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**)' and 'Draft Appendices to Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited" (**EMA/641479/2014**)'

Comments from:

Name of organisation or individual
EFPIA - European Federation of Pharmaceutical Industries and Associations
EBE – European Biopharmaceutical Enterprises
VE – Vaccines Europe

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

Introduction

EFPIA, EBE and VE welcome the opportunity afforded to comment on the EMA'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"* (referenced as 'draft Addendum' in these comments). EFPIA brings together 33 European national pharmaceutical industry associations as well as 40 leading companies undertaking research, development and the manufacture in Europe of medicinal products for human use. EFPIA and its member companies, as the largest contributors to clinical research in Europe, offer our perspectives on approaches intended to optimally balance public access to clinical trial information whilst ensuring more efficient patient access to new innovative treatments. EBE represents the developers of biological medicines and includes European based multi-national and small and medium-sized enterprise (SME) companies. VE represents innovative research–based global vaccine companies as well as SMEs operating in Europe.

Biopharmaceutical companies are indeed committed to advancing public health goals through responsible sharing of their clinical trial data in a manner which is consistent with the following imperatives:

- Safeguarding the privacy of patients;
- Preserving scientific rigor and the trust in the regulatory systems; and
- Maintaining incentives for investments in biomedical research.

Building upon the foundation of these imperatives, in 2013, EFPIA (along with the Pharmaceutical Research and Manufacturers of America) adopted Principles for Responsible Clinical Trial Data Sharing. These set out industry's commitments to: (i) enhance data sharing with researchers; (ii) enhance public access to clinical study information; (iii) share results with patients who participate in clinical trials; (iv) certify procedures for sharing clinical trial information; and (v) reaffirm commitments to publish clinical trial results[1].

Inherently, we fully support the provisions in the Clinical Trial Regulation that allow EU citizens to have access to information about clinical trials (Ref: Article 81(2))[2]. We regard a main benefit will be to enable patients and healthcare professionals to more quickly identify clinical trials and evaluate the relevance of these to an individual patient's condition. Access to information and enrolment in clinical trials should be key considerations together with establishing the right balance between openness and protection of personal and commercially confidential information when implementing Article 81.

Over the last several years, EFPIA has contributed ideas and commentary to the EMA on this topic during its public workshops and draft consultations attempting to achieve a balanced approach to the transparency of clinical trial information. We fully support EMA's aim expressed here that a "balanced approach is needed to protect public health and also foster the innovation capacity of European medical research, thus supporting the EU as a location for innovative, cutting edge research that results in development of novel products and research

[1] http://transparency.efpia.eu/uploads/Modules/Documents/data-sharing-prin-final.pdf [accessed 26 January 2015]
[2] REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

into new and better uses of existing products"[3]. Indeed, following our review, EFPIA believes that the proposals from the EMA, for the most part, support this aim.

EFPIA, whose views in this response are supported by EBE and VE, appreciates that the Agency has outlined important options for stakeholder consultation and we therefore offer these constructive comments to assist the EMA in achieving its essential intent to "strike the right balance"[3]. Within our specific comments we have addressed those EMA questions that EFPIA believes have a substantial impact on the innovative pharmaceutical industry. In addition, EFPIA, EBE and VE look forward to future opportunities to continue this dialogue with EMA to realise optimal solutions for these complex issues.

Major Comments

Proposed Timeline for Disclosure of Phase I Information and Results

EFPIA appreciates EMA's acknowledgement of the particular commercial sensitivity of Phase I trials (as outlined in lines 345-346) and the possibility to defer the disclosure of protocol-related information to be made public at the time of decision on the trial. However, EFPIA remains concerned that this acknowledgement does not extend to the commercial sensitivity of publishing summary results of Phase I trials and the potential for release of commercially confidential information (CCI).

EFPIA recognises and supports the requirement for results of all clinical trials to be made publically available. However, EFPIA remains concerned that the disclosure of Phase I trial results[4] within 12 months after completion of the trial may compromise CCI. Release of information regarding Phase I results within 12 months after trial completion would significantly narrow the window for filing and securing patents for new inventions. Therefore, even though the CT Regulation does not make an explicit exclusion for Phase I trial results as CCI, release of Phase I trial results within 12 months should be considered CCI and could compromise the EU's competitive balance. For example, at the time of Phase I, companies may not have enough information to secure all of the patents that will eventually be obtained since the support of clinical evidence may be necessary to file. In such circumstances a company (or researcher) may require longer than 12 months to prepare and file appropriate patent applications for innovative approaches or uses discovered during Phase I, as the results of the study may be needed to support these applications. It should also be noted that there might be prolonged development duration post completion of Phase I for a particular aspect of a product. There might also be practical challenges to preparing a summary report within 12 months (e.g. for vaccines, where there are delays in serology), which would entail the need for more time to prepare and file patents.

