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Date: 08.01.2010

Public Consultation on the Assessment of the functioning of the „Clinical Trials Directive" 2001/20/EC

Public consultation paper (9th October 2009)
European Commission

Comments of the German Pharmaceutical Industry Association
January 2010

It is widely accepted that since its entry into force in 2004, the Clinical Trials Directive (CTD) has improved the safety and ethical soundness of trials across the EU as well as reliability of clinical trials data and better protection of clinical trials participants. But a number of issues have emerged which have contributed to making the EU a much less attractive location to carry out clinical trials.

BPI would like to thank the European Commission for the opportunity to comment on the assessment and the proposed options for improving the functioning of the Clinical Trials Directive.

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With over 50 years of experience in drug research, development, authorization, manufacture and marketing, Bundesverband der Pharmazeutischen Industrie e. V. (BPI – German Pharmaceutical Industry Association) covers the wide range of pharmaceutical industry activities at national and international levels. The membership of BPI includes over 260 enterprises with some 72,000 staff: Classic pharmaceutical companies, businesses from biotechnology, phytopharmacy and homeopathy/ anthroposophy as well as pharma service providers. BPI represents both innovative pharma- and biotech-companies and companies with a small generic product portfolio. The diversified structure of BPI is also reflected by the fact that multinational companies as well as small and medium-sized enterprises are members of the association. The pharmaceutical industry employs some 643.000 staff in the 27 EU-Member States. BPI therefore represents more than 11% of staff working in the pharmaceutical industry in the European Union.

Regarding functioning and improvement of the Clinical Trials Directive, for BPI, the main topics to be adressed are:

The need for a centralized authorization procedure with a single and unique clinical trial application dossier, additional to the current procedures

The need for strictly application of current reporting requirements in accordance with the Detailed Guidance on the collection, verification and presentation of adverse reaction reports (ENTR/CT3 April 2006),

The need for harmonized definition of «substantial amendment», «non-interventional study» and «SUSAR».

The implementation of appropriate binding Annexes to the revised Directive or the adoption of a EU Regulation to replace the Directive.

Consultation item n°1: Can you give examples for an improved protection? Are you aware of studies / data showing the benefits of Clinical Trials Directive?

BPI has no studies or data available other than the ICREL results

Consultation item n°2: Is this an accurate description of the situation? What is your appraisal of the situation?

The assessment report provides a realistic description of the current situation with different requirements and different interpretations even of key issues in the Member States.

A sponsor of a clinical trial performed in more than one Member State (MS) needs to have very detailed knowledge about every country's national requirements for clinical trial authorizations from competent authorities and ethics committees and has to integrate the different requirements to the protocol and IMPD resulting from parallel submission in multi-national trials.

In addition to the accomplishment of divergent and sometimes conflicting assessments of different National Competent Authorities (NCAs), a high administrative burden arises by the fulfillment of different national requirements by different NCAs.

National requirements are not outlined clearly enough

- Attachment 1 to Guidance ENTR/F2/BL D(2003) is not comprehensive. For all countries websites have to be consulted, additionally
- Some NCAs do not have information online (English).

To this adds that each clinical trial is subject to an assessment by two distinct bodies, the NCA and the EC of each MS concerned. As the scopes of the respective assessments are not coherently separated in the Community, it is difficult for NCAs of different MS concerned to cooperate in the assessment procedure. This adds to the complication of the authorization of clinical trials by NCAs in the Community.

Even the „Clinical Trial Facilitation Group" initiated by the Heads of Agencies has no structured attempt towards aligning the ethics committee systems and approval procedures in the different countries.

The pilot procedure for harmonizing NCA review the „Voluntary Harmonized Procedure" „VHP, assumed that all NCA review a core CTA, with other documents being reviewing outside the scope of the procedure. While there are advantages to the concept of a harmonized NCA review, there are several failures in the pilot system therefore companies are not using this option.

