BIO DEUTSCHLAND

Statement

on the

revision

of the

guideline for the approximation of legislation and administrative regulations of the Member States about applying good clinical practice when conducting clinical trials with medicinal products for human use

(Revision of the ‚Clinical Trials Directive' 2001/20/EC)

submitted in the

public consultation of the European Commission of February 9, 2011

ABOUT

The Biotechnology Industry Organisation Germany (BIO Deutschland e.V.) is a trade association officially registered in the Union's Register for Interest Representatives. It represents German biotech companies and their business partners. Many of the 270 member companies are small and medium-sized enterprises (SMEs). BIO Deutschland is based in Berlin and have set themselves the goal of supporting and promoting the development of an innovative economic sector on the basis of modern life sciences. Further information about the activity of BIO Deutschland can be obtained at the association's offices or at www.biodeutschland.org

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BIO Deutschland's Appraisal of the

"CONCEPT PAPER ON THE REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC"

COOPERATION IN ASSESSING AND FOLLOWING UP APPLICATIONS FOR CLINICAL TRIALS

A single submission - Consultation item no. 1: Do you agree with this appraisal? Please comment.

BIO Deutschland agrees with the appraisal of the European Commission. A one-time submission via a joint 'EU portal' would in fact be welcomed. Such a procedure would bring about a significant relief in the administrative sector, especially with multinational clinical trials, as well as greatly reduced costs for the sponsors.

Sufficient financial resources and manpower would have to be made available to the *European Medicines Agency* for such a procedure, in order to ensure adequate IT infrastructure for the submission of applications and the relevant documentation as well as the distribution to the Member States concerned.

In addition, such a strong harmonising of data and applications for documentation can be made possible. Moreover it could have a supporting effect when dealing with additional national requirements of individual Member States, if necessary. The Member States should therefore be encouraged to reduce administrative requirements and to remove country-specific requirements from their respective federal

legislature, which do not contribute to a greater security and strengthening of the rights of the participants of clinical trials, and to adapt legislature accordingly.

The portal would allow an application to be submitted that is suitable to be reviewed by the proper national authorities and the respective ethics commissions. All applications would be submitted via the portal. It does not matter whether the clinical trial is conducted in only one Member State or several Member States. This would be excellent support for the expansion of the clinical development programme as well as for the inclusion of additional Member States.

The central validation of applications would ensure that standardized requirements would be introduced and published, which would lead to an improvement of a successful submission quote of applications ("first-time-right"). This would especially simplify matters for small and medium-sized companies and is therefore quite welcomed.

When submitting follow-up applications, being able to refer to information that has already been submitted via the EU portal would make managing the dossiers for investigational products much easier. Other sponsors could refer to information already submitted on the basis of a written agreement and additional Member States could be included in the clinical development at a later time.

The use of a reference language (in this case English) would reduce administrative costs for all submissions considerably. The protocol, in the form of a synoptic overview, the form for the written permission of patients after prior clarification, the information sheet for patients as well as specific documents for the respective ethics commission could be translated into the language of the country, in which the clinical trial is to be carried out and also be submitted as country-specific, supplementary documents via the EU portal.

The submitting of applications via a joint EU portal should at the same time bring about the distribution of information and the reviewing of applications for approval in all Member States involved. A review by the proper national authorities and ethics commissions would run parallel. In addition, the use of a standard portal would allow a speedy recheck and approval of the clinical trial, as, for example, the case already is in Germany.

A separate assessment - Consultation item no. 2: Do you agree with this appraisal? Please comment.

We agree with the assessment of the European Commission that an independent assessment by each individual Member State would probably not lead to reducing the potential for varying and conflicting views. Such an inconsistent application of law has a negative effect on the carrying out of especially multinational clinical trials. The quick start of a clinical trial is impaired by the submission of national applications, which requires additional information and also by the fact that one and the same CTA dossier is evaluated differently.

The varying interpretation and application of requirements in the various Member States would remain in force. Examples would be the local requirements for expiration dates of medical products or substantial changes regarding the extension of the shelf-life for certain countries. It should be mentioned here that there are varying interpretations of the expression 'substantial changes'. Furthermore, some Member States might have remarks about a certain trial after having obtained scientific support from the *Committee for Medicinal Products for Human Use (CHMP)* of the EMA or have a paediatric review plan of the Paediatric Committee of the EMA available. These remarks can require either a supplement of the clinical trial protocol or the removal of a certain country from the clinical trial.