As another example, the Phase I results of exploratory objectives may include biomarkers that could be used as 'hypothesis generating' for future studies. Disclosing the results of these exploratory objectives within 12 months of end of trial may preclude obtaining patents that

[3] 'Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014'

[4] In these comments, Phase I results refers to the publication of summary results of these trials in the Database. Phase I results may also routinely be included in documents such as the Investigators Brochure (IB), clinical and preclinical IMPD sections and the protocols for Phase II/III. By evident extension, this timeline should also apply similarly to the Lay Language Summary. As with the Phase I summary results, the Phase I results presented within these additional documents should be similarly and accordingly deferred.

would cover biomarkers and/or diagnostics themselves, as well as method of use patents directed to patient subpopulations[5].

EFPIA also believes that Phase I studies would not be expected to significantly benefit from the various improvements provided by the CT Regulation (such as a coordinated assessment). These studies are on the other hand subject to the new disclosure requirements according the EMA's draft consultation. In sum, disclosing results of Phase I trials within 12 months of the end of the trial would put the EU at a competitive disadvantage given that there is no equivalent disclosure in other jurisdictions.

Therefore, EFPIA believes that more deliberation and discussion is necessary regarding an acceptable mechanism and deferral period for release of Phase I trial summary results. Here EFPIA describes three potential approaches for the deferral of Phase I results that should be fully considered given their level of merit:

- ***Deferred until the granting, refusal, or the withdrawal of the marketing authorisation application (MAA) or at least 10 years after the end of the trial***. EFPIA believes that this approach would provide consistency with the '*Triggers for timing of publication'* proposed by the EMA in the draft Addendum (6.5). Given its uniformity, this approach would aid in resource conservation for sponsors and EMA. It would also standardise the release of information for products discontinued during development. Finally, this approach would minimise the potential for unintentional release of CCI.
- ***Where the trial is not to be used as part of a marketing authorisation application (MAA), release of information should be deferred until an established, finite period of time has lapsed following completion of the trial, at a minimum of 6 years***. This approach could be consistently applied and enable simplification of the Database operation.
- ***In any case, postpone a final policy decision until it is possible to align EU's deferral approach with international standards***. In the US, there are ongoing deliberations on the possibilities for release of Phase I trial summary results. Alignment of EMA's final determination would then establish one global ('gold') standard, minimise the possibility for confusion, and ultimately conserve resources.

EFPIA proposes further discussion with EMA and other involved stakeholders such as a workshop to agree to an optimal deferral approach.

In addition, it is unclear why the EMA draft proposal focuses on Phase I trials in healthy volunteers. Under specific circumstances, mainly based on ethical arguments, Phase I trials might have to be conducted in a patient population with the target disease and/or a combination of healthy volunteers and patients. Phase I is defined in doc EMA/641479/2014 p. 4 (footnote) as trials that" *usually involve healthy volunteers or sometime patients*". The same definition should apply consistently throughout both documents EMA/641479/2014 and EMA/768628/2014. For the reasons described, EFPIA believes that Phase I results from trials conducted in patients should be considered similarly sensitive as with Phase I trials conducted in healthy volunteers. If Phase I trials in patients would have the same transparency requirements as later phase studies, it would be a disincentive for sponsors to conduct these studies in the EU.

[5] Regardless of development Phase, since exploratory outcome measures may be CCI, results for these studies should not be disclosable publically. This would be consistent with the approach currently applied under Commission Guideline 2012/C 302/03, Point 5, para 1 and with that of other regulators worldwide.

Unless carefully accounted for, this outcome could contradict the original objectives of the legislation – boosting the EU's competitiveness as a place to conduct research and ensuring more efficient patient access to new innovative treatments.

Approach to Clinical Trials on Products without a Marketing Authorisation

EFPIA strongly supports efforts to share the results of clinical trials involving products that have achieved marketing authorisation as well as the results of trials for investigational products with discontinued development programs, regardless of outcome. EFPIA also strongly supports the EMA's position that particularly for trials on medicines without a marketing authorisation, certain documents should be considered to contain significant CCI. In the draft Addendum, EMA has proposed four options for the disclosure of clinical trial information for products without a marketing authorisation (MA).

