Draft advice to the European Medicines Agency from the clinical trial advisory group on legal aspects

Comments to draft final advice

Victoria Kitcatt
European Federation of Pharmaceutical Industries and Associations (EFPIA)

Line no.	Comment and rationale; proposed changes (if any)
General comment	EFPIA acknowledges that the draft advice document summarises the various representations and submissions of the participants in the Legal Aspects Advisory Group. Given the divergence of views expressed in the course of this exercise, it will be understood that EFPIA necessarily disagrees with some of the arguments presented in this document, especially in the section between lines 47 and 141, which we believe misunderstand and/or misrepresent the legal position, in several respects. As (non-exhaustive) examples, in lines 94-95 it is stated that pursuant to Regulation 1049/2001, MA applicants should have been aware at the time of submission that the MAA dossier "can be accessed upon request and thus available in the public domain". This ignores the fact that (a) the right to access under the Regulation is circumscribed by certain exemptions and does not equate to the whole dossier being made available to the public in general, and (b) the EMA has significantly changed its policy in recent years in relation to requests for access to the data in question. As a further example, in lines 138-139, it is stated that: "Contractual obligations entered into by sponsors cannot prevent disclosure as regulatory requirements can override specific clauses in informed consent forms." EFPIA strongly refutes that any specific regulatory requirements exist in the context of public access to data, such as to override the terms of the consent given by patients in clinical trials, which must otherwise be fully respected. In the circumstances, EFPIA assumes it is not appropriate to comment in detail on the parts of the document which summarise the submissions of other participants in the advisory group process; however this should not be regarded as acceptance on EFPIA's part of these points.
7	Comment: Clarify that the temporal scope of disclosure, which is the subject of this advice, is only after the grant of the MA or variation application. Proposed change (if any): Add "after grant of the Marketing Authorisation (or variation)" after "data".
28	Comment: Rewrite "without first consulting the MAH;" Proposed change (if any): "without respecting the commercially confidential status of the information, and also

Line no.	Comment and rationale; proposed changes (if any)
	separately consulting the MAH;”
32	Comment: Expand sentencing starting "However, many participants . . . ." Proposed change (if any): "However, disclosure of marketing authorization information, implemented irresponsibly, can likewise jeopardize patient privacy,reduce incentives for biomedical research and hamper innovation, abrogate intellectual property rights as well as recognized treaty obligations, and interfere with the regulatory new medicines approval process, in a manner contrary to the public interest. Many participants agree on the need for a balance between transparency and protection of confidentiality, intellectual property, commercially confidential information, and personal data."
34	Comment: Rewrite paragraph for clarity. Proposed change (if any): "Whereas some have defended that clinical-trial data contain no commercially confidential information that should prevent its proactive publication, others have opposed this view. Parties taking this latter position point out that confidential commercial information consists of information that a company protects from release because if it were released it could provide competitors a commercial advantage, and also point out that information in marketing authorization dossiers fits this definition. These parties also assert that an individual assessment and a consultation with the marketing authorisation holder (hereinafter, the MAH) should be conducted to allow the MAH to express its views before publication, and that these views must be respected by the regulators. This would strike a balance between transparency and the rights of industry and patients to have their confidential information protected."
94-95	Comment: See general comment above
138-139	Comment: See general comment above
151	Comment: Add additional text for completeness Proposed change (if any): after "innovative medicines", add "proprietary information regarding efficacy and safety measurements and statistical analyses; and"
155	Comment: Add additional text Proposed change (if any): After "public." add sentence "This framework reflects the common and well-accepted proposition that Commercially Confidential Information consists of information that a company protects from release because if it were released it could provide competitors a commercial advantage."

