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

Draft Advice to EMA with comments and amendments

The Advisory Group on Legal Aspects (the Group) has discussed about the legal aspects that the European Medicines Agency (the Agency) should take into consideration when designing a policy to proactively publish clinical-trial data after grant of the Marketing Authorisation (or variation). The adoption of this policy was announced at the workshop on access to clinical-trial data and transparency held on 22 November 2012.

The Group has discussed, in particular, the following three aspects:

a) whether or not clinical-trial data contain commercially confidential information whose publication could undermine the legitimate commercial interests of the author;

b) copyright aspects involved in the publication of data; and

c) legal remedies in case of disagreement with the decision to publish.

The list of participants is included in the Annex.

The Group participants have discussed about these aspects in two virtual meetings held on 30 January and 7 March 2013. Furthermore, they have been able to submit written comments. The present document contains the arguments raised both in the meetings and in the written submissions. An overview of the submissions is included in an attached document.

~~This document is now subject to consultation of the participants of the Advisory Group on Legal Aspects. Comments should be submitted to the Agency via email to CTdataGroup5@ema.europa.eu , **no later than Thursday 25 April 2013, E.O.B.**~~

~~These comments must be circumscribed to the arguments presented herewith. Arguments not included in this document will only be accepted as long as they were included in the written submissions albeit not reflected in this document.~~

1. Commercially Confidential Information

The Group has not managed to find an agreement about commercially confidential information. ~~The views have been quite polarised between those who consider that clinical trial data contain, or are, commercially confidential information and hence publication cannot take place without first consulting the MAH; and those who argue in favour of full transparency and oppose the views concerning of presence of commercially confidential information in clinical trial data.~~

~~Enhanced transparency of clinical trial data is widely recognised as a valid means to foster innovation, research and development of new medicines. However, many participants call for a balance between transparency and protection of confidentiality, intellectual property and personal data.~~

~~Whereas some have defended that clinical trial data contain no commercially confidential information that should prevent its proactive publication, others have opposed this view and have claimed that an individual assessment and a consultation with the marketing authorisation holder (hereinafter, the MAH) should be conducted to allow him to express his views before publication: this would enable to strike a balance between transparency and the rights of industry and patients to have their confidential information protected.~~

~~An argument subject to extensive discussion has been *conditionality*: publication of clinical trial data should be favoured on condition of *bona fide* independent research and as a means of expanding scientific knowledge. Although this has been an argument endorsed by many participants, again no total agreement has been reached.~~

~~In conclusion, the Group has not been able to find a common agreement about commercially confidential information and its effects on proactive publication of clinical trial data.~~ The reasons for the divergent views of the Group are presented below.

Arguments in support of proactive publication

~~Other~~ Some participants consider that clinical-trial data should be made transparent and support proactive publication. Their arguments are presented below:

a. Publication of clinical-trial data based on conditionality

Comment [f1]: The title of this section was misleading given its specific content

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. That is to say, if sponsors claim that the clinical trials data contain commercially confidential information, some participants pointed out that industry should first establish what information contained in clinical-trial data should be held as commercially confidential information and on what grounds. The Agency would then decide on the basis of a pre-defined set of conditions. This should normally never apply to an entire document, and the protection should not be timeless. This protection should be notified to the requesting person.

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.

a. 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.

b. 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.

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

It's argued 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.

~~***a. Consistency with Regulation 1049/2001***. 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. It must be noted that conditionality could easily be circumvented by making requests under Regulation 1049/2001.~~

~~***b.*** A proactive publication policy should be based on a consistent assessment of Regulation 1049/2001, i.e. documents should be published if, following a request for access to documents, they were disclosed. Moreover, proactive publication could be caught by Regulation 1049/2001 as it provides for the setting up of registers.~~

~~***c.*** Even if it was accepted that clinical-trial data should not be published, sponsors should provide a detailed, well-substantiated explanation at the time of submission of why their publication would prejudice their commercial interests. This should never apply to an entire document, and the protection should not be timeless.~~

Comment [f2]: The title of this section was misleading given its specific content

Comment [f3]: To be understandable, this paragraph needs an introductory sentence.