EFPIA believes that from the four options presented, the optimal proposed approach is a version of option "6.2 Proposal Two: The study specific and product specific documents (with the exception of the IMPD-Q section, which would not be made public at any stage) should only be made public after the earlier of the conditions set out in paragraph 6.5 below are met."[3, 6] Proposal 6.2 establishes clear milestones (i.e., at the time of MA or 9 years after the first summary results for the trial should have been published) for the disclosure of study specific and product specific documents (and therefore at least 10 years after the end of the trial). However, Section 4.4.1.2 acknowledges that product specific documentation (in particular the IB and IMPD S & E) contain CCI but does not provide an opportunity for identifying and redacting CCI which may remain after approval. This potentially compromises CCI in relation to indications under development i.e. outside of the particular indication and /or pharmaceutical form of the marketing authorisation and does not meet the requirements or objectives of the Regulation. EFPIA considers that the details in the IB which can be commercially confidential are not confined to a particular part but may be entered in many different sections and changes over the lifecycle of the product. Thus, the IB (like the protocol) should be treated as one entity for transparency purposes and should not be made public at any time, as detailed in our response to Question 7. It is proposed that Proposal Two, as referenced above, includes a sponsor-led redaction process of product specific documentation, particularly IMPD S&E, prior to release from the EU database.

The proposal described in 6.1 to release these documents at the time of **decision on the trial** may undermine the protection of commercial interests. As such, if this option were implemented, it would likely result in extensive rounds of redaction to remove CCI at this **early stage** thus burdening constrained agency and researcher resources without resultant added public value. This point is of particular importance since the Regulation already includes provisions for a summary of the protocol and the results for most trials to be made publicly available at the time of decision on the trial and within 12 months of last patient visit respectively.

The options listed under 6.3 and 6.4 would be unnecessarily complex to implement requiring a level of system sophistication that could actually delay Database availability. The complexity would only be exacerbated by the increasing number of clinical trials with adaptive design that are often viewed as dual Phase I/II, Phase II/III or Phase III/IV. It could also be anticipated that

[6] The exception for IMPD-Q should likewise extend to answers and assessment report sections.

advances in regulatory science such as use of adaptive pathways could add a further level of complexity for options 6.3 and 6.4. There are transformational changes in science and technology, in general, and it is important that EMA "future proof" the system.

Furthermore, EFPIA is concerned that the approaches presented in 6.3 and 6.4 would result in public availability of detailed results information while the regulatory decision making is ongoing. This release of information could, interfere with the regulatory review process. In summary, EFPIA supports option 6.2 as the most reasonable and pragmatic approach.

Determining Marketing Authorisation Status

EMA also proposes three options for consideration on how the status of marketing authorisation of the medicinal product should be applied since it must be taken into account in deciding which information/documents within the Database should be publicly accessible. EFPIA believes that proposal 1.3 (i.e., "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"[3]) is the only approach that would adequately protect CCI or guard against unintended consequences (e.g. breaches of intellectual property rights that might disincentivise future investment in R&D).

Indeed, information to be released after the MA decision should relate to the authorised indication and/or authorised pharmaceutical form that was studied during the concerned clinical trials. CTA information related to extensions of indication and/or line extensions could be released after the MA decision for this particular indication and/or pharmaceutical form has been rendered. Of note and in direct support of option 1.3, individual indications and particular formulations can be protected by patents that are separate to the composition of matter patent. Early disclosure of information relating to these innovations could adversely impact the ability for a sponsor or researcher to obtain such protection.

User-friendly and Harmonised with International Standards

To facilitate patient access to clinical trial information in a simple and user-friendly manner, EFPIA supports that the information is published through a single EU repository, harmonised with international standards (e.g., ClinicalTrials.gov).

Since clinical trial researchers are often required to submit information on clinical trials in both the EU and United States, EFPIA requests that EMA continues to collaborate and co-ordinate with U.S. regulators as it develops the set of data fields and standards. Developing a system with a set of data fields that will allow for information entry and validation from either database (i.e., EU Portal/Database or ClinicalTrials.gov) to be accepted by the other database will lead to substantial efficiencies for regulators, sponsors and researchers.

Finally, it is unclear if there are intentions to update CSR guidance in the near-term. If this is the intention, given that the content and format for CSRs is covered by ICH guidance, any adjustment would be accomplished through international agreement. Ideally similar harmonisation efforts could also be made in the case of the summary for laypersons.

Alignment of EMA's Policies and Processes

EFPIA believes that the policy for the management of clinical study reports (CSRs) submitted to the EU Database should be consistent with EMA's approach in its Policy 70 and the interaction between the two processes should be clarified. In particular, the draft Addendum does not appear to include any requirements for access registration or terms of use (ToU) of the information within the Database. The draft Addendum remains silent about "how" and under which terms and conditions, if any, the information, data and documentation, which will be included in the EU Database, shall be rendered publically accessible.

These aspects seem in contrast to EMA's recently released Policy 70 on publication of clinical data. Policy 70 requires that all users who access clinical data pursuant to the EMA's new policy agree, essentially, to restrict their use of the data to non-commercial research purposes. The legal rationale for imposing these ToU as explained by the EMA in Policy 70 is to provide protection for sponsors who have generated and submitted the data against unfair commercial use of that data, which necessarily applies equally to disclosures of CSRs and regulatory documents via the EU Database. Likewise, the agreed principles for redaction of clinical reports/regulatory documents as defined in Policy 70, the legal rationale for which is protection of CCI, should be consistently applied to regulatory submissions under the Clinical Trial Regulation. Indeed, we believe that the applicant/MAH/sponsor is best placed to determine whether the publication of such information may undermine the protection of its commercial interests, including intellectual property.