The carrying out of separate assessments in individual Member States will lead to potentially differing results and will not contribute to the harmonisation of regulatory and ethical standards. Because of this there is the danger of delaying access to important medicines for patients at certain locations, which are found in the clinical trial.

Single submission with subsequent central assessment - Consultation item no. 3: Do you agree with this appraisal? Please comment.

On the whole, BIO Deutschland agrees with the assessment of the European Commission that a central assessment, as was introduced in the concept paper, is an inflexible solution which is not suitable for clinical research. The trial process would become very cumbersome and lead to drawn-out decision making, since an extensive structure of committees with sustainable infrastructure would be necessary – that is, a scientific committee based on the model of the CHMP, which states an opinion and then follows a decision which is then adopted by the European Commission and translated into 23 languages, which is not necessary in most cases because clinical trials seldom include every single Member State of the EU. The procedure would lead to delays lasting longer than the 60-day time limit for approval and would mean higher costs.

There is a concern that the setting up of such a committee would needlessly take claim to the resources of countries not involved in the clinical trial. Thus the assessment of applications for clinical trials in one or two countries could possibly be delayed.

A carefully coordinated assessment process in a virtual environment, supported by a solid IT-infrastructure and including the right experts of the EU Member States, would perhaps be a pragmatic and speedy solution.

The concept paper ascertains that "ethic, national and local perspectives require in any case a parallel-running national assessment process". The actual national ethic commission would probably deal with the ethical issues which are currently regulated by the *Clinical Trials Directive* and well integrated into the approval process of a clinical trial within the European Community. A shared ethic position of the individual Member States is required, in order to overcome the various opinions on regional / local levels. Moreover, the tasks and areas of responsibility of the proper national authorities and the ethic commissions must be clearly defined within the approval process. The introduction of further national regulatory standards would not be acceptable.

Single submission with a subsequent ‘coordinated assessment procedure’

Scope of the coordinated assessment procedure (CAP) - Consultation item no. 4: Is the above catalogue complete?

In general, the catalogue of the commission is complete on page 5 of the concept paper. It is our view that the following aspects should be included under a):

- The regulation for *Good Clinical Practice* is to be the decisive basis for conducting clinical trials.
- More emphasis must be put on the safety of those participating in the clinical trial.
- Information about a certain clinical trial that follows the scientific report of the CHMP or a *Paediatric Investigational Plan* agreed upon by the *Paediatric Committee* of the EMA, should be taken into consideration for its pan-European applicability by the Member States.
- The possible introduction of a simplified dossier for investigational products.

All in all, BIO Deutschland agrees with the assessment of the European Commission, that a more flexible approach could be made possible by a coordinated assessment procedure (CAP).

The coordinated assessment procedure (CAP) could orient itself on the model of the *Voluntary Harmonisation Process* for the assessment of multinational applications for clinical trials, which is tested by the *Heads of Medicines Agencies' Clinical Trials Facilitation Group (CTFG)* of the EU and could profit from the experiences of the CTFG and the sponsors.

The concept paper states that a "coordinated assessment procedure (CAP) leads to 'individual decisions' by Member States which are based on aspect through CAP as well as ethic / local aspects of the assessment of a clinical trial". Even if the 'individual decision' contains only regulatory as well as ethic and local aspects, an overall regulation is still necessary by the proper national authorities and additional authorities and committees on national and EU levels, when genetically-modified organisms, medicine products, radiation, biobanks, etc. are involved.

Regarding medicine for innovative therapy *(Advanced Therapy Medicinal Products—ATMPs)*, the EMA committee deals with such medicine (*Committee for Advanced Therapies - CAT*) and plays a role. With regard to the work programme 2010-2015, published in November 2010, the CAT aims to cooperate with the CTFG to standardize the assessment of CTA applications for ATMPs together with the EU Commission. This should further the access and availability of ATMP for patients in the EU.

