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Brussels, May 13th 2011

Re : Public Consultation: Concept Paper regarding proposed Revision of the 'Clinical Trials Directive' 2001/20/EC

Dear Madam, Sir,

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 biopharmaceutical products available today.

Merck has reviewed the above referenced document and is providing the following comments for your consideration.

We appreciate the opportunity to comment on this document and hope that you will take our comments into consideration.
Should you need additional information or wish to hold further discussions with our company experts, do not hesitate to contact me.

Yours sincerely,

A. Joos

Angelika Joos
Encl.

COOPERATION IN ASSESSING AND FOLLOWING UP APPLICATIONS FOR CLINICAL TRIALS

1. Single submission with separate assessment

Consultation item no. 1

We fully agree that submission of a uniform dossier without any additional national requirements to a single portal would greatly reduce the administrative workload connected with national tailoring of submission documentation. The validation of documents by one administrator would ensure that standardized requirements are adopted and published which allow sponsors to achieve a "first-time-right" submission and save resources. Such approach requires that sufficient funding for human resources and infrastructure from EU or national level is made available to develop the appropriate submission infrastructure as a basis for enhanced virtual collaboration. In addition, we recommend that the standards for the submission process are developed in an inclusive process with all stakeholders, ie. agencies, researchers, industry etc., so that the needs of all parties are reflected. Eventually, the submission is only one step in the process, and other steps should be streamlined as well (for more see below) to achieve greater European harmonisation.

Consultation item no. 2

We agree with the Commission appraisal that a separate assessment would insufficiently address the issue set out above: The difficulties created by independent assessments would remain. Conducting separate assessments will continue to lead to potential different outcomes as a convergence of regulatory and ethical standards will not be facilitated across Europe. Different assessment processes may be also questioned from an equality perspective since it would lead to unequal access to clinical trials, depending where patients live. However, any centralised assessment should also reflect local conditions (infrastructure, healthcare system etc.); therefore certain flexibility may be necessary. In addition, opportunities for Regulator Peer discussions and training and capacity building may be lost.

2. Single submission with subsequent central assessment

Consultation item no. 3

We believe that a central approach should not be ruled out from the outset, but needs to be thought through in more detail. We certainly agree that a full Committee review structure and its associated high cost and inflexible meeting schedules would make the review process very cumbersome with limited flexible time schedules. In addition, the assessment of trials which are conducted in only 1 or 2 countries, such as Phase I studies may be slowed down. Imposing an EU level Regulatory system on authorizations that are only relevant for a limited number of participating countries would unnecessarily take resources from non participating countries. Such Committee would only make sense if all Member States are concerned by the assessment process. The approval would need to be followed by a Commission Decision translated into 23 languages, which is unnecessary in most cases, as trials will seldom involve every single member state in the EU.

A closely coordinated virtual assessment procedure supported by a very good IT infrastructure and involving the relevant country experts may provide a pragmatic and fast solution.
Nevertheless, a Community Decision on Clinical Trials in the EU would potentially make it easier to open additional sites in other EU Member States in case of recruitment difficulties. Such additional countries may be possible to be added quickly with very limited additional Ethics review by the responsible Ethics Committee.

3. Single submission with a subsequent 'coordinated assessment procedure'

Consultation item no. 4
Scope of the CAP : We believe that the catalogue is complete.

Consultation item no. 5
We agree that all aspects under a) should be included in the CAP.
However, we would suggest that the co-ordination of the national and local ethical aspects is also included in the scope of the CAP to ensure an overall coherent process which is completed within the legal timelines. In this respect, the ethical aspects need to be better co-ordinated with the regulatory approval to ensure that clinical trials can start in Europe as soon as possible.

In the long run, standards for CT in the EU should be on the same level, and a more co-ordinated approach would enhance common standards where feasible. Currently, the ethical review by local country ERC is a complex process and very different from one country to another. A better co-ordination at national level may be a solution and has just been initiated in some countries such as UK and Belgium. National agencies could be given more responsibility to actively manage the national ethics approval. In addition, equity considerations should also be included in ethical assessments in order to ensure equal access to CT in the EU.
Bullet one and three under b) could eventually be centralized within the EU (similar to e.g. the product information given to patients, etc.).