Finally, the management and release of documents submitted to the EU Database should indeed be consistent with the EMA Policy 70, not only in relation to CSRs, but also for publication of other parts of a CTA dossier such as the IMPD E+S sections and IB (e.g. redaction of CCI like certain methods, watermark on downloaded documents), if applicable.

Enable an Efficient System, Balancing Automation with Direct Sponsor Involvement

In keeping with the aim of the new Regulation to simplify processes, the identification of CCI and the process to maintain confidentiality throughout the lifecycle of the product should be simple, proportionate, predictable, clearly communicated, and involve the stakeholder who submitted the data. In the future as CSRs are submitted to the new EU Database, duplication of submissions (full or simplified CSR) at the national level must be avoided consistent with the overall objective of the Regulation to streamline provisions. We agree with the statements in Section 4.4.1 (LL493 – 500), that clinical trial-related documents contain a mixture of commercially confidential and non-confidential information. This point underscores the need for sponsor involvement.

Assess the Overall Value of the System

Based on experiences in enhanced disclosure of information (e.g., EU Clinical Trial Register, Pharmacovigilance information such as PRAC minutes, lay summaries for Risk Management Plans, and added detail in EPARS), all stakeholders should systematically and collectively reflect on the level of impact the disclosed information has on the public and more specifically on patients and HCPs. A thorough assessment should occur within 5 years to help balance the level of detail, complexity and methods of disclosure.

1. Detailed comments

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)*
30-35		Comment: EMA states that "The key instrument to ensure transparency of clinical trials is the new clinical trial portal and database". Please refer to EFPIA's Major Comments under the heading of "Assess the Overall Value of the System" since it's important that the impact of the Database is assessed.	
54-65		Comment: If a Clinical Trials Application (CTA) is withdrawn, before regulatory decision, it is unclear how information would be handled from a disclosure perspective. Having trials registered which, after all, do not take place in the EU could lead to misunderstandings. Proposed Change: Add the following after Line 65 "If a clinical trial application is withdrawn and the trial will not be conducted in any EU country, the information in the database will not be made public."	
80-82		Comment: Please refer to EFPIA's Major Comments under the heading of "Proposed Timeline for Disclosure of Phase I Information and Results". This section includes EFPIA's suggested approaches for deferral of the release of Phase 1 trial summary results.	
156-158		Comment: EFPIA disagrees with the statement that information being made available to the public should be downloadable without requiring further agreement or intervening restrictions. This is inconsistent with EMA's recently implemented Policy 70 as previously mentioned in	

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)*
		EFPIA's Major Comments under the heading of 'Alignment of EMA's Policies and Processes'. Thus, we recommend a statement be prominently displayed, for example with display of search results and when printing or downloading information, that notifies the user that the compound(s), methods of making such compounds, their formulations, methods of administration, dosing regimen, etc. disclosed on the site may be patented and access to information contained in the database does not grant or imply a license to any such patents. Proposed change: EFPIA believes that the text in lines 156-158 should be deleted. However, if the text is to remain at the end of the bullet point, at line 158, the following should be added: "Although viewable, searchable and downloadable, it is acknowledged that the information contained in the database may disclose patented compounds and/or methods. A notice informing users of this fact, and the fact that no licenses are granted with access to such information, will be prominently displayed on the site, for example, with search results and when downloading or printing data."	
232		Comment: In case a MAA is withdrawn and the sponsor plans to resubmit, a delay mechanism for disclosure of trial documentation for a certain period on time must be possible.	
237-240		Comment: As a matter of legal certainty, penalties can only be fairly imposed if the guidance is clear for sponsors on all	

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)*
		aspects.	
252		Comment: Clarification is requested regarding the requirements for the non-EU paediatric Article 46 trials in relation to the Portal and Database.	
294-295		Comment: The draft Addendum notes: "Rules to operate in an automatic way using the fields in data or metadata". Please refer to EFPIA's Major Comments under the heading of "Enable an Efficient System, Balancing Automation with Direct Sponsor Involvement". We understand that extensive and systematic redaction would be resource intensive and the proposal is that information will be entered in the database using a Structured Data Set, in a way that it will be marked to be disclosed or to be protected. However, full automation may reduce the level of flexibility that may be required in specific situations (e.g., when there is an overriding public health interest). A focus should be on achieving the right balance between the operational burden on sponsors to duplicate the entry or submission of data that has already been provided as part of the CTA documentation into structured data fields or notifications within the EU Portal/Database and the need to automate processes to achieve an appropriate level of transparency without compromising CCI and PPD. Therefore, a flexible system is recommended to balance these factors. For example, there could be a process to allow a manual override in exceptional circumstances to prevent	