BIO Deutschland wishes to point out the following crucial points to be taken into consideration in CAP:

- All requirements of documentation of an individual application are to be harmonised and clearly defined for all Member States.
- The development of a standard procedure of ethic commissions with common electronic applications would be desirable, thereby fully exploiting the benefits of CAP. For this purpose, the working method and areas of responsibility of ethic commissions in all of Europe must be harmonised and the ethic commission must be integrated into CAP, provided ethic decisions are made about the risk - benefit assessment (patient-relevant) and the control group (e.g. use of placebos or pseudo interventions to the patient) in CAP.
- A coordination that works between the individual Member States as well as between the proper national authorities and the ethic commissions is essential, to make sure that the participating Member States grant approval for a clinical trial within a fixed time frame.
- For the appointment of the rapporteur for the Member States, a clearly-defined procedure is necessary that will not have an effect on the timing and uniformity of the assessment of clinical trials, provided they are similar in form or have to do with the same diseases.
- A clearly-defined procedure is required for the inclusion of additional locations or Member States after an application has been submitted or a clinical trial has been approved.
- The repeated submission of scientific reports within the CAP is not necessary if a clinical trial is extended by the inclusion of additional Member States. All that is necessary is to check the ethic / local aspects and thus to receive the approval for the clinical trial from the Member States concerned.
- In certain cases, shorter time frames for re-examinations should be introduced to make possible quicker access to treatment possibilities in certain therapeutic areas and to fulfil urgent medical needs not yet covered. This should be permitted if the assessment is limited to new data, if the reviewed *IMP Dossier* has been complemented or if the clinical trial takes place on the basis of a scientific report or paediatric protocol agreed upon.

For this reason we urgently request that the European Commission and the EU Member States take this opportunity to specify a standard process of approval. This procedure is important to create a regulatory environment within the European Community that promotes clinical studies and improves the competitiveness of Europe as a location for the development of innovative medicines for the benefit of patients.

Consultation item no. 5: Do you agree to include the aspects under a), the risk-benefit assessment, as well as aspects related to quality of the medicines and their labelling, and only these aspects, in the scope of the CAP?

All in all, we agree that the aspects under a) are suitable for CAP. We welcome the approach of the European Commission and the distinction between aspects that are suitable for CAP and those that are not. In addition we propose that certain aspects in CAP be included (see reply to hearing no. 4).

BIO Deutschland also recommends the standardized use of the definitions 'Investigational Medicinal Product (*investigational compound*)' and 'Non-Investigational Medicinal Product (*compound not subject to the trial)*' in all EU Member States and all clinical trials. Possible effects on safety reporting or labelling should be handled uniformly in all Member States.

A common EU portal would reduce the amount of work for all parties concerned, including proper national authorities, ethic commissions as well as sponsors. Not only other sponsors would have the opportunity for cross-referencing in the framework of a clinical development programme, cross-references would also be possible for joint development of two investigational products (the EMA holds more and more to this concept in the field of oncology and promotes it). In this way, commercial clinical trials are not facilitated by scientific sponsors. See also the reply to hearing no. 1.

Disagreement with the assessment report - Consultation item no. 6: Which of these procedures is preferable? Please give your reasons.

In case CAP is used only when there are great differences of opinion with multinational clinical trials, BIO Deutschland advocates an Opt-Out-Option for the following reasons:

- We favour a system that aspires to a common pan-European decision, whenever possible, avoiding the complexity of a selection and reference system. There is a concern that the approval of a clinical trial could be delayed by references to the European Commission or the EMA for the evaluation of medicinal products.
- The clinical trial could begin in the Member States which support CAP, whereas the differences of opinion in the other Member States would have to be ironed out.
- Member States should have the chance to refuse their agreement due to 'differing medical practice' rather than 'severe risks for public health or the safety of the patient'. Otherwise the impression will arise that patients enjoy more protection in one country than in another country.
- The process of ironing out differences of opinion between Member States should not prolong deadlines and timelines. Appropriate measures have been taken for the submission of complaints.

Mandatory/optional use of the CAP - Consultation item no. 7: Which of these three procedures is preferable? Please give your reasons.

CAP should be possible for multinational clinical trials on request, while the national approval process for the clinical trial for early development is better suited for individual Member States. It is a commendable approach to introduce a simple and harmonised system as well as comparable standards throughout all of Europe.

