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To
European Commission
Enterprise and Industry Directorate-General
Consumer Goods
Pharmaceuticals

Via Mail
Entr-pharmaceuticals@ec.europa.eu

Heidelberg, January 9, 2010

ENTR/F/2/SF D(2009) 32674
Assessment of the Functioning of the "Clinical Trials Directive" 2001/20/EC – Public Consultation

Comments by the German Society of Pharmaceutical Medicine

Dear Sirs,

The German Society of Pharmaceutical Medicine (DGPharMed) – representing about 1400 professionals active in all aspects of Pharmaceutical Medicine - welcomes the EC initiative to review the functioning of the CTD 2001/20/EC via a public consultation and wishes to comment as follows:

Clinical trials in the EU

The Clinical Trials Directive: Achievements but also shortcomings 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?

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The Directive was an important first step towards an approximation (not harmonization as often quoted) of the requirements and processes between EU Member States. Indeed, the spirit of the Directive is now recognised within the Community since its application in the various member states since 2004.

- Approximation of the clinical trial process through the authorisation of a clinical trial by the National Competent Authority (NCA) and an Ethics Committee (EC) opinion at Member State level within defined approval timelines. The principle of a single EC opinion was only formally introduced in Germany but the spirit of the Directive was not implemented by allowing involvement of local ECs requesting partially different application standards and information increasing administrative burden in cases of multi-centre trials in Germany.
- Principle of parallel processing of clinical trial applications by the NCA and EC.

Key Issue N°1 to be Addressed: Multiple and Divergent Assessments of Clinical Trials

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

Overall, DGPharMed agrees with the description given in the Public Consultation Paper which reflects the current situation.

Individual Member States have imposed different requirements – some of which go beyond those set out in the Directive, others that appear disproportionate to the objective of protecting safety of trial subjects – resulting in different regulatory standards being applied by the Member States in granting clinical trial authorisations (CTA). Such differences have adversely impacted on the practicalities to carry out multinational clinical trials. SMEs and academic institutions are especially affected as they do not have sufficient financial and skilled manpower resources to effectively deal with different national requirements imposed by the Member States.

DGPharMed recommends:

- Harmonisation of data requirements for clinical trial applications across all EU Member States.
- A single CTA application. This will help to overcome the administrative burden experienced by sponsors and reduce costs for multinational trials increasing the attractiveness of clinical research inside the EU. In the meantime, an up-to-date list of national requirements should be available on a dedicated website. Translations requests by all parties concerned – including ECs - should be limited to the protocol synopsis and the Patient Information Leaflet/Informed Consent Form.

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- Identifying the roles and responsibilities of NCAs and ECs in the approval process. Appropriate allocation of responsibilities will increase efficiency during the assessment process and improve timelines for initiation of clinical trials in the EU. Furthermore the scope of responsibilities of the central Ethics Committee versus local Ethics Committees must be clarified. Ideally a single competent EC involvement should be sufficient (see example of system in France).
- Greater consistency and predictability in the scientific assessment of CTA applications for multinational trials.
- A pan-European agreement on the definition of an investigational medicinal product (IMP) versus non-investigational medicinal product (NIMP).

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

Overall, DGPharMed agrees with this description.

The Directive could provide potential for synergies and time savings. However, these potential benefits have not been realised which has led to Europe being seen as a less attractive location for clinical development, e.g. compared to the US, where a single approval by a single competent authority, i.e. the FDA is sufficient.

The administrative burden to identify and comply with additional local requirements is significant. Thus international pharmaceutical companies have put in place databases to record the divergent Member State requirements, which need to be regularly updated by the affiliated companies. Clearly, such task is time consuming and labour intensive which smaller companies and academic associations may not be able to handle. This leads to added complexity of the approval of clinical trials in the EU, without adding further in terms of health protection or improving patient safety.

Options to address the issue as regards the assessment by NCAs 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?

Overall DGPharMed welcomed the Voluntary Harmonisation Procedure which provides a useful platform for CTA applications in two or more EU Member States. This initiative is a step into the right direction towards greater

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harmonisation among EU Member States. However, DGPharMed felt that the proposed pilot process does not address the main issues arising from the uneven and inconsistent implementation of the Clinical Trials Directive. The VHP appears to be attempting to harmonise a process, which is a laudable and worthwhile ambition, but not necessarily harmonising the different national requirements and divergent questions from NCAs in relation to CTA applications.