Comment [f4]:

Comment [f5]: This is a separate point to the timing issue

~~***d. Standardised clinical tests***. 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 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 unlikely that the structure of any particular dossier would be commercially sensitive since any information to be gleaned from it in terms of how it is presented could and should in any case be validly provided to the pharmaceutical industry by the Agency.~~

~~**e.** There is, in any case, a public interest in ensuring that medicines to treat conditions in humans are not rejected on the basis of formal structural deficiencies. As such, if it was the case that additional guidance to the industry could be provided through giving public access to clinical trial data, this would in fact imply that there is an overriding public interest in making them public: this would override any putative commercial interest in denying competitors access to them.~~

~~**f. *Commercial interest of clinical trial data***. It is 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. Competing pharmaceutical companies will, through the marketing authorisation, be able to estimate when a competing product might arrive on the market and what characteristics that product will have.~~

~~**g.** But if still argued that clinical trial data remained of commercial interest, it would have to be shown, on a case by case basis that they could reveal, for a specific product, details of what other products would be developed.~~

~~**h.** Furthermore, 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.~~

~~i.~~d. ***Use of clinical-trial data in other jurisdictions***. It has been widely argued that generic manufacturers will use clinical-trial data to obtain marketing authorisations in jurisdictions without patent protection. It has not, however, been shown that the regulatory authorities in any such jurisdiction even require detailed clinical-trial data for their granting. If they demanded such data, this would surely imply that generic manufacturers would not be able to obtain a marketing authorisation in those jurisdictions today.

~~j.~~e. ***Legitimate expectations***. Regulation 1049/2001 subjects to disclosure all documents held by the Agency, unless one of the exceptions of Article 4 becomes applicable. It cannot therefore be argued that an applicant is not aware that, at the time of submission of a MAA, the dossier can be accessed upon a request and thus available in the public domain.

~~k.~~f. ***Declaration of Helsinki 2008***. The World Medical Association's "Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects" makes an ethical requirement the publication of results of clinical-trial data. Point 30 reads as follows:

> *Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.*

The participation of patients in clinical trials is conducted on the understanding that their participation will benefit the advancement of science.

~~l.~~g. ~~***Competitiveness***~~***Safety and efficacy***. ~~Competitiveness~~ 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. ~~It will also be beneficial to inform their decisions.~~ It will also be beneficial to inform health professionals to have access to reliable information based on full evidence, allowing them to choose the best available option among those available

~~m.~~h. ***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 fact that p~~P~~harmaceutical companies ~~can~~ 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 use the clinical-trial data ~~for various reasons:~~ 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 ~~; or~~ even wish to publicise any such inconsistencies. 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. 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.

~~n.~~i. ***Reliability and accountability***. Full transparency has shown to be necessary to ensure clinical-trial data reliability and public accountability of the regulatory system itself.

~~o.~~j. ***Patent protection and data exclusivity***. These are already existing incentives which allow pharmaceutical companies to recoup their investments in development of medicines and their placing in the market.

~~p.~~k. ***Terms of consent of clinical-trial subjects***. Contractual obligations entered into by sponsors cannot prevent disclosure as regulatory requirements can override specific clauses in informed consent forms. It is hardly acceptable the argument that sponsors' and researchers' commitments to patients can justify a restriction on use and disclosure of data, and the same can be said about invoking respect of patients and their privacy interests as a ground to limit disclosure.