Even though there is some basic harmonization in the process for CTA review and there are many common elements in CTA contents across all EU countries, the diversity in NCA requirements for CTA contents often leads to diverging comments across the EU for multi-national trials. For example, some countries like France, Germany and the Netherlands request much more detailed viral safety information for biologics than other countries and focus the review of CMC data on these aspects. Some countries like Germany have additional national requirements (gender distribution statement etc.). It is hard to see why these additional requirements might be beneficial in some countries but not in others.
Some NCAs request to review Informed Consent Forms, which may lead to comments in addition to those usually received from the ECs.

Consultation item n°3: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

The assessment report describes the main weaknesses of the CTD:

1. the increased administrative costs for clinical trials, and thus clinical research, without added value.
2. the „patchwork" of separate assessment procedures of clinical trials by the various national competent authorities of the MSs concerned,
3. the time-lag between the finalization of the clinical trials protocol and the „first patient in" and
4. the increasing number of staff for scientific evaluation as well as administrative tasks in NCAs in the MSs although the same assessment is carried out (and the report drafted) separately by all national competent authorities of the MSs concerned.

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Divergent assessments can not only lead to a delayed start of the clinical trial but also to several rounds of amendments in order to have one harmonized protocol in all participating countries.

And this generates some additional problems, especially concerning the different costs for substantial amendments, variing amongst MS.

The use of a harmonized system for substantial amendments should streamline the core submission preparation. However, as there is no harmonized assessment of what constitutes a substantial amendment and since some MSs also require certain non-substantial amendments to be submitted, such a streamline process has not been fully optimized.

Consultation item n°4: Can you give indications / quantifications / examples for the impact of each option? Which option is preferable? What practical / legal aspects would need to be considered in further detail?

To improve the current procedure of an independent assessment of the request for authorisation of a clinical trial done by the NCAs of the various Member States concerned, the assessment report proposes several options like the „reliance on voluntary cooperation of NCAs" and the „community-wide streamlining of NCA-authorization process for clinical Trials".
It is very important that the development of a medicinal product in the EU must not be hindered due to a centralized review process. The review needs to be flexible, so that the primary objective, that patients get access to effective and safe medicines is still met. The intent of the Paediatric Legislation to promote the development of Paediatric Medicines was positive. However due to the strict assessment a significant number of companies have stopped their development due to the high development costs associated with the PIP.

1. The „Voluntary Harmonized Procedure" „*VHP*", set up by Member States without the involvement of the Commission or the Community legislator should offer in theory the advantages of a harmonized review, however it is limited in the following aspects:

- Review time is up to 60 days (for a core review) plus a further 20 days (for national approval): For many MS this extends the review period: In addition, to an additional 20 days beyond the statutory 60 days, many MS aim to (and achieve) approval within 30 days (if no questions are asked), like Austria, Belgium, UK. This does not make the VHP particularly appealing. At this time, it seems to be more an educational effort in order to achieve harmonization across EU NCAs than a genuine benefit for sponsors.

- The procedure does not allow for additional MS to be added after the review has been completed: This is impractical since many studies, particularly in certain indications, often require the inclusion of further MS to facilitate timely recruitment.

- Many of the issues of concern in CTAs are those that are outside the scope of the core review (such as local consent forms) moreover the time available for their resolution is compressed into 20 days. These are the types of issues that are often addressed by both MS and ECs and, as such, can lead to contradictory requests e.g. changes to ICFs

- It has some pitfalls (e.g. national applications with diverging documentation requirements still required after VHP step).

2. A procedure similar to that of the mutual recognition / decentralized approach for MAAs, with a RMS and decision making procedure:

- This could be acceptable if all of the issues described for the VHP are satisfactorily addressed, in particular the decision making procedure would need to extend to decisions made by new MS introduced to the study after the initial approval. Timelines need to be competitive with national approval timelines.

3. A procedure similar to that of the centralized procedure for MAAs, managed by the EMEA and with Commission decision making:

- As above, this could be acceptable if all of the issues described for the VHP are satisfactorily addressed, in particular the Commission decision making procedure would need to be relatively quick, compared to that applicable for MAAs.