It is difficult to introduce a 'completely harmonised' approach for all Member States because there are many differing factors to consider with development and implementation. The flexible selection of the most suitable procedure for a CTA is especially welcomed for small and medium-sized companies.

For trials at one location or in one country – especially during phase I – faster processes should be introduced which are then controlled by the respective Member State. Nevertheless, the same principles and requirements should apply for all clinical studies carried out in the EU. This ensures that the competitiveness of the EU as a location for clinical research will be improved.

It is to be recommended that also for purely national approval processes, harmonised processes for CAP be used, e.g. the planned submitting portal, the list of required documents or the standard language (submission in English possible). Otherwise the harmonisation and clarity obtained would be lost, and small companies would face administrative requirements difficult to assess when conducting studies in another country. Moreover, studies begun in only one country can easily be extended into other countries, which is important for studies with ATMPs that cannot be transferred into other countries at short notice.

Tacit approval and timelines - Consultation item no. 8: Do you think such a pre-assessment is workable in practice? Please comment.

It is basically our view that there should be a simplified, quicker procedure for the approval of clinical trials, which can be carried out with an approved compound in agreement with the admission to the market.

A preliminary test by the sponsor, to determine such 'type A' studies, could be helpful here. Currently there is a reporting system in Great Britain in the testing phase.

It is feared, though, that a preliminary test will generally lead to more bureaucracy and a heavier workload as well as a delay of the timeline for the CTA in the EU. For this reason we can see only limited advantages of this additional step towards conducting such studies.

Even though categorizing seems like a good idea at first, it will be difficult in practice to define and implement criteria for individual categories – in particular when the various Member States have different interpretations for the categories. In this regard we would like to point out that the criterion in subitem b) is somewhat vague and therefore allows various interpretations in practice.

The system of tacit approval has proven to be useful as it sets a clear cut-off date. If the Member State does not act before the cut-off date, there will be legal consequences. For this reason we support the agreement as the basis for a foreseeable and predictable timeline.

We propose the following timelines:

- Tacit approval within 30 days for clinical trials which will be conducted on the basis of a scientific opinion or within a *Paediatric Investigational Plan* or when there are no questions by the proper national authorities or ethic commissions

- Approval within 60 days for clinical trials with medicinal products for innovative therapy (ATMPs) or with questions about the clinical trial
- Approval within 30 days in the event that an additional Member State takes part in a study that has already been approved for another Member State in connection with a former CAP assessment.

In addition, the advantage of a speedy re-examination, as is practised in some Member States (e.g. Belgium, Germany and Great Britain), should not be rejected.

BETTER ADAPTATION TO PRACTICAL REQUIREMENTS AND A MORE HARMONISED, RISK-ADAPTED PROCEDURE TO THE PROCEDURAL ASPECTS OF CLINICAL TRIALS

Limiting the scope of the Clinical Trials Directive

Enlarging the definition of 'non-interventional' trials - Consultation item no. 9: Do you agree with this appraisal? Please comment.

In general we agree with the temporary assessment that it would be more advantageous to introduce harmonised and requirements in proportion, which are to be applied to all clinical studies within the current *Clinical Trials Directive*.

The integration of observational studies into the *Clinical Trials Directive* would lead to additional administrative work for the sponsors and should be avoided.

We plead instead for a clear definition of observational studies in the legislature, which the Member States must adhere to. Currently the definitions for observational studies vary among the Member States. For this reason, an application for a clinical trial is mandatory in some Member States, but not in others.

We would also like to point out that the guideline 2010/84/EU for pharmacovigilance codifies instructions for regulatory monitoring of all non-interventional safety studies after the approval. These instructions are reviewed by the committee for pharmacovigilance and risk assessment. These studies are thus already subject to the regulatory supervision of the EU.

Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive - Consultation item no. 10: Do you agree with this appraisal? Please comment.

We agree with the temporary assessment that uniform and comparative requirements for clinical studies should apply for all sponsors. The kind and severity of the requirements and obligations should not depend on the status or identity of the sponsor.

It is of central importance that, in the interest of protecting the patient, the same rules apply for all scientific and commercial sponsors.