Arguments objecting to proactive publication

The reasons advanced by participants arguing that clinical-trial data contain or amount to commercially confidential information and objecting, to a lesser or greater extent, to proactive publication are the following:

a. ***Existence of commercially confidential information in the area of control proceedings and manufacturing***. Some c~~C~~linical-trial data are commercially confidential and not only in exceptional circumstances, as they contain information such as know-how, intellectual property information regarding the manufacturing, technological approaches and development of innovative medicines proprietary information regarding efficacy and safety measurements and statistical analyses; and~~;~~ the innovator's clinical-trial design and product development strategy as well as the MAH's confidential strategies for managing its clinical development programme. That and other information, which is not in the public domain and for which the author has taken active steps to maintain confidential, would damage the company's commercial interests if made public. 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. In this regard, the Commission has recently stated that "keeping valuable information secret is often the only or the most effective way that companies

have to protect their intellectual property (such as the results of their research and innovation efforts)".[1]

If clinical-trial data were made public, know-how, commercially confidential information, ~~–~~and trade secrets would be disclosed. The efforts incurred in developing novel medications by companies are high; the costs are ever-increasing, thus companies treat the know-how in research and development in their therapeutic areas as highly confidential and take considerable care to avoid such information being available to competing innovators or generic companies~~competitors~~. 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~~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~~.

On the judicial side, the Court of Justice of the European Union (the Court) has held in several cases 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 ~~that there exists a general presumption that documents submitted by a party to a specific administrative procedure and thus confidentiality under Article 4(2) of Regulation 1049/2001 should be~~ favoured.[2] In case C-139/07, the Court held that

> *[…] for the purposes of interpreting the exception laid down in Article 4(2), third indent, of Regulation No 1049/2001, the General Court should, in the judgment under appeal, have taken account of the fact that interested parties other than the Member State concerned in the procedures for reviewing State aid do not have the right to consult the documents in the Commission's administrative file, and, therefore, have acknowledged the existence of a general presumption that disclosure of documents in the administrative file in principle undermines protection of the objectives of investigation activities* (paragraph 61).
>
> *That general presumption does not exclude the right of those interested parties to demonstrate that a given document disclosure of which has been requested is not covered by that presumption, or that there is a higher public interest justifying the disclosure of the document concerned by virtue of Article 4(2) of Regulation No 1049/2001* (paragraph 62).

In case C-404/10, the Court acknowledged again the existence of such presumptions, noting that "such general presumptions are applicable to merger control proceedings because the legislation governing those procedures also lays down strict rules as regards the treatment of information obtained or established in those proceedings" (paragraph 118).

This view was also endorsed in case C-477/10P, where the Court held that "the first and third indents of Article 4(2) of Regulation No 1049/2001, interpreted in the light of the specific legislation on merger control proceedings, enables the Commission to apply a general presumption that the disclosure of the documents exchanged with the notifying parties and with third parties in the context of such control proceedings undermines, in principle, the protection of the commercial interests involved and the protection of the purpose of investigations relating to those proceedings, without the Commission being obliged to carry out a concrete and individual examination of those documents" (paragraph 84).

~~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*~~

[1] See http://ec.europa.eu/internal_market/consultations/2012/trade-secrets_en.htm

[2] Case C-477/10 P, Agrofert Holding v Commission, Judgment of 28 June 2012

~~*thereof, an abridged procedure which, after the expiry of a period of 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).~~

b. ***Consistency with Regulation 1049/2001***. 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.~~A consistent approach with Regulation 1049/2001 should be adopted whereby, first, the Agency should not assume that data is not commercially confidential without considering the data on an individual basis; and second, it should judge whether or not there is an overriding public interest, for which the purpose of the request is critical to determining the public interest in disclosure/publication~~. 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.

c. ***Confidentiality of bilateral agreements***. Bilateral agreements normally protect strategic partnerships in the development of know-how in research and development of the product and the underpinning technology. Such agreements usually contain a confidentiality clause upon the contracting parties that is actionable in case of breach. It is generally expected that the confidential nature of such information (particularly that concerning the manufacturing and control of the product and detailed pre-clinical testing data and clinical strategic plan) is respected by the competent authorities during the course of the regulatory review.

d. ***Regulatory data protection***. Enforcement of regulatory data protection, unlike patents, is the responsibility of the regulatory authorities. Clinical study reports and other information are ~~Information contained in clinical trial studies is~~ submitted to the regulatory authorities as part of, and solely for, the granting of a marketing authorisation. This protection is particularly important where no meaningful patent protection is present for a product or indication, as provided for in Article 14(11) of Regulation 726/2004 and Article 10(1) of Directive 2001/83/EC.