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158	Comment: Add additional text Proposed change (if any): after "know-how," add "commercially confidential information,"
159	Comment: Add additional text Proposed change (if any): after "incurred in" add " developing novel medications"
161	Comment: reword "competitors" Proposed change (if any): "competing innovators or generic companies"
161 to 166	Comment: delete text Proposed change (if any): Delete "Lack of protection would as a result lead to impeding innovation and an increase of clinical trials conducted in third countries with a view to safeguarding innovation and intellectual property. This would also contradict the main objective of the current Commission proposal on clinical trials (COM(2012) 369), namely to improve the legal framework for clinical trials within the EU in order to increase the number of trials performed within the Union and to support clinical research and development."
168	Comment: reword for clarity Proposed change (if any): "that there exists a general presumption that documents submitted by a party pursuant to a specific administrative procedure, and their confidentiality under Article 4(2) of Regulation 1049/2001, should be"
192-209	Comment: delete text Proposed change (if any): Delete the following: "The Court has also acknowledged that where applications for a marketing authorisation in the abridged procedure are concerned, national authorities do not disclose clinical data to patients and therefore do not prejudice its confidentiality (Case C-457/10 P): As regards the appellants' argument that AZ still held exclusive rights over the clinical data in the file which were still confidential, that argument fails to have regard to the fact that, as the General Court observed at paragraph 681 of the judgment under appeal, Directive 65/65 in any event created a limitation to those alleged rights by establishing, in point 8(a)(iii) of the third paragraph of Article 4 thereof, an abridged procedure which, after the expiry of a period of

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	exclusivity of six or ten years, allows the national authorities to rely on that data and the manufacturers of essentially similar medicines to benefit from its existence for the purposes of being granted a MA. The General Court was therefore fully entitled to find, at paragraphs 670, 674, 680 and 830 of the judgment under appeal, that Directive 65/65 no longer gave AZ the exclusive right to make use of the results of the pharmacological and toxicological tests and clinical trials included in the file (paragraph 151). Moreover, in so far as the national authorities do not disclose that data to applicants in the context of the abridged procedure, the finding of the second abuse, as the Commission points out, does not result in competitors being granted access to the clinical data and does not prejudice its confidentiality (paragraph 152)".
209	Comment: A legal argument against proactive disclosure is that Regulation 1049/2001 requires an application for access to a document held by the EMA. One the one hand, it might be regarded as a formal requirement that can easily be circumvented by making requests under the Regulation (see also CTAG5 – draft advice, p. 2, arguments in support of proactive disclosure, lines 50-57 "Consistency with the Regulation 1049/2001"). On the other hand, it is a procedural step required by the Regulation that provides the opportunity to control the process of disclosure e.g. to identify the party making the document requests; to assess the documents requested case-by-case; to inform the MAH and allow the MAH to object prior to disclosure and take legal remedies, etc. Proposed change (if any): "A consistent approach with Regulation 1049/2001 should be adopted whereby, first, the Agency should install a procedural step to control the process of disclosure before any data will be made publicly available; second, the Agency should not assume that data is not commercially confidential without considering the data on an individual basis; the MAH's assertions regarding the commercial sensitivity of the information must be carefully considered; and third, it should judge whether or not there is an overriding public interest in disclosure, for which the purpose of the request and the ability to prevent subsequent improper use following disclosure, is critical to determining the public interest in disclosure/publication."
213	Comment: Comment: Consultation with the MAH is an important step in assessing whether or not data submitted in the authorisation process contain commercially confidential information. Proposed change (if any): Add "In light of the presumption that MA dossiers may contain commercially confidential information, consultation with the MAH on a possible disclosure is always needed, in line with Article 4(4) of Regulation (EC) 1049/2001, unless the MAH in advance indicates that there is no confidentiality concern."
222	Comment: Clarify text Proposed change (if any): Delete "Information contained in clinical trial studies is" and replace with "clinical study

Line no.	Comment and rationale; proposed changes (if any)
	reports and other information are”
224	Comment: add text Proposed change (if any): after "where no" add "meaningful"
228	Comment: rephrase "competitors” and geographical scope for clarity Proposed change (if any): delete “competitors, either in the EU or elsewhere” and replace with "innovators or generic companies, especially outside the EU"
229	Comment: Add additional text Proposed change (if any): After sentence ending in "absence of such rules" add: "Specifically, a competitor could use the publicly disclosed information to submit their own full marketing authorization application for the same medication, rather than developing a generic medicine and submitting an abridged application."
234	Comment: delete text Proposed change (if any): delete "(e.g. generic companies)
249	Comment: add text Proposed change (if any): At the end of the sentence, add: “, and whether disclosure advances science and public health.”
251	Comment: rephrase sentence starting "Competitors can use this data” Proposed change (if any): "Competing innovators and generic companies can use this data to benefit from the efforts of the MAH, to avoid conducting their own clinical trials, and to obtain a marketing authorisation either in the EU or elsewhere."
253	Comment: delete text Proposed change (if any): Delete "The Agency should adopt a proportionate approach whereby information of a commercially confidential nature or such that could prejudice intellectual property rights should not be disclosed unless a genuine overriding public interest is present."

