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TO: European Commission
DG Enterprise/Pharmaceuticals
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Brussels, December 22, 2009

MSD response to Assessment of the functioning of the "Clinical Trials Directive" 2001/83/EC – Public consultation paper

Dear Sirs,

Enclosed are our company's comments on the public consultation paper, which I am providing you on behalf of Merck Sharp & Dohme (Europe) Inc. MSD (Europe) Inc. is an affiliate of Merck & Co., Inc. (USA).

Merck & Co., Inc is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved lives and improved the quality of life for millions of people globally.

This consultation paper has been reviewed by our interdisciplinary team composed of clinical research, regulatory affairs and legal experts, who have extensive experience in their respective field to successfully operate under the current EU Regulatory framework.

Overall, we support the aims to achieve a greater harmonisation and coordination of regulatory oversight regarding the conduct of multinational clinical trials. Administrative simplification should be the major Policy objective to enhance the competitiveness of the European Research arena whilst ensuring the current patient protection. Our detailed comments on the consultation items are listed below:

Consultation item 1:

Generally, we believe that due to the hamonisation of minimum requirements at EU level, the protection of patients across all EU Member States has been increased due to the same degree of Regulatory scrutiny of any study application. There is a benefit to patients in such that all information is now reviewed in much more depth and the full scope and context of the study is overseen by the regulators. In addition, the stringency of GCP inspection by agencies, e.g. like the MHRA, is reassuring for patients. Nevertheless, adequate national resources to enforce the requirements in all EU countries need to be available to guarantee the same level of protection across the Community.

Consultation item 2:

We agree with the assessment of the Commission.

In addition, to the experience that the definitions and interpretations of some issues, such as substantial amendments, Non-IMPs or SUSAR reporting requirements, cause difficulties for applicants to implement a global study protocol, specific national legal requirements create even more hurdles. For example, in the UK, the MHRA ask for specific text within a protocol relating to UK legislation or have

different approaches to contraception. In France, detailed data related to biotechnology compounds are required due to local law. In Sweden, the non-acceptance of a QP Declaration and the requirement for GMP certificates create hurdles. In Poland, genetic testing is not allowed which results in national tailoring of the protocol due to the need to omit certain text on genomics testing.

Other requirements due to divergent national guidance, such as the requirements in the Czech Republic of at least 6 month real time stability data, make a harmonized approach for multi-country trials very difficult. These various requirements can lead to local protocol amendments with differences in specifications or shelf life for IMPs. The independent review also results in different approval dates, depending on whether or not NCA concerns need to be addressed.

The scope of the assessments by NCAs and ECs should clearly be defined to be synergistic instead of overlapping.

For example, in addition to the clinical protocol, some countries' ECs and NCAs assess also the informed consent form which adds to the potential of study start delay due to a resulting iterative revision process.

Furthermore, for example in the Netherlands the evaluation of the IMPD is done by the EC, whereas in other countries this is done by the NCA, which makes it impossible for NL to participate in the Voluntary Harmonisation Procedure (VHP). For a clinical trial with an IMP that has already been approved in the past it is only possible to have a simplified IMPD, if the CTA is also reviewed by the same EC.

Consultation item 3:

In agreement with the findings of the ICREL survey, we believe that the administrative workload has undoubtedly increased and with it cost of conducting clinical research in Europe.

Resources at sponsor level have to be increased to comply and remain up-to-date with all documentation requirements, safety reporting and detailed record keeping and tracking expected by the GCP inspectorates. Strictly speaking, we note that currently all NCAs require a slightly different set of documentation.

In addition, some Member States have also committed significant resources for the assessment of CTAs. Larger Agencies with more dedicated resources are in general genuinely committed to try and get the approvals through in the required timeline and to resolve issues with sponsors that would give rise to initial refusals.

In our experience, current delays in overall approval times for CTAs are mainly due to sometimes complex procedural set up and resourcing of EC reviews per country or region or site. Additional requirements per individual EC for specific documents to be submitted for review contribute to the complexity.

A clearer definition of substantial amendments based on the impact of the change on patient safety under the responsibility of sponsors may perhaps help reducing the high amount of amendment procedures resulting in relieve of some administrative burden and resources. For example, the amendment procedure for the quality sections of the IMPD could further be simplified by harmonising the requirements for initial filings and amendments.

Consultation item 4:

Option (a) relies upon a rapid assessment, rapid consultation and rapid agreement between the various NCA in order to achieve an approval within the given time period. At present, the best NCAs are able to arrive at a national decision within a 60 days period. However, this does not include consultation and consensus building with other Member States. The existence of divergent national submission requirements and filing of an application in all participating countries with various level of IT infrastructure is unlikely to reduce the existing administrative burden.