DGPharMed very much welcomes the potential options discussed in the consultation document for streamlining the authorisation process for clinical trial applications, building on experiences with a similar approach in the procedures already in place for marketing authorisation of medicinal products.

In our view, the first option described in section 3.3.2.1 (a) – that of decentralized / mutual recognition procedure – would be more complex, and entail a more lengthy process.

We would prefer the second option described in section 3.3.2.1 (b), which is similar in concept to the centralised drug approval procedure. Such an authorisation would be valid throughout the Community. It could be worthwhile to test option 3.3.2.1 (b) on a voluntary basis for some years to judge on its usefulness compared with the currently established procedures. These options should be available independent of the nature of the trial or the investigational product(s).

Further consideration would need to be given to how the EC review will be performed in the context of Community-wide authorisation procedures. It is acknowledged that there is a difference in the regulatory assessment procedure in Member States as well as the importance placed on regulatory versus ethics review.

Options to address the issue as regards the assessment by ECs 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?

DGPharMed would be in favour of the option outlined in section 3.4.1: a one-stop shop for submission of assessment dossier. It is desirable to have one single point of entry for submission of the request for authorisation of a clinical trial to both NCA and EC. One application dossier only would, from our perspective, be ideal.

While ethical issues clearly fall within the remit of Member States and would remain there, the Commission suggests working towards better co-operation

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and exchange among national ECs to improve the ethical review of clinical trials. However, we would need some further clarification as to how the network of national ECs involved in multinational clinical trials would work in practice, given the following statement:

"Concerning ethical issues, Member States could "opt out" as regards the final result of an assessment of a request for authorisation of a clinical trial."

DGPharMed supports the option (section 3.4.3) to revise the Directive to ensure that there is legal clarity on the respective scope of assessment by NCAs and ECs in Member States. This would result in a clearer identification of their respective roles and responsibilities in order to avoid "overlaps" in the assessment process of clinical trials, thus improving trial start up times. It is important to have a true parallel approach to the NCA and EC approval process in Member States.

Key Issue N°2 to be Addressed: Inconsistent Implementation of the Clinical Trials Directive

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

Overall, DGPharMed believes this is an accurate description.

We would also like to highlight the following example of inconsistent application of the Clinical Trials Directive which has a high impact on the conduct of clinical trials in terms of costs, resources and timelines:

Different interpretation of the definition of an investigational medicinal product

DGPharMed Members reported that multicentre trials conducted in more than one Member State pose practical difficulties. This is because some Member States may consider products such as challenge agents and concomitant and background treatments as an IMP, while others do not.

We note that the term "NIMP" has not been defined in the Directive. The concept was introduced by the Commission guidance for the request for authorisation of a clinical trial to the competent authorities and expanded in the guidance on IMPs and other medicinal products used in clinical trials.

In addition, the interpretation of IMP raises a potential ethical conflict. This could be viewed as a financial inducement for the sites (and in some cases the patients) to participate in the studies if companies are required to pay for comparator products and other concomitant medications.

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The guidance on IMPs is certainly open to interpretation and has not met the purpose of presenting a common understanding across EU Member States on the definition of an IMP. There is a need for pan-European agreement on definitions.

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

DGPharMed broadly believes that the description is accurate, at least in principle. However we would suggest rewording the statement "insufficient patient protection". Most notably, we do not believe that the issue with SUSARs as such is that they cause insufficient patient protection but rather, that they offer a huge distraction to ECs from their actual work which then, in turn, might lead to negative repercussions for patients.

Options to address this issue - 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 case-by-case basis?

DGPharMed would be in favour of the option outlined in section 4.3.2 - Adopting the text of the Clinical Trials Directive in the form of a Regulation, which would be binding in its entirety and directly applicable in all Member States**.** In our view a Regulation is most likely to provide the appropriate legal framework if this is possible from a EU legal framework perspective. If this meets fundamental concerns especially by the Member States, then a solution as centralised as possible would be desirable.