Regulatory data protection is found to be important by industry participants as an~~a vital~~ incentive for research and development of new medicines. Proactive disclosure would have the effect of undermining data exclusivity and would support MAA by innovators or generic companies, especially outside the EU~~competitors~~, either in the EU or elsewhere, by allowing third parties to circumvent existing regulatory data protection rules or by taking advantage of the absence of such rules. 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. This would leave innovators with little inducement to undertake the investment necessary to develop new cures and treatments options for patients.

The Australian legislation (reference should be added so that information can be checked; otherwise delete this reference), for instance, provides 5 years of data exclusivity to certain active components of new therapeutic goods on condition that the information is not available to the public. In addition, in the EU there have been situations in which competitors ~~(e.g. generic companies)~~ have attempted to use data obtained in this way for the purposes of submitting their own regulatory application. This calls for a robust system whereby the Agency conducts a case-by-case analysis taking into consideration the nature of the information to disclose, the recipient of the information and the purpose for disclosure.

The Commission, in its current proposal for a Regulation on clinical trials, states that "clinical trials are an indispensable part of clinical research which in, turn, is essential to develop medicines and improve

medical treatment. Without clinical trials, there would be no new medicines, no further development of existing medicines, and no evidence-based improvement of treatments with medicines".[3] Therefore, transparency measures ~~must~~ should not undermine the legitimate intellectual property or regulatory data protection rights which exist in law to encourage and safeguard the innovative research and development of medicines.

e. ***Public interest***. Publication of commercially confidential information contained in the MAA is not generally justified by an overriding public interest in disclosure: publication as such does not lead to an improvement of public health. It is vital that the Agency assesses whether or not information is well suited for publication and guides the public in its use~~, ,~~ , and whether disclosure advances science and public health.

Competitors would be favoured by this publication, as proved by the fact that the majority of current requests for access to documents are from industry. 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.~~Competitors can use this data, a) to avoid conducting their own clinical trials, and b) to obtain a marketing authorisation either in the EU or elsewhere. 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~~. 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.

~~In this regard, access to clinical trial data should be provided within an appropriate framework which ensures that that overriding public interest is served and that the data are appropriately used and protected in terms of data privacy, intellectual property rights and commercially confidential information considerations. The terms of such access should be based on the nature and purpose of the request and be accompanied by appropriate safeguards to prevent commercially confidential information and intellectual property rights being undermined by further disclosure and use of the data.~~

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.

f. ***Existing transparency measures***. Transparency in the interest of public health is well served by a number of provisions in EU pharmaceutical legislation including Regulation 726/2004 whereby a comprehensive set of transparency measures makes documents available to the public and healthcare professionals e.g., the EU Clinical Trials Register and EPAR. In addition, the significant results of a clinical trial are frequently published in academic and medical journals by the principal investigators.

g. ***Protection under TRIPS***. The EU is a party to the WTO and thus bound by the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), in particular Article 39(3). Clinical-trial data are undisclosed test data and hence must be protected under TRIPS. The European Commission has recognised, in a case involving Turkey, that:

> *With respect to protection against non-disclosure (the confidentiality obligation), the interpretation to be given clearly implies that the undisclosed data generated by the originator may not be disclosed to anyone other than those few officials who need to use it for marketing authorisation purposes of the particular innovative/original products concerned. Under the confidentiality principle, it is self-evident that the undisclosed data cannot be disclosed to and eventually used by generics manufacturers in order to enable them to produce by reference their own data.*