Line no.	Comment and rationale; proposed changes (if any)
255	Comment: add text Proposed change (if any): Add at end of paragraph: "There is no public health benefit or interest in disclosing clinical trial data to requestors who intend to use such information for commercial purposes that is sufficient to outweigh the public benefits that are achieved by protecting commercially confidential information from disclosure."
256	Comment: rephrase the paragraph for clarity Proposed change (if any): "Access to clinical-trial data could be provided within an appropriate framework that serves the public interest in information about approved medicines but that also ensures (1) the data are not inappropriately used in the EU or elsewhere and (2) data privacy, intellectual property rights, and the protection of commercially confidential information are fully respected. The terms of such access should be based in each case on the nature and purpose of the request and must include safeguards (including consultation with the MAH) to prevent commercially confidential information, patients' sensitive personal information and intellectual property rights from being undermined by further disclosure and use of the data."
264	Comment: Add text for accuracy and clarity Proposed change (if any): Before "Regulation 726/2004", add "EU pharmaceutical legislation including".
266	Comment: add text Proposed change (if any): Add at end of paragraph: "In addition, the significant results of a clinical trial are frequently published in academic and medical journals by the principal investigators."
308	Comment: add text Proposed change (if any): After sentence ending "provided in the MAA" add: "Once information in MAA is disclosed, it becomes "prior art" and cannot later serve as the basis for an invention and patent application. Thus, marketing authorization applicants would no longer be able to use the currently confidential information to obtain patents for the inventions relating to the information in a MAA if the MAA is disclosed to the public."
316	Comment: rephrase paragraph for clarity Proposed change (if any): "Proactive release of this information will lead to the publication of numerous third party and

Line no.	Comment and rationale; proposed changes (if any)
	in some cases unreliable, contradictory, or unsubstantiated analyses as well as conflicting messages. Confusion could mount among medical practitioners if unsubstantiated or simply incorrect assertions regarding the safety and efficacy of medicines find their way into the public domain."
320	Comment: rephrase for clarity Proposed change (if any): "The Agency must respect the legitimate expectations of applicants who, at the time of submitting their applications for the sole purpose of obtaining approval, had no reason to expect that the Agency would later decide to disclose part of the MAA."
324	Comment: clarify text (reposition the word "new") Proposed change (if any): "Therefore, the Agency's new policy should only affect data submitted after its adoption."

Christiane Abouzeid and Lincoln Tsang
BioIndustry Association

Line no.	**Comment and rationale; proposed changes (if any)**
	Comment: BIA provides the following general comments to re-iterate the need to adopt a balanced approach to public access to clinical trial data: The Public Access Regulation should be proportionately applied. The current debate on proactive publication should be considered in the broader context so that EU remains competitive in this globalised knowledge based economy. • Focus has been placed on the public interest to gain access the data contained in regulatory submissions. Equally, it is in the public interest that EU has a vibrant and competitive life sciences sector where the private rights are respected and protected to encourage innovation. • Right to public access to documents held by EMA should be balanced against the data owners' rights to ensure that commercially sensitive information is not disclosed as this will seriously undermine its commercial interests and competitive position. • The information found in any regulatory submissions contains commercially sensitive information about the

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	roadmap to research and development of an innovative medicine. The R&D corporate strategy would not ordinarily be disclosed by the company to a third party. • Transparency in the regulatory decision-making has already been in operation since 2004 through the need to publish summary basis of product approval or refusal in the form of a public assessment report. This requirement strikes a right balance of ensuring transparency in decision-making whilst recognizing that the dossiers contain commercially sensitive information • 62% of the patients in pivotal trials submitted in marketing authorisation applications (MAAs) to the Agency between January 2005 and December 2011 were recruited outside of the European Economic Area (EEA) and Switzerland (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/04/news_detail_001758.jsp&mid=WC0b01ac058004d5c1). [New policies should support sponsors to conduct clinical reserach in the EEA and not further jeopardize such research] Proposed change (if any):