VHP is a procedure that currently pilots this option. Due to the excellent commitment of some agencies the few procedures which were assessed in such a consultative way went rather well. However, given

the overall number of the CTA applications and the participation of many Agencies in this process stringent legal mechanisms and procedures would need to be implemented for scheduling work and consultation.

Further, the current mutual recognition system for marketing applications clearly shows some of the weaknesses of the system, whereby some agencies are overloaded with applications and slots are fully booked for 2 years in advance.

This is an unacceptable situation if mirrored for a thriving research Community where development times impact even more on patient access to new safe and effective medicines.

Nevertheless, we believe that this option may have a benefit for some clinical trials involving a very small number of countries. However, trials which are performed in only one country, e.g. such as First-in men trials, would not benefit from this option.

Option (b) is preferable for the assessment of multi-national clinical trials. The co-ordination of the assessment would be lead by a dedicated central function using EU or national assessor resources based upon availability or expertise. Adequate expert resources for the assessment of a large number of applications need to be ensured.

One single application submitted to a central level and resulting in a Community wide approval would save both time and money. As such, we fully support the EFPIA proposal for an optional Community Procedure.

Consultation item 5:

We believe that a clear identification of roles and responsibilities of NCAs and Ethical Committees during the assessment of a CTA is paramount for streamlining the system.

All ECs are using internationally agreed standards such as the Declaration of Helsinki as basis for their assessments. Although, there will be issues of varying medical practices across member states and to a lesser extent this occurs even within regions of countries. Nevertheless, we believe that an opinion form a Central EC on the methodology of a clinical trial can be acceptable for the Community. We note that the Commission in fact already uses only one European EC to give opinions on research proposals under their FP7 framework program.

Local ECs to judge the suitability of the investigator, site capacity and capabilities would provide added value.

3.4.1 We believe that this option could work specifically for multi-national trials, as the central co-ordination body will also plan the EC consultation in a similar way to the NCA approval. It would mirror the NCA approval mechanism and may have the best chances to align within the current timelines. A stronger link and co-ordination of assessments between the two distinct functions would optimize efficiency and probably outcomes.

3.4.2 A strong leadership is required for the co-ordination of a Network of ECs working together. Based on the experience gained from the MA approval process, this may take a long time to set up and build trust in order to come to an acceptable output.

In general Member States should only be allowed to "opt" out exceptionally and in well justified cases. A similar clause as in the Advanced Therapy Regulation may be a solution. It is clear that in case a Member State "opts" out, the clinical trial cannot be performed in that country.

3.4.3 Good communication between the two functions and a clear distinction of roles and responsibilities is required to allow an efficient and value added parallel review.

Consultation item 6:

We fully agree with the Commission assessment.

There are amendments to the implementing guidelines necessary to address inconsistencies regarding:

- Interpretations of what constitutes an IMP
- how to interpret drug labelling / re-labelling requirements (in for example Annex 13 of the EU GMP guide)
- which changes require a substantial amendment and which changes may perhaps only be brought to the attention of the Agency, but need no procedural review

- clarification of notification requirements of approved substantial amendments from one body (either the NCA and the EC) to the other body, specifically if it concerns country-specific documentation like informed consent forms, advertisement materials etc., to avoid potential confusion
- reporting of SUSARs to EudraVigilance and alignment of Safety reporting requirements to international standards (ICH)

Consultation item 7:

We generally agree with the Commission's assessment.

Nevertheless we would like to point out that the increase in administrative cost should be stratified against the increase of cost related to more stringent GMP and GCP requirements in all countries which are certainly a benefit for patient protection.

Some aspects may need to be reconsidered in this respect to balance the increased cost with the actual patient benefits considering various existing practice in Member States, e.g. using GMP facilities to re-label clinical supplies in some countries (but not in others) may need to be reconsidered based on actual data.

We agree that the divergence in SUSAR reporting requirements has created a complex system. In order to immediately lower the administrative burden within the current system while maintaining the patient protection, we would propose that SUSARs need to be notified only to the respective Regulatory Authority. Further, all SUSARs should be made available to all Agencies via EudraVigilance and the provision of the Annual Safety Report to NCAs and ECs.

Consultation item 8:

MSD favours the adoption of a new Regulation versus the amendment of the current Clinical Trials Directive to achieve the primary objective of greater harmonization of the EU Clinical Trial authorization system across the Member States.

Administrative simplification should be the major Policy objective to enhance the competitiveness of the European Research arena whilst ensuring the current patient protection.

The Regulatory framework around clinical trials should preferably be integrated into the overall regulatory process during the development of new medicines to allow good communication and continuous regulatory oversight.

A Regulation would supersede existing national laws and provide the basis for a harmonized system which could then be further build on to develop existing national divergences related to scientific aspects and ultimately contribute to the convergence of the diverging national requirements.