[3] Commission's proposal for a Regulation of the EU Parliament and of the Council on clinical trials on medicines for human use, and repealing Directive 2001/20/EC, COM (2012) 369 final, 17.7.2012, page 2, available at: http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf

Further, the principle of confidentiality implies that there must be efforts taken to safeguard the data against impermissible disclosure, thus leading to a satisfactory, effective and reliable overall protection system.[4]

The Agency is therefore obliged to protect undisclosed test or other data under Article 39.3 TRIPS since it forms an integral part of the Union's legal order.

h. Lack of a legal basis. *A* proactive disclosure would require a clear legal basis, which neither Regulation 726/2004 nor Regulation 1049/2001 provide at present. Following the example set by the regulatory procedures for novel foods, Directive 2001/83/EC and Regulation 726/2004 could be amended to include each a provision allowing for the submission of complete, confidential application, and a public version where the commercial and private confidential information is deleted.

i. *Personal data and informed consent of clinical-trial subjects*. As a precondition for allowing researchers to undertake trials within their jurisdictions, some countries require that there be no secondary research uses of participant data without additional permissions from national authorities, and or unless their own native citizen-scientists are included as co-authors on additional publications that have re-used participant-level data. Therefore, if the Agency were to bind pharmaceutical companies to make participant-level data available from completed clinical trials used to support MAA, then this could effectively conflict with the conditions under which some trials were done in various non-EU jurisdictions.

Furthermore, under current legislation of personal data protection, any disclosure of personal data affecting clinical-trial subjects must be expressly consented by the individual subjects. The informed consent given for past and existing clinical trials may not have encompassed the disclosure of personal data identifiers to the public (nor even, in some cases, to the regulatory authorities) under the newly envisaged process.

It is important to note that the limitations of the informed consent given by the trial subject with regard to the possible uses of the clinical-trial data are also an important ethical/medico-legal consideration, independent of data privacy and confidentiality.

j. *Patent protection*. Patents do not only relate to active substances but also to, *inter alia*, formulations, isomeric and crystal forms, pro-drugs and metabolites, processes, further medical uses, dosing regimes, combination therapies, drug-drug interactions, contra-indications and safety measures, etc. Information underpinning inventions relating to any of those can be found in clinical and non-clinical-trial data, and it is possible that marketing authorisation applicants create these inventions through analysis of the information provided in the MAA. 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. Hence, the Agency's proactive publication policy could prejudice later patent filing on subsequent inventions made on known products.

The effect that this could have on the market is that companies will have to make a judgment as to when it is more profitable to file their MAA in the EU. If they find that the most profitable option is to do it outside the EU, they will only submit a MAA in the EU when it has obtained all the possible value from the clinical-trial data generated to back such a MAA. As a result, this will delay the progress of medicines onto the EU market as well as EU patients' access to new drugs.

k. *Conflicting messages*. Proactive release of this information will lead to the publication of numerous third party and 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 ~~Proactive publication carries the risk of publication of a host of sponsored analyses and conflicting messages. Confusion could mount among medical practitioners if unsubstantiated claims regarding the safety and efficacy of medicines find their way into the public domain. Wrong conclusions about medicines could also be drawn.~~

[4] Report to the Trade Barriers regulation Committee. TBR proceedings concerning Turkish practices affecting trade in pharmaceutical products. European Commission, Directorate-General for Trade, of 13 September 2004

I. *Legitimate expectations*. ~~The Agency must respect the legitimate expectations of MAH at the time of submitting their MAA, who were unaware that the Agency intended to disclose part of the MAA submitted for the sole purposes of obtaining a marketing authorisation. Therefore, the new Agency's policy should only affect data submitted after its adoption.~~ 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.

Therefore, the Agency's new policy should only affect data submitted after its adoption.

2. Copyright

On copyright, the discussion has been much more limited than with the issue of commercially confidential information. Various options have been highlighted to ensure that the Agency is not found in breach of copyright or even database rights.