Florence Vandevelde
PRESCRIRE

Line no.	Comment and rationale; proposed changes (if any)
30	Comment: cf. my comments at each meeting and our written submission Proposed change (if any): Please add: "and consider that clinical trials data, which are scientific data, represent a public good. They point out that clinical trials' participants put themselves at risk of unexpected adverse drug reactions in the hope that their contribution will benefit the advancement of science."
32	Comment: Transparency allows for much more than fostering innovation; during the meetings many public health issues where discussed to justify the request for more transparency. As Prescrire's representative, I also insisted on the need to have access to clinical trials data not only of research purposes but also for the provision of reliable information to health professionals and to the public.

Line no.	Comment and rationale; proposed changes (if any)
	Proposed change (if any): after "development of new medicines", add: "but also to foster the robustness and reliability of clinical trials, to limit selective reporting (reporting of the results which are the most favourable to the product), to protect public health by allowing earlier detection of safety signals". And add: "It was pointed out that the aim of transparency goes beyond reanalysis purposes. For example, drug independent bulletins need full information of clinical trials not for research purposes but for education purposes in health areas. A watchdog activity is highly useful to citizens and also for drug regulatory bodies."
32	Comment: maybe usefull to specify in brackets who are those participants? Proposed change (if any): (industry and their representatives)
32	Comment: The same people were always talking but were not that many Proposed change (if any): replace "many" by "some"
35	Comment: Proposed change (if any): after proactive publication, add: "as did the European Ombudsman in previous rulings, and they emphasied that even if it were the case, an overriding interest, namely public health, would suffice to justify disclosure. The Declaration of Helsinki requires public disclosure of clinical trials results."
38	Comment: In our written comments, we contested this approach: the Agency's mandate is to regulate pharmaceutical industries, not to "obey" to Marketing authorisation holder instructions. Proposed change (if any): delete "this would enable to strike a balance (…) protected" because it gives the impression that the Agency already decided to consult with MAH
39	Comment: Several participants (at least Trudo Lemmens and I) requested industry for concrete examples of what clinical data could fall into the "commercially confidential" category according to them, and not a single example could be given. We (Prescrire) wrote in our written contribution "pharmaceutical industry representatives failed to give concrete examples for exceptional circumstances under which data can be claimed to be commercially confidential." Proposed change (if any): Add: "Despite questions, oponents to disclosure did not give any concrete examples for

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	exceptional circumstances under which data can be claimed to be commercially confidential according to them."
42	Comment: Prescrire's presentation at the end of our written submission made it clear that disclosure is important to us because of our education work in health areas Proposed change (if any): after "scientific knowledge", add "including for education purposes in health areas"
43	Comment: In the 2nd meeting, it was specified that post-efficacy and post-safety studies results fall into the scope for the proactive disclosure Proposed change (if any): Please add the above sentence, from the minutes of the 2nd meeting: "[It was precised that] the scope for the pro-active disclosure would be CTd submitted for marketing authorisation assessment, including raw data, and would include the life-cycle of the product, i.e. authorisation, supervision and other regulatory procedures [including post-efficacy and post-safety studies results"
58	Comment: We never said or wrote that "clinical-trial data should not be published"!!! (cf. the minutes of the 2nd meeting: "Other participants, on the contrary, pointed out that industry should first establish what info contained in CTd should be held as CCI, and on what grounds. The EMA would then decide on the basis of a pre-defined set of conditions, which should apply temporarily and not indefinitely."); and in our written contribution we wrote: "Any exceptions to freedom of information should require a detailed substantiation by the sponsor that there would be an "unreasonable degree of prejudice to the commercial interests if the information would be disclosed" based on objective elements for justification. It should be done at the time when the sponsor provides the Agency with the data, never apply to an entire document (only the concerned parts or figures can be blacked out), and should only be granted on a temporary basis notified to the requesting person." Proposed change (if any): - delete "Even if it was accepted that clinical-trial data should not be published"; - replace the 1st sentence by the sentence from the minutes of the 2nd meeting: ["If sponsors claim that the clinical trials data contain commercially confidential information"], "some participants pointed out that industry should first establish what info contained in CTd should be held as CCI, and on what grounds. The EMA would then decide on the basis of a pre-defined set of conditions". - complete the 2nd sentence by: "; this duration should be notified to the requesting person."