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)*
		disclosure of information that normally would be automatically disclosed.	
313-317		Comments: The status of the EU Clinical Trials Register following implementation of the Portal/Database is unclear. This should be clarified and there should be a streamlined mechanism to fulfil the objectives of the CT Regulation.	
322-324		Comment: There is an extensive list of data that is proposed to be released as part of the 'main characteristics of the trial', EFPIA considers that the totality of these 'main characteristics' will already essentially provide a summary of the protocol. It is therefore questionable as to why there also needs to be a separate protocol summary to be provided and released at the time of the decision on the trial.	
328		Comment: The *[date of]* the start of the trial will not necessarily be known at the time of the decision on the trial; sponsors have up to 2 years to start a trial in a MS after a decision on the trial has been made and 15 days to make a notification in the database after the trial has started in each concerned MS. The proposal should note that the *[date of the]* start of the trial in a MS will be notified within 15 days of the start of the trial in each concerned MS.	
359-361		Comment: These lines incorrectly suggest that Article 81(6) addresses the **making public** of personal information included in the database. Article 81(6) states that "The EU database shall **contain** personal data only insofar as this is necessary for the purposes of paragraph 2" [emphasis added]. The latter paragraph states that the database should: enable	

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)*
		cooperation between competent authorities of the Member States, facilitate communication between sponsors and Member States; enable sponsors to refer to previous clinical trial applications; and enable citizens to have access to information on medicinal products. It is not clear that any of these purposes justifies public disclosure of personal information that is necessarily contained in the Database. The EMA should provide guidance on what exactly will be considered 'personal data', as this differs in the Privacy Laws of the Member States. The definition of personal data in Reg. 45/2001, i.e. "any information relating to an identified or identifiable natural person" may not provide enough specificity in this context. EMA Policy 70 also states: "both identification and re-identification of patients need to be avoided". Proposed change: "Personal data (other than trial subject data which are not included in the database) <u>are</u> included in the database ~~are made public~~ only to the extent required for application of <u>Article 81(2) of</u> the Regulation (Article 81(6))."	
382-410 Question 1		Comment: The proposal enhances the level of sites information available for patients and care givers looking for clinical trials. As mentioned above, EFPIA supports the increase of awareness about clinical trials and their location and believes it is important to enhance recruitment timelines, and contribute to acceleration of the clinical development cycle.	

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)*
		However, EFPIA is concerned that the draft Addendum requires that the name and position of the investigator or principal investigator in charge of the trial at a site and their CV be included in the database and publicly disclosed. The investigator's agreement is required to allow any personal information to be made public. Furthermore, the need for publication of investigator CVs is questionable. EMA comment that CVs should be made public as they document the qualification of the investigator to conduct the trial. This information will have been reviewed by Member States, who are more appropriately placed to assess investigators' suitability. Thus, there is no need for this information to be released.	
411-416 Question 2		Comment: per article 9(1) - Persons assessing the application: "Member States shall ensure that the persons validating and assessing the application do not have conflicts of interest, are independent of the sponsor, of the clinical trial site and the investigators involved and of persons financing the clinical trial, as well as free of any other undue influence". EMA propose that personal information on MS experts will not be made public. Rules applying for the Member States personnel in charge of assessing or inspecting the Clinical Trials in terms of qualification and economic interests that might influence their impartiality should equally apply for the CT Investigators and their staff.	
417-425		Comment: In line with current practice, EFPIA agrees that	

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)*
Question 3		general or central contact information (such as site phone or site email) should be made available to the public at the time a decision on a trial is made. This would permit the public to contact the sponsor about a trial. As a matter of security there should not be disclosure of individuals' names or other personal information (e.g. name, direct email address or phone number). If the name of the project leader of a clinical trial is provided in the protocol, it should be redacted. This condition should likewise be consistently reflected in Appendix 1 – C.1.3.	
426-436 Question 4		Comment: Disclosing names of investigators listed in the CSR at the time of CSR posting (i.e., 30 days after MA) would seem to be consistent with the objectives, provided that the investigators have given their agreement (see also response to Q1 and comment on lines 359-361). However, the redaction or retention of any other personal information in CSRs before submitting the CSR to the Agency as part of Policy 70 (and subsequently that same redacted CSR would be the one submitted to the EU Database) should be elaborated and subject to further discussions. In addition, EFPIA proposes that no personal information be made public on MAH/applicant personnel identified in the CSR. This includes the names and position of CSR authors (CSR Section 6). While EMA's proposal seeks to provide privacy to trial subjects, it does not afford the same privacy to company employees. Since clinical and nonclinical research can 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)*
		sensitive area, EFPIA has significant concerns regarding public release of this information.	
437-446 Question 5		Comment: See response to Question 3.	
462-466		Comment: Please note that the nature of the sponsor organisation conducting the trial may be important for determining what may be commercially confidential.	
480-484		Comment: An overriding public interest should not be considered "the general public interest in having information made publicly available." If that were the case then there would not be a need for an exception because this general interest would exist in every case, meaning that CCI would never be protected. Such a broad reading of the public interest in effect reads the exception out of the rule. Rather, someone seeking disclosure in the case where CCI as defined at lines 457-59 is shown to exist should have to put forth a specific public interest in disclosure applicable to the CCI at issue.	
485-490		Comment: We suggest that the Database functionality and decision making processes to be applied when invoking the use of "overriding public interest" should allow for consultation with the sponsor prior to disclosure of CCI. Such a consultation will ensure a balanced decision that takes into account any risk of loss of CCI; there should also be an opportunity for appeal of the decision before the information is made available.	
584-609		Comment: Please refer to EFPIA's Major Comments under the	

