**	**Proposed change (if applicable)**
E.1 MEDICAL CONDITION OR DISEASE UNDER INVESTIGATION		
Section E	Some information in sections E1, E5 and E7 is acceptable to be made public subject to the comments below. All other E fields are irrelevant to the public or are covered by information in other sections. The level of detail is not likely to be of interest for the target users. Only the basic datasets should be made available.	Delete sections E2, E3, E4 and E8, and simplify.
E.1.1 and E.1.1.1	The condition being studied is likely to be included in the study title, so the need for a separate field for this information is unclear. "Medical condition in easily understood language" is subjective. Different sponsors could use different descriptions for the same condition, which would lead to confusion for the public, devaluing the public availability of the study information. Standard language here is exceptionally important for searching.	Suggest use of something like the MeSH dictionary, as used on ClinicalTrials.gov
E.2 Objective of the trial		

E.2.3.	It is not clear what constitutes a "sub-study". This information is not likely to be of interest to, or understood by, the lay public.	Provide clarification on the meaning of "sub-study".
E.5 - E.5.2.1	Endpoints and timing could be proprietary and are not likely to be of interest to the lay public. This benefits competitors, not the public.	Recommend not including detailed information such as time points of evaluation of endpoint for public disclosure on EudraPharm.
E.6 Scope of the trial		
E.6	We are not sure that this is of public interest/benefit.	
E.8 Design of the trial		
E.8.3 – E.8.6.2	The information requested in these fields may change during the trial, but the information in EudraCT may not be updated, either because a change would not constitute a substantial amendment, or because the change concerns sites located outside of the EEA. For this reason, and as the information is of limited interest or benefit to the public, it should not be made public.	Recommend not including this information for public disclosure on EudraPharm.

F Planned population of trial subjects		
Topic name	**Comment and Rationale**	**Proposed change (if applicable)**
F.1 Age span		
Section F	Section F should be limited to the population to be recruited i.e. whether both genders are eligible to enter the trial and the age range. It is not always possible to plan in advance or anticipate the distribution of the trial subjects in the various age span	For section F.1, provide sufficient information to inform the public the age span of the population that may be included in the trial. Delete Section F.3.1

	categories (e.g. in the case of vaccine trials). It would not be appropriate to require that this information be systematically provided. In addition, field F.3.1 asks about healthy volunteers which does not seem to be consistent with the statement that Phase I trials are not made public	
F.4 Planned number of subjects to be included		
F.4	The information concerns "planned" trial details, which may change over the duration of the trial. We question whether it is really relevant for the public to know how many patients are planned in an individual country or in the trial. This information is more likely to be of benefit to competitors than to the public.	Recommend not including such detailed information for public disclosure on EudraPharm. The WHO target sample size requirement would be more appropriate.

N Review by the Competent authority or Ethics Committee in the country(ies) concerned		
Topic name	**Comment and Rationale**	**Proposed change (if applicable)**
First 2 lines	There is no obvious reason for making these fields public. Rather than publishing detailed information on Competent Authority(ies) or Ethics Committee(s) approvals/opinions it might be more relevant and useful to publish the anticipated or actual date of enrolment of the first trial subject.	Recommend that only information serving the stated objective of the legislation in relation to transparency and communication is posted and that it is presented in such a way it can be easily understood by any member of the lay public.
3rd line	It should be clarified if this refers to the status of the study	

	globally, or to the status in the European Community. The forms submitted by applicants do not supply information regarding the start of the study. How would the information be collected?	
6th line	Suggesting that the anticipated date of availability of results will be no more than end of trial date plus twelve months is confusing in this list of data fields to be made available in a public database because this is not required by the law for products which have not yet been authorised. Furthermore while promptly making information on trial results available to the Regulatory Authorities is supported, there is no identifiable benefit to the public of making results information available for new products not commercially available prior to marketing authorisation, or for already authorised products before the trial information has been assessed. Publication of summary trial results, following assessment and approval of new products, indications and dosing information, would provide the public with information placed within the context of the Regulators assessment and at a time when the product was likely to be labelled and commercially available for that use. However industry would support the posting of paediatric clinical results for an investigational products that has failed in development especially when they have significant medical importance	Clarify that trial results may be made available in the EudraPharm database when the medicinal product has been authorised.