- It should be clarified how the resources of many agencies would be adversely be impacted by the need to contribute to a CTA review for which is not being conducted in a given MS. An alternative centralized approach could be considered, that involves only those MS where the study is to be conducted. A mutual recognition process for additional MS added to the study after the initial approval would be required.

- While a process for „arbitrage" is proposed for the procedure above, it should be clarified whether a similar process would be available in this centralized approach.

- It should be clarified if a role similar to that of the (co-) rapporteur would be established and, if so, whether this MS would continue to act in this capacity if the product is ultimately the subject of a centralized marketing authorization.

- The role of Norwegian and Icelandic regulatory authorities should be clarified. It is recommended that they also participate in the process.

- It is stated that this procedure would result in a continuum between the clinical trial process and the marketing authorization process. It should be noted that currently this type of continuity does not always occur within individual MS between the stages of scientific advice and CTA submission. As such, it should be clarified how this can occur between the stages of CTA submission and MAA submission. Thus, there is no guarantee that agreement on trial related issues obtained during national scientific advice, will

continue to be valid at the time of submission of the CTA. This can occur where MS assessors for scientific advice and for CTAs are not the same.

The paper suggests different options for the scope of streamlining the CTA review process

- All CTAs: This would be appropriate for a mutual recognition type procedure i. e. if the study starts only in one country the CTA will be reviewed only by the concerned MS CA. If the study is extended to include more countries a mutual recognition should be obtained.

- Only for CTAs that are the subject of a multinational trial: Decentralized or centralized procedures seem to be the most appropriate.

- Only for IMPs with certain characteristics: This option is not supported by BPI as the experience of sponsors is that MS divergences in outcome may be more common for products with novel characteristics, however, less novel products can also be the subject of divergent decisions.

BPI would therefore recommend to have the possibility for different types of CTA procedures depending on specific study and/or product situations **as long as the current procedures remain** and are not replaced by the new system. The new system should be additive. The sponsor should be free to choose the currently existing procedures in all cases.

The new Centralized Procedure: one central authorization of a clinical trial performed by one body for the entire EU (”one-stop-shop” system) An appropriate legal body should be in place where all Member States are represented by rapporteurs, to perform the review process of one single and unique clinical trial application dossier. The authorization would be valid throughout the EU and the clinical trial could be conducted in the entire EU without additional follow-up authorizations needed by additional Member States concerned.

However, this centralized authorization procedure **must not lead to higher costs for sponsors.**

National CTA procedure for trials which are performed in only one MS should be still an option. In cases where such a trial is extended to more MS, a mutual recognition procedure with the MS where the initial CRA had been approved should be implemented.

A third option, the Decentralized Procedure, DCP, should be in place for sponsors who would like to perform their trial multinational, however, in only few MS, according to the granting of a marketing authorization for a medicinal product in more than one Member State, as described in Article 28(1) of Directive 2001/83/EC. This could be a preferable option for SME.

Consultation item n°5: Can you give indications / quantifications / examples for the impact of each option? Which option is preferable? What practical / legal aspects would need to be considered in further detail?

It is agreed, that there is no established dialogue between Ethics Committees and responsible Health Authorities about clinical trials approval during the CTA process. This should be formally established to avoid prolongation of the approval process due to substantial amendments required by one of these two parties in the clinical trial approval process.

The assessment report proposes different options to improve the assessment by Ethics Committees:

- One-stop shop: This is intended to reduce the administrative burden only with national EC reviews being conducted. It is not clear what aspects of the submission would be reviewed and whether it would be a mutual recognition or centralized approach. It is not clear how this review can be undertaken in one place, since many administrative issues are subject to national requirements e.g. insurance. Since each country has implemented varied processes for review, this would require considerable harmonization.

- Strengthening national networks: This provides for an optional adoption on an opinion. While it provides the opportunity for ECs in different countries to discuss and attempt to resolve issues, it may become a forum without any concrete decision making.