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)*
Question 6		heading of "Determining Marketing Authorisation Status". As explained in detail under our 'Major Comments', EFPIA believes that proposal 1.3 (i.e., "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") is the optimal choice.[7] Proposed change: The disclosed information should likewise be specific to the actual 'dosage strength' within the marketing authorisation.	
610-642 Question 7		EFPIA fully agrees with the EMA's proposal and reasoning that the IMPD-Q section on IMP Quality and related lists of questions, responses and assessment report sections should be considered commercially confidential and not be made public for any trial at any time. However, in addition, EFPIA believes the same arguments against the release of these documents, at any time, should equally apply to the IB. In particular: 1. IBs are not connected to any specific clinical trial, do not give a lot of details about any given trial, are not included in Marketing Authorisation Applications (MAAs), and are not used by EMA as part of their evaluation of MAAs.	

[7] However, if EMA were to adopt a proposal other than 1.3 for the definition of marketing authorisation, then there would need to be additional protections in place for CCI for indications, formulations or strengths still in development. In this case, the triggers for timing of publication related to Question 10 (lines 709-721) may not provide adequate protection of CCI on new/future pharmaceutical forms or indications included in the study or product specific documents."

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)*
		2. IBs are not tied to a single MAA; they are often connected to a number of MAAs over a period of years. It can well happen that the first MAA (i.e., the fastest indication to market) is not the most important. The CCI that warrants for not disclosing an IB before the first MAA, should also apply to follow-up MAAs. 3. As pointed out in § 4.4.1.2 b), IBs contain extensive details of a commercially confidential nature, they have to be updated on a yearly basis and therefore are very difficult to redact. 4. International regulations require Industry to maintain a single IB including all indications and forms of a compound so long as the efficacy and safety profiles are related, even though these different forms would be approved and marketed as separate products. For example, an IB for a product already on the market will as well keep information for a new route of administration which is still in Phase I and years away from filing an MAA. All of the latter information would have to be considered CCI, and the two are not easily separated. 5. The purpose of transparency as set in the objectives of the Regulation (EU) 536/2014 will be achieved via the dispositions that will allow all the main characteristics of clinical trials and a summary of their results that are encompassed in a given compound IB to be accessed through the Portal and Database. Proposed change: We therefore believe that the § 4 of section	

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)*
		4.4.3 (lines 636-640) should also mention the Investigator Brochure as follows: "*Regardless of marketing authorisation status, the IMPD-Q section on IMP quality and the related lists 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, as this deals with the manufacturing and related pharmaceutical development information which continues to be CCI, indefinitely, post marketing authorisation*". *Likewise, the Investigator Brochure, given its product specific nature, the fact it presents a detailed and permanently updated development summary for the compound is therefore extensively filled with up-to date CCI and should not be made public for any trial, at any time.*	
643-654 Question 8		Comment: EFPIA agrees with the EMA information on Phase IV trials may contain CCI (e.g., exploratory endpoints). Therefore EFPIA advocates that clinical trials with authorised products be treated by default the same as Phase I-III trials rather than to systematically disclose study-specific information (e.g., full protocol) at the time of decision on a CTA. Also, of note, some Phase IV trials (low-intervention or "real-world" trials) run for a long time and interim reports may be prepared before the actual end of the trial. In this case, disclosure of trial information should be deferred until the time that the summary of final trial results is made public. There is a need to clarify in the Addendum the principles on which this deferral will be granted (i.e., based on a request by the	