Line no.	Comment and rationale; proposed changes (if any)
109	Comment: The sentence "It will also be beneficial to inform their decisions" refered to health professionals being able to make more informed decisions if they have access to full evidence Proposed change (if any): "It will also be beneficial for health professionals to have access to reliable information based on full evidence, allowing them to choose the best available option among those available"
148	Comment: The examples given focus on control proceedings and manufacturing so the subtitle "a. Existence of commercially confidential information" should be modified as follow: Proposed change (if any): "Existence of commercially confidential information in the area of control proceedings and manufacturing" and add: "Some" before "Clinical trials data are confidential"
221	Comment: We are very surprised by the peremptive tone of the whole paragraphs d. and e. It gives the impression of copy pasted arguments from industry submissions and that the content of the submissions are endorsed by the Agency. A rewording is needed, to show a little bit more distance Proposed change (if any): Replace "must" by conditional forms ("should" or "could"); line 248 delete "vital" (to be replaced by "found to be important by industry participants") Add reference to the Australian legislation so that the information can be checked; Add references about the accusations of generic companies, so that the information can be checked. In case no reference is available, it would be better to delete these examples. NEW LINE (SORRY I CAN'T ADD A NEW LINE) Part 3. Legal remedies Line 358 Comment: In our written comments, we contested this approach: the Agency’s mandate is to regulate pharmaceutical industries, not to "obey" to Marketing authorisation holder instructions. please add the sentence from the 2nd meeting: "Some participants pointed out that industry should first establish what info contained in CTd should be held as CCI, and

Line no.	Comment and rationale; proposed changes (if any)
	on what grounds. The EMA would then decide on the basis of a pre-defined set of conditions".

Mark Barnes and David Peloquin
Harvard Law School and Ropes & Gray LLP

Line no.	Comment and rationale; proposed changes (if any)
1	Comment: Restrictions on Content of Clinical Study Reports: The EMA has indicated that it could consider restrictions on the content of clinical study reports (CSRs) submitted in support of a marketing authorization. For instance, the EMA suggested that pharmaceutical companies would likely be strongly discouraged from discussing additional indications for use of a drug in the reports. Such a policy is problematic because it infringes on the free speech rights of pharmaceutical companies to inform government about additional indications for use of a drug in the CSR. If the EMA is going to require CSRs to be made publicly available, it will need to live with the consequence that some of the information disclosed may be of a type that the EMA would have preferred to keep out of the public domain as direct representations from industry sponsors of clinical research. Proposed change (if any):
2	Comment: Challenges to EMA's Decision Making: If patient-level data are made publicly available, advocacy groups are likely to use such data to challenge particular EMA decisions regarding drug approval. If the EMA policy only requires disclosure of data pertaining to drugs for which a marketing authorization has been approved, the EMA should be prepared for disease-specific advocacy groups to reanalyze data to argue that the drug should be authorized for a broader indication, and for industry to make the same arguments. If, on the other hand, the EMA policy requires disclosure of data for all trials used to support a marketing authorization, regardless of whether the drug was in fact authorized, the EMA can expect advocacy groups to harness all available data to argue that the drug should have been approved. This is not necessarily an adverse outcome, but it is something the EMA should be prepared for. Proposed change (if any):
3	Comment: Disclosure of Ethics Committee Member Names: During a recent EMA call, it was suggested that the names of the members of ethics committees and IRBs that approved a given study be made public as part of the data disclosure process. Such a practice would be highly problematic because it would almost certainly deter people from serving on such research ethics committees. Members of ethics committees and IRBs who are involved in approving highly controversial studies will not want to face a backlash from persons, groups, or companies that