- Clarifying the role of the EC and NCA: It is agreed that there should be no overlap of responsibilities of each body. An overlap with regards to documents like Informed Consent Forms or investigator contracts seems unnecessary and leads to overlapping and sometimes conflicting comments. While review of the same document may be undertaken by both, it should be for different purposes. Many countries have already established an overlapping assessment procedure. A strict separation of IMP / Study design related issues to be evaluated by the NCAs and site / patient related issues to be evaluated by ECs would be very supportive in regards of time and resource saving. UK and Belgium implemented this approach and can be taken as example.

- Further recommendation: It is recommended that all ECs use the EudraCT form in applications.

Consultation item n°6: Is this an accurate description of the situation? Can you give other examples?

Concerning the implementation and interpretation of the CTD there are some inconsistencies among Member States as already listed in the report:

Substantial amendments:
The definition of 'substantial' is not clear and permits considerably different interpretations by sponsors, Competent Authorities and Ethics Committees. Also the term 'otherwise significant' does not help with the understanding of the type of amendments that are expected to be submitted for approval. Certain MS have created an additional category of amendment where documents must be submitted „for information" (this does not relate to notifying the agency of a substantial amendment that affects the EC but not the CA). One of the criteria for establishing whether or not an amendment is substantial is whether or not it impacts the conduct of the study.

Other examples of diversity across EU member states concern e.g. the definition and requirements for non-IMPs, or the need to apply to additional regulatory bodies (data protection agencies, radiation boards etc.).

Reporting of SUSARs

A multitude of different reporting procedures exist in the MS leading to multiple reporting of the same SUSAR

The different reporting regimes impact on data quality either by duplicate reports being generated or by some reports not being submitted at all, thus reducing the NCAs' ability to monitor safety data and thereby address potential risks for clinical trial participants.

Ethics Committees have neither the capacities nor the competence nor digital means to do ‘signal detection’ or otherwise systemically identify a change in benefit and risk of the clinical trial. On the contrary, their capacities for protecting the patients are blocked by this administrative burden. Other ways need to be identified to enable Ethics Committees to make the required judgements, recognizing that Competent Authorities already take appropriate action on receipt of such SUSARs.

A more efficient approach would therefore be a separation of responsibilities for Competent Authorities and Ethics Committees

Non-interventional studies:

The Clinical Trials Directive 2001/20/EC only applies to “interventional trials”, not to “non-interventional” studies (NIS). As the Commission report states, the main characteristics of NIS are accepted by all CAs, but the borderline between “interventional trials”, not to “non-interventional” studies is drawn differently in individual Member States. Moreover, the report underlines that there are divergent interpretations of the term “non-interventional”, especially with respect to "no additional diagnostic or monitoring procedure and use of epidemiological methods".

According to NtA Vol. 9a Part I N° 7 a variety of d esigns may be appropriate for post-authorization safety studies including observational cohort studies, case-control studies or registries. The design to be used will depend on the objectives of the study (Registries, Comparative Observational

Studies, Cross-sectional Study (Survey), Cohort Study, Case-control Study, Clinical Trials, Large Simple Trials, Descriptive Studies).
It is not clear how further refinement of the wording in Volume 9A will clarify this, however it is recommended that the detailed definition of “non-interventional” be included in the revised legislation. This will reduce the likelihood of inconsistent interpretation.

Even concerning the design, there is currently a divergent interpretation at Member State level: Some Member States accept controlled studies without systematic allocation of treatment (e.g. without randomization) as NIS. Other Member States interpret all designs with comparison of groups even without randomization as falling under the CTD.

Therefore, BPI recommends to provide clarification in this respect for example by creating an intermediate category: “Low-risk-intervention” not falling under the CTD and no need of authorization by CA.

A clear definition, differentiation and harmonization between Member States is urgently needed.

Consultation item n°7: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

The weaknesses highlighted in the report concerning insufficient patient protection and increase of administrative costs. It is agreed that inconsistent reporting of SUSARs leads to an increased risks of undetected factors influencing the risk-benefit balance. It is also agreed that divergences in applications result in an increase in administrative costs for sponsors due to the need to customize applications more than is appropriate.