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)*
		sponsor, acceptable justification).	
655-708 Question 9		Comment: EMA proposes four options for clinical trials on products without an MA. Please refer to EFPIA's Major Comments under the heading of "Approach to Clinical Trials on Products without a Marketing Authorisation" for our full rationale as to why Proposal 2 under 6.2 is the optimal approach.	
709-725 Question 10		Comment: EFPIA questions the proposed requirement to make study- and protocol-specific documents submitted to the clinical trial database public where no MAA is submitted. A compromise to consider would be to recommend the use of abstracts as a means of achieving a more minimalistic form of disclosure. In this way, transparency regarding the trials conducted would still be achieved.	
726-746 Question 11		Comment: As explained in EFPIA's Major Comments under the heading of 'Proposed Timeline for Disclosure of Phase I Information and Results', EFPIA appreciates EMA's acknowledgement of the potential for particular commercial sensitivity of Phase I trials and the possibility to defer the disclosure of information to be made public at the time of decision on the trial. As outlined, EFPIA also proposes a path forward.	
747-752 Question 12		Comment: EFPIA believes that the proposal meets the requirements that this information should not be published and agrees with the rationale provided by the EMA in its proposal.	

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)*
		Furthermore, it is also worth noting that the aggregated compensation data collected and published as per the HCP EFPIA code or Member states national specific requirements on transparency (or rules of publication of contracts) should provide adequate information in this respect.	
753-762 Question 13		Comment: EFPIA agrees with the EMA proposal that the draft AR will not be submitted through the Portal to the Database nor made public.	
778-796 Question 14		Comment: EFPIA is concerned that the EMA proposed disclosure of inspection reports is too broad. Only site information and a brief conclusion should be disclosed to the public. Information should not be disclosed where this would undermine the confidence in the purpose of inspections, investigations and audits – full disclosure without context may be misleading for the public and undermine confidence in the inspection and regulatory system. In Europe, similarly with other major regulatory agencies, information should be limited such as to the investigator's name, site (city), date and type of inspection without naming the study. In case of sponsor inspection, information should be limited to the date and the type of inspection. Question 14 appears to refer to Member State inspections carried out in context of the of the CTA or MA procedure, According to Article 53, the CTA applicant is also requested to submit through the Portal all inspection reports from third countries. It is assumed that reports from third country	

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)*
		authorities are not disclosed, as they would require consent. At present the EMA proposal states that inspection reports shall be redacted by the responsible inspectorate. In line with EFPIA's Major Comment under the heading 'Enable an Efficient System, Balancing Automation with Direct Sponsor Involvement', the process for redaction should involve the sponsor.	
797-802 Question 15		Comment: EFPIA agrees with the EMA proposal. The report on Union Control is in the public interest and the Commission will be able to redact CCI and PPD. It should be made public in line with the principles set out in accordance with the exceptions under Article 81 (4). The same approach as for inspection reports (Question 14) could be used when providing public information.	
803-843 Question 16		Comment: During the process, disclosure of serious breaches may jeopardize countries' ability to act per the article 81(4)(d). For this reason, it is important that serious breaches are not disclosed until after they have been investigated and the conclusion has been reached. Under point 1.6, it should also refer to exception 81(4)(d). In terms of information made public once the action plan has been set up and the breach has been solved, this information should be limited to the site and study concerned, a factual description of the serious breach and corrective actions. Industry should be afforded the opportunity to comment on	

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 format and content of the template that will be implemented EU-wide for the reporting of serious breaches, to ensure consistency with current practice.	
844-858 Question 17		Comment: An unexpected event should not be disclosed during the assessment process. In some instances, it could be seen as part of the normal procedure of CTA modification to be implemented after approval. The EU Database/Portal should have a path allowing linking of serious breaches, Urgent Safety Measure (USM) and unexpected events (e.g. an unexpected event leading to a USM).	
859-872 Question 18		Comment: Please refer to EFPIA's Major Comments under the heading of "Alignment of EMA's Policies and Processes". The policy for the management of CSRs submitted to the EU Database should be consistent with EMA's approach in its Policy 70 and the interaction between the two processes should be clarified. The draft Addendum appears to give confusing messages on what needs to be submitted as part of a CSR once the product has received an MA. Line #861 states, "Clinical study reports including all appendices [emphasis added] except those listing individual patient data, will be submitted to the database", Appendix 7 of the draft addendum provides a list of the CSR appendices to be submitted, EMA's Policy 70 requires a different set of appendices to be submitted; consistency is needed. EFPIA proposes that the requirement to submit CSRs to the EU database should be aligned with Policy 70. Thus, the CSRs (and their appendices) that EMA has determined will 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)*
		released under Policy 70 should be the same CSRs (and appendices) that are to be submitted to the EU database. As there will be duplication of submitting CSRs to the EMA, over time, EFPIA strongly recommends that a process be implemented to streamline and make consistent the CSRs submitted as part of the MAA process, considering the EMA should avoid unnecessary duplication between EMA systems as per Art 81 (2) '...and hyperlinks shall be provided to link together related data and documents held on the EU database and other databases managed by the Agency. If applicable, the redaction principles (CCI) laid down in the EMA Policy 70 for certain parts of Module 2 and 5, should also be relevant to parts of IMPD Efficacy and safety section (e.g., certain innovative methods, bioassays, immunogenicity assays).	
861-870		Comment: It is unclear if there are intentions to update CSR guidance in the near-term. If so, EFPIA supports the concept of developing guidance outlining the information, data and documentation that may contain CCI, prior to them being loaded into the system. If this is the intention, given that the content and format for CSRs is covered by ICH guidance, any adjustment would be accomplished through international agreement. EFPIA would welcome the opportunity to work with the EMA in progressing this idea.	
895		Comment: Please refer to EFPIA's Major Comments under the	