A participant pointed out that *sui generis* rights in the European Database Directive only apply to data in databases, so the question remained open whether or not this directive – and copyright – would apply to all/most data submitted to the Agency. Data published or shared from a clinical trial could be in a variety of formats, such as tables/spread-sheets which might be available as single or multiple CSV/Excel files.

This participant also stressed that copyright does not usually apply to data/facts, only the way in which they are presented. His understanding was that it is the case for UK/EU and US law. In Australia the law focuses on originality rather than creativity – and copyright could apply to research data. The question is then whether or not 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. This approach, however, may not always be 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.[5]

The Agency should then consider waiving copyright in de-identified datasets which are not part of a database, such as spread-sheets and tables. Regarding other data formats, many clinical study reports may be submitted as part of this policy. They may 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. Maybe 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,and Nature's EMBO journal) 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.

As to Regulation 1049/2001, Article 16

~~Article 16 of Regulation 1049/2001~~ only addresses the obligations of third parties in terms of copyright, yet it illustrates its general importance. Clinical study reports are drafted in a specific way to clearly and comprehensively present the result of the clinical trial and are carefully worded; similarly, compilations of individual trial subject data can be protected as databases. Therefore, the Agency should respect the copyright therein present.

[5] 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/

Furthermore, the option of access on the spot should be favoured rather than the sending of documents, which are normally subject to copyright or database right protection.

It was also suggested that the Agency should adopt a system whereby a license would be granted in order to use the data only for non-commercial purposes and to restrict its use to only assessing the benefit-risk balance of the authorised product. Article 16 of Regulation 1049/2001 gives a proper legal basis for this differential access. Two reasons support this differential licensing policy: a) it satisfies the public interest in ensuring that, where required, the Agency provides full data sets to organisations properly concerned with an independent analysis of these data in the interest of patient safety; and b) if such a policy was not developed, the Agency could be found in breach of the copyright of the applicant's documents, and even contributing to the copyright breach caused by a third-party making use of the documents (*contributory liability*).

It was also proposed that the Agency should use a symbol or alike to anticipate future usage of clinical-trial data documents.

3. Legal Remedies

The advice provided by the Group points to the reinforcement of the current system of legal remedies.

At present, before the Agency implements a decision to give access to documents that goes against the opinion expressed by the MAH in a previous consultation, or where no consultation has taken place because the Agency considers that the documents can be disclosed, it gives him ten working-days to file an order before the General Court of the European Union to suspend the implementation of the decision (interim relief). The request for interim relief is normally accompanied by an order to annul the decision.

Some participants have suggested the reinforcement of the present system of legal remedies system in the event of disagreement, for instance, by introducing an in-house formal appeal system to hear claims about commercial confidentiality.

Some participants pointed out that industry should first established what info contained in clinical-trial data should be held as commercially confidential information, and on what grounds. The Agency would then decide on the basis of a pre-defined set of conditions. It has been also suggested that the Agency should always consult the MAH unless he has indicated in advance that there are no confidentiality concerns.

Other participants consider that the current ten working-day timeframe to seek interim relief is too short: it should be extended to the standard 2 months and 10 days to be in line with actions for annulment. This would be justified by the general principle of effective legal remedies, as enshrined in Article 47 of the Charter of Fundamental Rights of the European Union.

A comment submitted to the Agency noted that consideration should be given for an independent review of the decision for disclosure conducted by a neutral third-party. One participant pointed out, however, that in case T-201/04 Microsoft v Commission, the Court held that any decision to abdicate the role entrusted to the Agency under Regulation 1049/2001 to decide whether or not a document can be released, would be contrary to EU law.