Line no.	Comment and rationale; proposed changes (if any)
	may be opposed to a particular study. The only information regarding ethics committees and IRBs that should be made public is the fact that a given study was approved by an IRB or ethics committee; there is no need for the names of the members of such groups to be made public. Proposed change (if any):
	Comment: Risk of Reidentification: The EMA should further consider the potential for re-identification of data that would appear to be "de-identified" under current standards. Because clinical trials often have very specific participation criteria, knowledge of such criteria can be used to re-identify participants. Orphan drugs and pediatric trials pose special concerns, because the population eligible to participate in such trials is extremely limited. Multi-year trials also increase the likelihood of re-identification, due to the increased specificity contained in multiple data points gathered at specific times over longitudinal periods. Furthermore, as technology advances it becomes increasingly likely that re-identification of subjects will be possible using genetic data that would not have allowed for re-identification previously. Given the reality that "de-identification" is becoming increasingly uncertain as a method of shielding research participant identities, the EMA policy must ensure that it does not rely solely on de-identification to protect participant privacy. Other alternatives would be, in addition to "de-identifying data," establishing intermediaries to limit access to data to appropriate parties who have agreed to terms and conditions that include a pledge not to attempt to re-identify participants. Proposed change (if any):
	Comment: Participant Consent: The EMA policy must address the issue of participant consent on two levels. First, the release of data from past studies requires analysis of the consent forms used in those studies to determine if the data sharing now required by the EMA was adequately explained to the participant, or was otherwise arguably accommodated or included in the consent terms. In cases in which data sharing was not contemplated by the language of the consent, the EMA must decide whether retroactive participant consent will be required and also consider the feasibility of obtaining such consent. Second, on a prospective basis, consent forms must be modified to inform participants of the new EMA data sharing policies. Ideally the consent form should make participants aware of what data will be shared, who will control access to the data and what restrictions will be placed on the use of the data. Proposed change (if any):

Line no.	Comment and rationale; proposed changes (if any)
	Comment: Gatekeeping Function: The EMA policy should provide for a learned intermediary to control access to all data released. As part of the data release process, the data requester should be required to submit an appropriate and scientifically valid study protocol and to demonstrate experience in the statistical analyses needed to make proper use of the dataset. The learned intermediary can evaluate whether the proposed data use meets a true public health need or is an attempt to gain a commercial competitive advantage or otherwise harass or harm research sponsors, researchers and or participants. Furthermore, the learned intermediary should require that the data recipient sign a data use agreement restricting how the data can be shared with others and prohibiting re-identification of participants. The EMA may wish to establish civil or criminal penalties for violation of the data use agreement so that violators face sanctions beyond breach of contract liability. Proposed change (if any):

Fergal Anthony O'Regan
European Ombudsman

Lines 26-46
Delete for the following reasons:

This entire introduction is problematic. It simplifies nuanced and differentiated views. Indeed, it is potentially very misleading.

For example, we do not exclude the possibility that clinical trial data could contain commercially confidential information. However, we make the point that the starting point of the analysis is that documents held by EMA should be made public unless it is demonstrated (it must be reasonably foreseeable) that an exception applies (i.e. no general presumption can be made that an exception applies). If it were successfully argued that an exception applied, it would still be necessary to determine if there is an overriding public interest in disclosure. Given the nature of the documents, which relate to the protection of public health, it would normally be the case that such an overriding public interest would exist.

The first paragraph ignores this nuanced approach.

We disagree with the first sentence of the second paragraph. It should not be presented in this section, which is a general introduction seeking to summarise the views of a number of participants. Our view is that if documents released through the

public access rules can in fact be used to develop new medicines, it is highly likely that Article 4. 2 first indent applies. Rather than being an argument for disclosure under Regulation 1049/2001, the argument presented in the first sentence of paragraph 2 is an argument against such disclosure!

Our view is that the first three paragraph should be redacted to leave only the first sentence of paragraph 1.

Lines 50-85
Edit as follows:

a. Publication of clinical-trial data based on conditionality

As regards the argument that public access should be replaced by a form of conditional access to clinical-trial data, it should be underlined that a policy to proactively publish clinical-trial data based on conditionality must not be understood as an alternative to public access under Regulation 1049/2001. Rather, if applied, conditional access to clinical-trial data would be complementary to the rights of public access under Regulation 1049/2001.

As a result, any proactive disclosure policy based on conditionality could be, entirely legally, circumvented through any member of the public making requests for public access under Regulation 1049/2001.

The useful purpose of a proactive disclosure policy based on conditionality is therefore doubtful.

It is also difficult to imagine how a system of conditional access could be enforced.