There is an urgent need to get rid of unnecessary regulatory requirements, as they do not serve the safety of the patient nor improve the quality of data. We would like to emphasize that unnecessary, complex administrative guidelines, imposed either by the legislature of the European Community or by the national legislature of a Member State, in connection with a lack of the predictability of the regulation process, could have a negative effect on innovation efforts and possibly lead to higher costs for clinical development. This could directly affect the Life Science sector and in particular small and medium-sized companies.

In certain therapeutic fields (e.g. oncology), data from clinical trials of scientific sponsors is included in the applications for approval as supporting clinical trials. This possibility should remain and not be endangered by making possible distinctions between requirements for clinical trials from scientific sponsors on the one hand and commercial sponsors on the other hand.

More precise and risk-adapted rules for the content of the application dossier and for safety reporting - Consultation item no. 11: Do you agree with this appraisal? Please comment.

BIO Deutschland agrees with the proposal of the EU Commission to introduce a common risk-adapted policy for the dossier to apply for clinical trials and for safety reporting. A national interpretation of a guideline can affect the procedure and cause a deviation of the requirements. There might be differences in the translation and interpretation of the guideline as well as the in the coordination of the timeline for implementing and applying of such regulations in all of the EU Member States.

A more acute awareness, more intensive discussions and a better understanding of what is comprised in a risk-based approach regarding the process-technical aspects of clinical trials are all absolutely necessary. In this regard it must be pointed out that such a risk-based approach must be consistently used, while keeping clearly-defined criteria and considering the respective development phase.

We favour the inclusion of the detailed guidelines of the EU Commission (CT-1, CT-2 and CT-3) as an amendment to upcoming legislature, so that it is binding for all EU Member States. With regards to the Decree 2010/C82/01 we are of the opinion that the text should be adjusted to prevent Member States from gathering additional information or from wanting to keep track of nationally regulated processes. Eventually it might become necessary to convert the guideline into a regulation, to make sure that all guidelines within the EU Member States are harmonised.

The concept paper finds that international efforts at standardisation would be taken into consideration by the compiling of these amendments – for instance, the guidelines of the International Conference for Harmonisation (ICH). There are a series of ICH guidelines, especially in the area of quality assurance, which is inappropriate in the restrictive environment of clinical trials and is clearly stated in the guidelines that a clinical product is outside this scope. It concerns for example ICHQ1A and the extensions of ICHQ1E and ICHQ3A. Problems can arise when some of the national authorities strictly follow the rules which apply for commercial products in the development phase. Such a request is completely inappropriate and disregards the fact that product development is a step-by-step process.

Consultation item no. 12: Are there other key aspects on which more detailed rules are needed?

Member States should be supported in abolishing all duplicate or additional national requirements which cannot be justified when viewed objectively. Local legislature should be adjusted at places that are currently preventing effective harmonisation. All requirements named and/or planned should be scrutinized, by analysing whether any one requirement would help with the risk-benefit assessment of a certain clinical trial and whether the safety, rights and well-being of patients taking part in the trial are taken care of. A harmonised listing of the requirements would reduce bureaucracy and not endanger the greatest common denominator of all Member States. In addition, the possibility of implementing requirements in the national legislature in different ways would be minimized.

Every new / revised legal act should present a series of detailed processes and provide clearer definitions (e.g. IMP, legal representation, reporting). Moreover, a simplified process should thereby be introduced for the approval of a clinical test procedure or more flexible requirements that would be applicable for trials, which is conducted with an approved compound according to the authorisation of the product.

In the following are a few crucial points which are in need of detailed regulations:

- Member States continue to work with differing interpretations of the expression "essential modifications". It is a good idea to make a detailed list of essential modifications so as to enable the proper national authorities as well as the sponsors to come to the same interpretation.
- The information from the safety reporting of clinical trials must be beneficial and meaningful, so that there is a thorough understanding of the safety profile of the product and processes of the clinical trial after the analysis. The securing of such modifications in the SUSAR-Reporting-Model could possibly (medically relevant) produce safety reports of high significance, which would contribute to the safety of those participating in the clinical trial as well as that of the patients.