ANNEX

List of participants

European Medicines Agency

Alessandro Spina	Chairman – Agency's Legal Sector
Tomasz Jablonski	Agency's Legal Sector
Santiago Barón Escámez	Agency's Legal Sector
Giuseppe Gilio	Agency's Legal Sector

Remote participation via Adobe Connect

	Title	First Name	Last Name	Affiliation	Organisation name
1	Dr	Christiane	Abouzeid	Industry	BioIndustry Association (BIA)
2	Ms	Sigrid	Achenbach	Industry	Bayer Pharma AG
3	Ms	Rosita	Agnew	Government authority	European Ombudsman
4	Dr	Lillian	Auberson	Industry	Novartis Pharma AG
5	Mr	Mark	Barnes	Law firm	Ropes and Gray
6	Dr	Judith	Barwig	Industry	Boehringer Ingelheim GmbH
7	Mr	Stephen	Besseau	Academia	Unité de Recherche en Epidémiologie nutritionelleUMR U 557 Inserm / U 1
8	Dr	Helga	Blasius	Industry	AESGP
9	Mr	Peter	Bogaert	Law firm	Covington & Burling LLP
10	Mrs	Pascale	Boulet	Other/Unknown	Drugs for Neglected Diseases Initiative (DNDi)
11	Ms	Cecile	Chauvier-Guillard	Industry	Sanofi
12	Mrs	Catherine	Defabianis	Consultant	A.R.C. Pharma
13	Mr	Florian	Dexel	Regulator	Federal Institute for Drugs and Medical Devices, BfArM
14	Mr	Bryan	Driscoll	Industry	Takeda
15	Prof.	Stefan	Elbe	Academia	University of Sussex Centre for Global Health Policy
16	Prof.	Nikolaus	Forgó	Academia	Leibniz Universität Hannover
17	Mr	Silvi	Gavrilov	Patients' organisation	National Patient Organization
18	Dr	Roland	Gordon-Beresford	Healthcare professionals' organisation	Bio.be
19	Dr	Marco	Greco	Patient	EPF / EFCCA
20	Mr	Christian	Hrobar	Industry	Baxter AG
21	Mr	Iain	Hrynaszkiewicz	Media	Faculty of 1000
22	Prof.	Didier	Jacqmin	Healthcare professionals' organisation	European Association of Urology
23	Mrs	Victoria	Kitcatt	Industry	EFPIA, Pfizer
24	Dr	Tomasz	Kluczynski	Industry	FSP Galena
25	Dr	Stefan Philip	Kruszewski	Healthcare professional	Stefan P. Kruszewski MD and Associates;
26	Prof.	Trudo	Lemmens	Academia	HeLEX Centre for Health, Law, and Emerging Technologies, University of Oxford
27	Mr	Bennet	Lodzig	Academia	Leibniz Universität Hannover
28	Ms	Leanne	Madre	Academia	Clinical Trials Transformation Initiative
29	Ms	Janice	Mallison	Consultant	Regulatory and Drug Development Consulting
30	Mr	Gareth	Morgan	Healthcare professionals' organisation	Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians UK
31	Dr	Alexander	Natz	Industry	EUCOPE
32	Ms	Ilaria	Passarani	NGO	BEUC - The European Consumers Organization
33	Dr	Borislava	Pavlova	Industry	Pharmig – Verband der pharmazeutischen Industrie Österreichs
34	Dr	Jens	Peters	Industry	BPI German Pharmaceutical Industry Association
35	Dr	Àlex	Rovira	Academia	Hospital Universitari Vall d'Hebron
36	Dr	Diederick	Slijkerman	Government authority	CBG-MEB
37	Dr	Marc	Stauch	Academia	Leibniz Universität Hannover
38	Mrs	Magalie	Treguer	Industry	Biogen Idec Ltd
39	Dr	Mustafa	Unlu	Government authority	Food and Drug Administration
40	Dr	Florence	Vandevelde	Healthcare professionals' organisation	Prescrire
41	Dr	Rupert	Weinzierl	Industry	Bionorica SE
42	Mrs	Henriëtte	Westerling	Public health organisation	RIVM (National Institute for Public Health and the Environment)
43	Mr	Marc	Wilenzick	Academia	Harvard Mutli-Regional Clinical Trial center at the Global Health Institute