It would thus be advisable to have a proactive policy which is consistent with Regulation 1049/2001: documents should be released proactively if they would in any case be released subsequent to a request made under Regulation 1049/2001..

b. Proactive publication under Regulation 1049/2001

Regulation 1049/2001 allows for, and indeed encourages, proactive publication (Article 12 of Regulation 1049/2001).

To apply a proactive publication policy under Regulation 1049/2001, sponsors can be informed that they are free to provide a detailed, well-substantiated explanation at the time of submission of the clinical-trial data explaining why the publication of

that specific clinical-trial data would prejudice their legitimate commercial interests. This should normally never apply to an entire document, and the protection should not be timeless.

Regulation 1049/2001, correctly applied, allows for the redaction of information from a document if the disclosure of that information would undermine the protection of legitimate commercial interests (Article 4(2), first indent of Regulation 1049/2001). It should be recalled, in this regard, that the examination to be carried out in order to determine if an exception under Regulation 1049/2001 applies must be specific in nature. It must be reasonably foreseeable and not purely hypothetical that disclosure of the document would harm the protected interest.

If a company is of the view that Article 4(2), first indent of Regulation 1049/2001 applies to all, or parts, of the documents it is submitting to the Agency, it should explain to the Agency at the time of submission of the clinical-trial data why this is the case. The company should indicate specifically what information would be of use to competitors to an extent which would meet the test described above.

But even if the Agency agrees that disclosure of the documents in question would undermine the protection of commercial interests, the documents must be released if there is an overriding public interest in disclosure. Given the nature of the documents, which relate to the safety and effective of medical products used on humans, an overriding public interest in disclosure exists.

c. ***Standardised clinical tests***. As regards the argument that releasing clinical trial data would reveal commercially sensitive information on how best to format an application to the Agency, it should be noted that study reports containing clinical-trial data are based on standardised clinical tests. It would thus be unusual that any given data would reveal any significant information, as regards their format, which would not already be known by industry.

There is, in any case a public interest in ensuring that MAA are refused not on formal grounds, but rather on the basis of the substantive content of a dossier. Hence, it is not a legitimate commercial interest to prevent the Agency from disclosing how best to format clinical-trial data to be submitted to the Agency.

d. ***Timing of the release of clinical-trial data.*** As regards the timing of the publication of clinical trial data, while it may be reasonably foreseeable that public access to a clinical trial dossier submitted to the Agency as part of an on-*going marketing authorisation procedure* may reveal to competitors sensitive information about the likely timescale for the arrival on the market of a competing product, and the characteristics of that competing product, this concern disappears once a MA is granted. Competing pharmaceutical companies will, through the marketing authorisation decision itself (which is a public document), be able to estimate when a competing product will arrive on the market and what characteristics that product will

have. It is thus difficult to imagine how clinical-trial data on which a MAA is based could be of strategic and operational use to a competing pharmaceutical company *after* the granting of the marketing authorisation.

e. Use of clinical-trial data to develop other products

It's argued that that the disclosure of clinical-trial data would allow competitors to develop new products. In order for this argument to be sustained, it would have to be shown, on a case-by-case basis, that the clinical-trial data could reveal, for a specific product, details of what other products would be developed.

No evidence has been put forward of a specific case where information contained in clinical-trial data reveals details of what other molecules might be developed. Indeed, it would seem very unusual that such data, designed to test the safety and effectiveness of a specific molecule, would reveal any information in relation to the development of other molecules.

Lines 109-131
Edit as follows:

f. ***Safety and Efficacy***. Safety and efficacy in the pharmaceutical industry will benefit from full transparency, as independent analysis of clinical-trial data will become available to all parties.

g. ***Public interest***. Scientific bias, selective publication and withholding of important safety data should become more difficult if clinical-trial data were actively disclosed, this way reinforcing public health and public trust in medicines. As such, clinical-trial data must be regarded as a public good intended for the public interest; and human rights must be interpreted in the light of data transparency, which is to be boosted by meta-analysis and confirmation of claims about safety and efficacy of medicines.