Clarifying the definition of ‘investigational medicinal product’ and establishing rules for ‘auxiliary medicinal products’ - Consultation item no. 13: Do you agree with this appraisal? Please comment.

A generally-accepted definition of an 'Investigational Medicinal Product' and a 'Non-Investigational Medicinal Product' is needed in all EU Member States as well as in data specifications for both compounds. There is still a legal uncertainty in the definition of IMP.

BIO Deutschland is of the opinion that introducing the expression 'medical auxiliary products' could lead to confusion. This covers no additional intervention in medical testing. Medical auxiliary products could be defined by their purpose of use and by the way they are administered. The appropriateness and existing information should be taken into consideration for these products. If a complete dossier cannot be delivered, the sponsors must then give exact reasons why not.

Auxiliary products are NIMPs (rescue, background, challenge agents) as well as aids such as infusions, salt solutions, etc.

Compounds for so-called 'basic therapy' (frequently administered to the poor) require a more exact clarification. The current guideline is frequently not followed by proper national authorities and for some

authorities IMP is the approved product and for other authorities NIMP. A pragmatic, reliable and consistent approach for all Member States would be desirable. The reasons should also be contemplated, why an active substance applies as IMP for basic therapy and there are greater differences in the requirements for safety reporting, labelling and documentation to be fulfilled.

Insurance / Indemnification- Consultation item no. 14: Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

BIO Deutschland considers the proposed solutions to be inappropriate. The requirements for insurance protection are to be met for all clinical trials. Insurance cost is not the deciding factor that prevents companies from conducting clinical studies in the EU.

Regardless of the potential risk, an effective protection should be provided for all participants of clinical trials by insurance or compensation for possible damages.

Compulsory insurance protection for all clinical trials would provide legal security and clarity for all parties concerned in cases of injury or death. In case the individual Member States are to provide insurance protection, it would probably cause insecurity and have less appeal for sponsors / testers to take part in the clinical trial.

Single sponsor - Consultation item no. 15: Do you agree with this appraisal? Please comment.

BIO Deutschland agrees with the appraisal of the European Commission. It is our opinion that the concept of 'one sponsor' per clinical study should be maintained to guarantee a clear division of functions and responsibilities.

For scientifically sponsored trials, the sponsoring will possibly have to be distributed among several institutions that do not form a legally-binding consortium. Such multicentre trials in several geographic regions can possibly process important research issues and should be supported. For this reason, the legislature should make possible the founding of sponsor consortia on the basis of binding contractual obligations which stipulate all the obligations and responsibilities towards the participants of clinical trials.

Emergency clinical trials - Consultation item no. 16: Do you agree with this appraisal? Please comment.

BIO Deutschland agrees with the proposal of the Commission, which provides a perfect analysis and also a viable solution according to current international agreements. We support an extensive harmonisation of regulations, which apply for urgent clinical trials in all EU Member States.

ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

Consultation item no. 17: Do you agree with this appraisal? Please comment.

In general, BIO Deutschland agrees with the appraisal of the Commission and the proposed procedure. We support further international cooperation with the regulating of clinical trials and promoting dialogue between interested representatives about the topic of *Good Clinical Practice* (GCP)-Compliance as well as capacity building in appropriate third countries.

We support the requirement to document clinical trials (interventional trials) in a public-accessible registry, while pointing out that coordination with already-existing requirements for registry and publication in other ICH regions is worth striving for. Use through the WHO certified registry, for example Clinicaltrials.gov, is recommended. The WHO offers an *International Clinical Trials Platform* which guarantees the accessibility of an extensive overview of the entire status of research for all decision makers in health care.

An obligatory inclusion of clinical studies, conducted in third countries, into the data base of EudraCT, would complicate the process and involve additional administrative work without any apparent advantages for public health. The European Union should rather work closer together with other regions, in order to coordinate the transparency of clinical trials without the unnecessary duplicating of registration and without unnecessary deviating requirements.

We would also welcome a more detailed explanation of the connection between the GCP-Compliance in trials which are conducted in third countries and their entry into a registry, since the registration of a clinical trial does not necessarily mean compliance / non-compliance to *Good Clinical Practice*.

It should be clarified whether the registration for a clinical trial can be retroactively conducted - even after concluding a study.

Germany, Berlin, May 13, 2011