Consultation item n°8: Can you give indications / quantifications / examples for the impact of each option? Which option is preferable? What practical / legal aspects would need to be considered in further detail?
In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a caseby- case basis?

BPI would like to recommend, according to the „Good Manufacturing Practice (GMP)“ Guidelines to set out appropriate binding Annexes to a revised Directive (see also Consultation item n° 12)

Consultation item n°9: Can you give examples for an insufficient risk-differentiation? How should this be addressed?

To impose the same requirements for Phase IV studies as for phase I – III studies seems not to be appropriate.

Consultation item n°10: Do you agree with this description? Can you give other examples?

It is agreed that a more flexible approach regarding the definition of a sponsor could be helpful in some instances; however any revised definition should clearly state where liability for the study lies.
The concept of one unique sponsor often leads to issues, in particular in the academic environment, but sometimes also when e.g. a US company and an EU based company pursue a common clinical development project.

Consultation item n°11: Can a revision of guidelines address this problem in a satisfactory way? Which guidelines would need revision, and in what sense, in order to address this problem?

The revision of the guidelines might be useful, but only if the Member States are really willing to adhere to the spirit of these guidelines. The guideline on IMP labeling and CTA contents should definitely be revised to align national requirements.
The guideline on CA submissions in its current format does not adequately reflect national diversity as it does not even list all additional national requirements (like local application forms, additional memos etc.).

The proposal seems to imply that different standards might be applicable for commercial and non-commercial sponsors, because data from the latter are not necessarily included in clinical trials. It is critical that common standards are applied, regardless of the nature of the sponsor. The purpose of the legislation is to protect trial subjects and generate good quality data. The extent of protection required is independent of the intended purpose of the data. Subjects are entitled to the same level of protection regardless of how the resulting data will be used. Similarly, subjects agreeing to participate in a trial have the right to expect that the quality of data generated through it will be of the same high quality, regardless of how that data will be used. It should also be noted that the final use of data is not dependant on the whether or not the sponsor is commercial. Large numbers of interventional clinical trials are conducted with marketed products, where the sponsor is commercial. If different standards are to be applied, this should not be dependent on the nature of the sponsor.

Consultation item n°12: In what areas would an amendment of the Clinical Trials Directive be required in order to address the issue? If this was addressed, can the impacts be described and quantified?

An amendment to the Directive is necessary for the following in order to legally binding implementation:

- Specific CTA review approach i. e. NP, MRP, DCP or CP as discussed in consultation item no. 4.
- Strict separation of review responsibilities NCAs / ECs

May be this can be only achieved by a Regulation (Commission Regulation?) or with binding Annexes to a revised Directive according to the “Good Manufacturing Practice (GMP) Guidelines (see also Consultation item n°8).

Consultation item n°13: Would you agree to this option and if so what would be the impact?

As indicated above, requirements should not be based on whether or not the sponsor is commercial. This removes protection from the patient.

There is a certain percentage of academic clinical trials (10 - 20 %) which are conducted in more than one country, and their conduct would possibly be negatively affected if (probably diverging) national legislation would apply.

Consultation item n°14: In terms of clinical trials regulation, what options could beconsidered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?

To improve the current situation, a legislative harmonized, risk based approach for special types of clinical trials such as paediatric trials, trials in emergency situations or trial on patients with dementia or psychiatric disorders is needed.
It would be welcomed that a convertible legislation how to consent patients into paediatric or emergency trials is available in all MS.

Consultation item n°15: Should this issue be addres sed? What ways have been found in order to reconcile patient's rights and the peculiarities of emergency clinical trials?
Which approach is favourable in view of past experiences?