(The current wording of this paragraph does not appear to reflect accurately the point made in our submission. We argue that it is ***also*** *in the public interest that competing pharma companies identify errors in submitted data. The wording suggested in the draft seems to imply that it would be problematic the competing pharma companies would use the data for such purposes):*

The fact that pharmaceutical companies seek public access to the clinical-trial data of a competitor does not imply that such public access does not serve the public interest. It is reasonably foreseeable that such competitors will used the clinical-trial data to identify possible errors in that data and in their analysis by the Agency; to identify possible inconsistencies in the manner in which its competitor markets its product, or in the manner in which that product is analysed in scientific journals. They may even wish to publicise any such inconsistencies. It is also reasonably foreseeable that independent researches will

benefit from publication of clinical-trial data in their pursuit to, among other things, identify potential inconsistencies and publicise them. In this case, it cannot be maintained that a pharmaceutical company has a legitimate commercial interest in ensuring that deficiencies in its clinical-trial data remain undiscovered, or that claims made in relation to its product cannot be cross-checked with the clinical-trial data.

There is indeed a public interest in ensuring that the parties that have both an interest in identifying deficiencies from clinical-trial data, and the technical capacity to identify such deficiencies, benefit from their publication. These are, potentially, independent researchers but also competing pharmaceutical companies: it hence becomes a relevant argument in determining whether there is an overriding public interest in disclosure.

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My understanding is that sui generis rights in the European Database Directive only apply to data in databases, so I question whether this directive – and copyright – would apply to all/most data submitted to the EMA. Data published or shared from a clinical trial could be in a variety of formats, such as tables/spreadsheets which might be available as single or multiple CSV/Excel files. Here is an example which I also shared with the confidentiality group, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3104487/ ; the dataset supporting this paper is available as online supplementary material – a single CSV file, not a database.

As I'm sure you know, copyright does not usually apply to data/facts, only the way in which they are presented. I understand this is the case for UK/EU and US law, although I am aware that in Australia the law focuses on originality rather than creativity – and copyright could apply to research data. So my question is whether there will be any copyright in some of the data submitted, and about how the copyright status of the data, particularly datasets released publicly, could be made clearer. One solution to dealing with these issues – where it is unclear whether or not copyright applies due to jurisdictional differences – is to use a license or waiver specifically for data, which waives copy and related rights so that those reusing data are not legally restricted from reanalysing, sharing, building upon and integrating those data with data from other sources for future research. I recognise that this approach is not always possible – it is most relevant to data which can be made public i.e. de-identified data. However, applying the Creative Commons CC0 waiver (http://creativecommons.org/publicdomain/zero/1.0/) to data, to waive copyright and dedicate data to the public domain, is

an approach increasingly being taken by data repositories. A good example is the Dryad (http://datadryad.org/) repository, which includes data from different life science disciplines including medicine. Here's an example data package, http://datadryad.org/resource/doi:10.5061/dryad.6544v and here's an explanation about why Dryad uses CC0 and the benefits from doing so:
http://blog.datadryad.org/2011/10/05/why-does-dryad-use-cc0/

My suggestion is therefore that the EMA consider waiving copyright in de-identified datasets which are not part of a database, such as spreadsheets and tables. Regarding other data formats, I understand that many clinical study reports may be submitted as part of this policy. I also understand these are lengthy documents which include tabular information and words/text. Copyright could conceivably apply to the majority of report, due to the effort in creating it, but a table within the report – reporting patient demographics, adverse events etc. – could be considered "data" and so not covered by copyright. I wonder if a secondary investigator could argue that by reusing only the "data" from these reports there would be no breach of copyright. An approach to address this would be to, again, apply a CC0 waiver to any data within these reports. Some journal publishers (including F1000Research, where I am now employed http://f1000research.com/ and in Nature's EMBO journal; http://www.nature.com/emboj/about/authors.html#a5.6) have begun to take this combined approach, of waiving copyright in data which they publish, and the authors retaining copyright in the remainder of the publication.

Also, I noticed a typo:
However, it is also reasonably foreseeable that independent researchers will benefit from publication of clinical-trial data in their pursuit to, among other things, identify potential inconsistencies and publicise them.

Finally, a comment on terminology. Why does the EMA continually say "proactive publication"? What do they mean by "proactive"? Publication is publication – do we need the adjective? I made this suggestion to the group on confidentiality, and it has been implemented.