Clinical trial results information		
Topic name	**Comment and Rationale**	**Proposed change (if applicable)**
General comment on availability of Clinical trial results information	With reference to the timing for making clinical trial results information public, see above comment	
Administrative information	Is this information going to be located separately from the registration information? If not, this is redundant information. In addition, it is not clear what "trial report number" means.	Unless the protocol-related information and results will be in different locations, we recommend not including this information, as it is redundant.
Background for conducting the trial	Scientific background is not included in the ICH E3 synopsis format, and is not likely to be of interest or benefit to the lay public. This information is more suited for a journal article.	
Participants of the trial	The paper requests information on the locations where data were collected, "to assess external validity of the trial". Is this saying that the public will be making decisions on the external validity of the trial based on where the trial was conducted? Locations are provided with the protocol-related information.	
Blinding	This information is probably already included in previous sections (Trial design, randomisation implementation), so its inclusion here seems redundant.	Recommend deleting this section.

Statistical methods	The detailed description of all additional statistical analyses performed may not be understood by the targeted users of the database. Detailed information may overload the database whose objective is to be informative to a large public and therefore should be kept simple.	Consider simplifying
Participant flow	With reference to protocol deviations, the sponsor is required to discuss important protocol deviations in the final study report, to be able to evaluate whether they have an impact on the validity of the data. This will be been considered in the "discussion and interpretation of study results" and can in its detailed form not be informative to the public, who do not have all the elements and knowledge to evaluate the importance and impact of the deviations. The information should be limited to numbers of patients. This will bring the European public database into line with that of NIH. Furthermore in order to keep the database simple detailed information should only be provided for the final analyses	This section should be reworded to indicate that only the numbers of patients who did not complete the trial/were not considered, due to protocol deviations. This is consistent with how other countries are handling the inclusion of protocol deviations with results reporting.
Recruitment	This is not going to be of interest or benefit to the lay public.	Recommend deleting this section.
Trial Interruption	The sponsor is required to confirm whether the trial was interrupted and provide reasons for the interruption. There are many legitimate reasons why a trial may be interrupted, this is not considered valuable information to patients, their carers and health professions particularly when the reasons for trial interruption are remedied	Suggest section is removed.
Ancillary analysis	It is not clear what information is expected here. Is this requesting results of all the post-hoc analyses?	

	Ancillary analysis is often of an exploratory nature to be further confirmed in other studies and therefore not of benefit of the public.	
Adverse Events	In the final study report, the sponsor is required to analyze all safety-related data. Different displays are required to be able to put these data in the right context related to exposure (dose, duration, number of patients), time-dependence, and demographic characteristics.	Any listing of adverse events should be put into the correct context and in a form that is easily understood by those without access to the complete study report.
Discussion and interpretation of study results.	It is not appropriate to include the sponsor's interpretation of the results or their conclusions. FDA DDMAC in the US has already warned sponsors that interpreting the data or including conclusions in sponsors' results summaries could be considered promotional and subject to fines. Furthermore an electronic forum is not conducive to discussion and interpretation of study results. Discussion and interpretation of study results is best handled in a regulatory review setting involving the technical expertise of the regulatory authority, investigators and sponsor. This electronic forum does not lend itself to open discussions, clarifying questions, alternative interpretations and the like that is needed to properly interpret the data and draw appropriate conclusions	Recommend deleting the section on providing interpretation by sponsor. Competent authority interpretation of trial results should be provided following a formal scientific assessment of a MAA or post authorisation variation/follow up measure when all concerned competent authorities /CHMP and the sponsor have had opportunity to comment and final assessment reports are available. Thus it is proposed that when the results of the trial are published in a peer reviewed journal, a link to that scientific publication may be made or a reference given. It should be clear who has the responsibility to make such links in the database. It must also be realised that the links will in the majority of cases redirect the reader towards fee-based access to scientific journals. Links to the EPAR/PAR will also be possible when formal regulatory assessment has taken place.