It is agreed that greater harmonization in respect to the management of clinical trials in emergency situations approach towards managing clinical trials in emergency situations. The CT Directive addresses the principles for trials for incapacitated adults however no such text exists for emergency situations. In some instances, the emergency may associated with incapacitation such as being unconscious; however there are other circumstances where the emergency does not result in such incapacitation (although this might depend on the definition of incapacitation). Similarly, incapacitation can be associated with non-emergency situations such as that associated with mental incapacitation, therefore separate legislation should be included to address this. Consideration might be given to defining emergency, incapacitation and legal representative in the CT Directive. However, the latter two terms may already be defined in MS legislation and may be

challenging to revise. Similarly, each MS currently manages the consenting of unconscious adults differently (possibly in legislation) which may also be challenging to amend. For example, the UK legislation defines a hierarchy of persons who should be consulted in the consent for a minor or incapacitated adult in an emergency, when the responsible parent / legal representative is not available. The need also to obtain parent / legal representative consent when possible is also addressed.

Consultation item n°16: Please comment? Do you have additional information, including quantitative information and data?

Pharma companies perform clinical trials in third countries for several reasons, such as the need to accelerate recruitment of patients, the required number of which is increasing. The data are also used in marketing applications for those third countries, where locally generated data is required. There is a wide range of benefits from such studies:

- Large populations
- Treatment naïve patients
- Ethnic diversity
- Wide range of indications
- Good recruitment and retention
- Regulatory framework
- GCP, ethics and protocol compliance
- Qualified and experienced site staff
- Fewer competing trials
- Established infrastructure
- Strong investigator-patient relationships
- Often good standards of medical care
- High quality of data.

The legislation in third countries is developing and evolving thus, for example, Latin American countries are already revising their CT legislation and the Middle East is currently drafting theirs.
In addition, as reported by BPI member Companies, including CROs, India requires CROs to be registered (something that is required currently in the EU only in Italy) as well as fingerprinting of volunteers.
Countries are implementing appropriate parts of ICH, under the umbrella of the Global Co-operation Group in ICH, which recently began to include a number of regulatory authorities in its discussion. ICH GCP E6 has been implemented in, for example, Latin America and Asia from the 1990s to early 2000s, with GCP compliant ECs in operation. Arguably some third countries apply more controls than EU / EEA countries, with respect to requirements of the Declaration of Helsinki, 2000, that were not adopted by the EU / EEA (or the USA). Thus, in Brazil, use of placebo may be justified only if there is no alternative treatment, although (as in India) supply of post study drug is usually mandatory for indications such as HIV and oncology. Moreover, while EU/EEA countries hermit first in man studies, Indian (currently) and China do not, unless the sponsor is a domestic one. In addition to ICH E6 GCP requirements, companies implement local requirements. Thus, in addition to requesting patient informed consent, informed consent of a village chief, such as in Africa and certain parts of India, or of a female patient's husband, such as in Saudi Arabia, is also requested.

Consultation item n°17: What other options could be considered, taking into account the legal and practical limitations?

To increase transparency of CT, public information needs to be available for all trials, e.g. registry, with a minimum data set for all trials, easy to read and available in key languages. All results of CT need to be made public. Also Publication of non-EU clinical trials in EudraCT (requires additional legislation).
BPI therefore recommends one CT-Database or compatibility of all databases in all ICH regions (like EudraCT, ICTR, clinicaltrial.gov).

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Consultation item n°18: What other aspect would you like to highlight in view of ensuring the better regulation principles?
Do you have additional comments?
Are SME aspects already fully taken into account?

Difficulties for SMEs are in parts similar to those of larger companies.
However, there is a higher burden for SMEs due to the increased need for staff for preparation and management of clinical trials as well as for pharmacovigilance tasks, due to the investment required to adapt IT systems to the new safety reporting requirements, and due to an increase of subject indemnity insurance fees. This leads to an overall increase in resources required for the performance of clinical trials in the new regulatory framework which is especially a burden for SMEs.

Although the "SME Office" at the EMA is already launched to promote innovation and the development of new medicinal products by SMEs BPI recommends extending the duties of the "SME Office" to support smaller companies also with regard to clinical trials.

The Commission should also consider implementing a legal basis for fee reductions for clinical trials when SMEs are concerned as sponsors.

Berlin, 08.01.2010

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