It is recognised that there are significant differences in interpretation of rules and implementation of the Directive across EU Member States. Such differences have hampered clinical development of medicinal products in the Community.

<u>Key Issue N°3 to be Addressed: Regulatory Framework Not Always Adapted to the Practical Requirements</u>

Requirements not always risk-commensurate - Consultation item n°9: Can you give examples for an insufficient risk-differentiation? How should this be addressed?

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DGPharMed believes that data requirements should be proportionate to the protection of the safety and well-being of clinical trial participants. We support a risk-based approach to regulation of clinical trials, taking account of the IMP characteristics. This would reduce workload and costs.

Requirements not always adapted to the practical circumstances - Consultation item n°10: Do you agree with this description? Can you give other examples?

DGPharMed has no further comments on this item. We believe that the concept of a single sponsor works well.

Review of existing implementing guidelines - 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?

In the short term, a revision of guidelines would be useful though this will not address the fundamental issues. DGPharMed believes that the Directive should be reviewed in order to achieve harmonisation, transparency and consistency in the approval and conduct of clinical trials across EU Member States.

Review of the existing Directive and adaptation of the requirements to practical necessities - 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?

Amendment of the Directive is required to ensure greater clarity, certainty and predictability of regulatory requirements for the approval and conduct of clinical trials. This would address definitions, content of clinical trial applications, roles and responsibilities of NCAs and ECs, and help streamline review processes with clear approval timelines as well as harmonised rules for safety reporting and IMP labelling.

The removal of unnecessary bureaucracy would benefit companies/academic institutions and patients by improving the development and access to innovative medicines. This will make Europe a more competitive environment for clinical research and a leading region for innovation.

Review of the existing Directive and excluding clinical trials of "academic" sponsors from the scope of the Directive

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

We recommend taking a risk-based approach rather than a distinction between academic and commercial trials.

Key Issue N°4 to be Addressed: Adaptation to Peculiarities in Trial Participants and Trial Design

Option to address this issue – adapting the Clinical Trials Directive
Consultation item n°14: In terms of clinical trials regulation, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?

As regards studies in children performed in accordance with a development plan for medicines (the paediatric investigation plan (PIP)) we believe that the binding elements of the PIP should not be re-assessed by the NCA when the assessment of the CTA application is made.

Consultation item n°15: Should this issue be addressed? 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?

DGPharMed favours an approach that facilitates emergency clinical trials by detailed specifications in the protocol but does not require impractical on the spot approvals by (untrained/unfamiliar) non-investigational staff. This approach should sufficiently safeguard the safety of the trial participants in emergency situations. The rules of transparency should apply.

Key Issue N°5 to be Addressed: Ensuring Compliance with Good Clinical Practices ("GCP") in Clinical Trials performed in Third Countries

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

DGPharMed agrees with the descriptions given in the Public Consultation Paper. Usage of non-OECD countries is often essential in cases of rare diseases or diseases with a regional predominance (e.g. Malaria). No formal additional information or quantitative information is available. However, anecdotal experience by members is that the data quality delivered by non-OECD trial sites can be equivalent to OECD trial sites if GCP principles are

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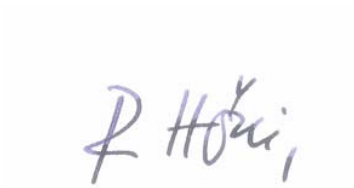
applied by sponsors. Administrative hurdles in non-OECD countries can be an obstacle to rapid roll-out of clinical trials.

Options to address this issue - Consultation item n°17: What other options could be considered, taking into account the legal and practical limitations?

Options given in the Public Consultation Paper appear comprehensive.

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?

DGPharMed observes a development of local requests – e.g. by local/national Ethics Committees - for clinical trial registrations and publication of clinical trial results in addition to the foreseen requirements by the European Commission (EUDRACT Data Base). Timely clinical trial registration and results publications - especially if local language is requested - will be an increasing administrative burden especially to SMEs. Dedicated, trained and multi-lingual personnel is required to fulfill these requests. Requirements and formats of local trial registers are not harmonized. It would be desirable to include a clause into a revised CTD/CT Regulation that publication in EUDRACT exempts from publications in local data bases.



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