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)*
Table 2, Section 4.3		headings of "Enable an Efficient System, Balancing Automation with Direct Sponsor Involvement" and "User-friendly and Harmonised with International Standards". Also, the draft Addendum states that a manual override may be used to remediate errors where information has been published contrary to the established rules, or where data processing errors have occurred. The inefficiencies associated with remediating errors could be reduced if the system provided a means of enabling sponsors to preview a public representation of the data and documents that would be published in the future. According to the functional specifications document, the public interface will allow queries and download functionalities. Similar to the EMA Policy 70 on proactive disclosure of Module 2 and 5, EFPIA recommends that a watermark is applied (at least to IMDP section E+S)? "The protocol synopsis and protocol should be separate and have different publication rules applied to each. " It is assumed that "protocol synopsis" is referring to the protocol summary to be made public by default after CTA decision. As stated in our comments to Lines 322-324, information for the synopsis should come from the relevant fields of the CTA form. Within this table and throughout the document, EMA uses	

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)*
		several terms for a product such as "therapeutic" and a combination term "therapeutic/prophylactic". Since vaccines are not (generally) considered therapeutic, the combination term could be used throughout the document or it could be defined/footnoted at the beginning of the Addendum.	
895 Table 2, Section 4.3		Comment: In terms of technical standards, the draft Addendum states that the "system should identify all data and documents in the EU database regarding their public or non-public status and any timeframe/event to trigger that publication, and include the necessary rules to ensure their availability at the required time." To improve predictability and clarity for the sponsor, EFPIA recommends that the Database schema be published, documenting the unambiguous business rules applied to disclosure of individual fields and documents with the associated timing for release. In addition, EFPIA is concerned that there is no auditable requirement to ensure the system is adequately secured. EFPIA, therefore also recommends that as a part of the evidence provided to the auditors of the CT Portal/Database, the EMA should provide results of independent penetration testing of the system.	
Appendix 1 D.3.11.4 Page 20		Comment: For explorative combinations (including biomarkers), encompassing phase I and phase IIa, patents may not be in place and information should be considered CCI. The disclosure should be delayed until a confirmatory trial is available or later.	

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)*
Appendix 1 E.6.10 Page 31		Comment: Pharmacogenetics are explorative (potentially retrospectively) modelling and pattern recognition. The decision disclosure should be delayed until a confirmatory trial is available or later.	
Appendix 1 E.8.6.2 Page 37		Comment: Trial being conducted completely outside of the EEA: if the trial is conducted completely outside the EEA, there is no EU decision on the trial as no application has been made.	
Appendix 1 N Page 47		Comment: Ethics committee opinion (per Member State) is listed in the information to be disclosed. This is not relevant for the functioning of the CTR given that we expect the AR for Part I, AR for Part II and Decision per Member State. Proposed change: Replace 'Ethics Committee Opinion' with 'Conclusion on Part II of the assessment'. Also, regarding the AR for Part I, in order to protect commercial interests of the sponsor/MAH, public information should be limited to the outcome i.e., 'the conduct of the clinical trial is acceptable', 'is acceptable under conditions' or 'is not acceptable'.	
Appendix 2 E Page 51		As per comments to line 636-640, the row regarding IB should be turned to red, indicating that it will not be made public due to CCI.	
Appendix 2 page 53		Comment: Reference is made to the "EMA SAWP public information", which refers to EMA advice only. In some cases meeting minutes from third country HA advice might be part of a CTA dossier. It is assumed that this data will not be made public.	
Appendix 7		Comment: All sections and appendices of the CSR are marked	

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 "Green", indicating that they will be made public. Only those appendices required under EMA's Policy 70 should be submitted to the database (see also response to Q18). In support of this position, it should be noted that the following sections and appendices of the CSR will contain personal information that must not be disclosed to the public: 6 Investigator & Study Admin Structures; 16.1.3 List of IEC / IRBs; 16.1.4 List of investigators 16.1.5: Signatures In addition, it should be noted that full transcripts of publications in appendices 16.1.11 and 16.1.12 are subject to copyright, and so should not be made public through the Database.	