Consultation item 9:

We are generally against a system introducing standards based on sponsor classification. However, we support the principle that the requirements for the regulatory oversight should be proportional to the actual risk of the clinical study for the participants. The level of the "risk" may for example depend on the phase of clinical development, the mechanism of action of the new compound, existing clinical experience, the characteristics of the patient population exposed and the involvement of an external Data Safety Monitoring Board (DSMB). The legal framework could perhaps define certain criteria which would provide for lower level of regulatory oversight due to lower risk of the proposed research. Sponsors should be able to make such risk assessments for their proposed study and include a justification into the clinical protocols.

The current rigid regulatory system provides hurdles for conduct of "low" risk studies, which make it impossible to conduct clinical trials in some countries. Currently, the requirement for a biological product used first time in humans is the same as for a clinical trial involving a licensed product. We had, for example, a recent experience, where the labelling requirements for the use of a licensed Ophthalmic product in a very small container could not be met in some countries due to lack of space. This does NOT present risk to a patient who will get information through the mandatory patient

information sheet. As a consequence the trial could not be conducted in those countries and patients could not participate in the clinical research.

In alignment to a more risk proportionate regulatory oversight, monitoring and insurance requirements could be adapted as well. In France, a lower insurance fee for academic studies exists already today.

Consultation item 10:

Pharmaceutical Industry has been able to work under the current rules and this requirement has not presented any hurdles. However, we acknowledge the bottleneck this may create for academic centres when conducting multi-national protocols. We would support the adaptation of this requirement to better reflect the practice of academic research in order to maintain the high level of scientific expertise, Industry-Academia collaboration opportunities and make research in Europe more efficient and dynamic in the future.

Consultation item 11:

We agree that in the short-term, the revision of the existing implementing guidelines is needed to achieve a greater harmonization in parallel to more long-term legislative changes. It would be important to involve all stakeholders in the revision process of the guidelines to ensure that the revised requirements can be implemented into the practice. The revision of the guidelines should be driven by the overall objective of risk proportion, harmonization and seamless integration of clinical research into drug development. A strong leadership commitment from the Commission to move the process forward in a timely manner would be very welcome.

Consultation item 12:

We believe that most of the Clinical Trials Directive text would need to be amended and the existing Q&A documents would need to be included into the legal texts to provide more binding clarification. However, we fear that such modification may not address the current issues completely because national transposition may continue to result in divergent national requirements. In addition, such revisions would not be implemented in practice within the next 5-7 years.

Consultation item 13:

The legislation was adopted to harmonize patient protection and safety and having differing standards would undermine this objective. Therefore, we are against the creation of a system based on sponsor classification, but support a proportionate system based on the risk to the participants.

Consultation item 14:

We do not believe that the clinical trial legislation would need altering to promote paediatric trials. The legislation as such does not create a hurdle for conducting paediatric clinical trials and the requirements for all clinical studies should follow the same principles.

In our experience patient recruitment and complex trial designs may be causes creating bottlenecks for paediatric research today.

Political support at the EU and national level to promote research in children and educate parents about the realities of clinical development is needed.

The conduct of global paediatric study programs with simplified designs as agreed with EMEA and FDA may solve some of the issues.

To support a speedy paediatric drug development, we would suggest considering incentives to provide, for example, priority evaluation of paediatric studies designed to address an unmet medical need within a shorter timeline, or allowing a hospital pharmacy to produce paediatric enabling formulations for the conduct of a specific trial without the requirement to have a GMP certification.

Consultation item 15:

We believe some uniform practical legal provisions to handle informed consent in emergency situations would be helpful to avoid legal uncertainty for treating physicians. The ethical considerations should be carefully balanced against the urgency of the situation in which time is usually very critical.

A simplified process to obtain consent from legal representatives or an independent second doctor may be considered after general approval of the protocol by an Ethics Committee.

Consultation item 16:

All clinical research conducted by global pharmaceutical companies is according to internationally agreed principles. Sponsors usually have internal quality control and assurance functions to ensure robust data generation, data integrity and GCP compliance. Statements to certify GCP and GMP compliance are included in the regulatory submission documentation.

Today, GxP inspections are carried out by a NCA under the co-ordination of the EMEA and further initiatives for closer transatlantic and international collaboration to maximize inspection capacity are underway.

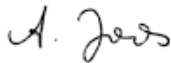
EU support programs to facilitate capacity building in third countries for supervision and enforcement of international principles could be an option.

Consultation item 17:

We would support the member states to work toward a harmonized inspection standard that would further promote consistency in the conduct of inspections and which would focus on the highest risk compliance attributes based on regulation. Such harmonization may further serve to reduce the number of inspection observations by the various inspectorates that are not necessarily based on codified "regulation" but which are rather cited based on a particular inspectorates view point of how sponsor processes would optimally be executed.

We welcome the opportunity to comment on this Commission consultation and look forward to further discussions. Please do not hesitate to contact me if you have any questions.

Yours sincerely,



Angelika Joos