Consultation item no. 6
Disagreement with the assessment report: Considering that CAP would only be initiated for multi-country trials, in case of disagreements, we would prefer that the concerned Member States could raise justified serious risk to public health issues, and opt out in case of major disagreements. This specifically is related to ethical concerns and differences.
Member states must have the opportunity to raise their justified concerns for a peer discussion. The concerned Member States should try to arrive at a common decision on public health and patient safety throughout the EU whenever possible. It is important, that the process for solving Member State disagreements does not prolong the legal timelines. Adequate appeal mechanisms should be foreseen.

Consultation item no. 7
Mandatory/optional use: The CAP should be optional for all multi-country clinical trials. It is a good approach to achieve a simple and harmonized system and set similar standards across the EU. For single site or single country trials, specifically Phase I studies, faster procedures facilitated by the national agency concerned should be adopted. Nevertheless, the same principles and requirements should apply to all clinical trials conducted on EU territory.

Consultation item no. 8

Tacit approval and timelines: Pre-assessment by the sponsor may be a good proposal. A system similar to that currently in operation in the UK with a table or Q&A defining the criteria would be an interesting option. However, if the pre-assessment step in general adds to the overall timeline for all clinical trial assessments, there may be limited benefit in having such step to identify certain Type A trials with potential shorter timeline.
Tacit approval for Agencies as well as Ethic Committees in case the legal timeline has passed is supported to allow a predictable development timeline and planning.

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

1. Limiting the scope of the Clinical Trials Directive

Consultation item no. 9

Enlarging the definition of 'non-interventional' trials : We agree that a narrow definition of Clinical Trials should be stated in the legislation to provide clarity and avoid any divergent interpretation. The FDA has recently adopted the following wording: "Clinical trials are any prospective investigations in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects."
In addition, we propose that the definition of "non-interventional studies" should be deleted from the Directive to avoid any legal uncertainty.

According to the recently adopted Pharmacovigilance legislation (amending Directive 2001/83/EC), Chapter 4, protocols for all non-interventional post-authorisation safety studies are reviewed and approved by the new Pharmacovigilance and Risk Assessment Committee. As such a part of non-interventional studies are already conducted under European regulatory oversight. This new legal requirement needs to be considered when developing a comprehensive system without any potential for duplication. Any potential for conflicting guidance, as conflict with existing ISPE guidance, Volume 9A, and still to be written "Good Pharmacovigilance Practice" is quite possible and should be taken into account.

Currently, non-interventional studies are locally regulated, but regulation is very different from one country to the others; Harmonization of the requirements in EU are certainly useful to better compare the results and enable EU wide compliance oversight. However, we believe that such harmonization efforts should perhaps be done through a different legal instrument and not embedded into the Clinical Trials legislation.

Consultation item no. 10

Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive : We fully agree with the appraisal. "Patient safety" is the primary objective, not the nature of the sponsor organisation

2. More precise and risk-adapted rules for the content of the application dossier and for safety reporting

Consultation item no. 11

We agree that more detailed rules enshrined in EU legislation would help achieving greater harmonization of these aspects at local level. Specific attention should also be given to synchronizing the timelines for national implementation of such rules across all EU countries.

Consultation item no. 12

Please consider writing EU –wide rules on the definition of "risk-based-approach".
In addition, local guidance exists in several therapeutics areas (e.g. Diabetes) which conflicts with international guidance usually applied for global protocol design. EU-wide guidance related to specific clinical trial design aspects should be linked to the relevant regulatory development guidance governed by the CHMP/EMA.

3. Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'

Consultation item no. 13

Auxiliary medicinal products could be defined by the intention of usage as well as the mode of administration (e.g. parental vs. local capsaicine) and sponsors should be able to justify, if a complete data set cannot be provided.
Auxiliary products would include both non-IMP (rescue, background, challenge agents) as well as ancillary materials, such as infusion/saline solutions, etc. Please add specifically PET tracers used as a diagnostic agents and other diagnostics to the list of auxiliary medicinal products.

4. Insurance/indemnisation

Consultation item no. 14

Policy options: We question how and who would define the "low-risk trials"?
If indemnisation by Member States is only optional, there is a risk that Member States will not offer such insurance mechanism. How would compensation in those cases be ensured?
If Member States are made responsible to offer insurance schemes for those "low-risk trials" we believe that such coverage should be mandatory.

5. Single sponsor

Consultation item no. 15

We can support both policy options.

6. Emergency clinical trials

Consultation item no. 16

We agree with the appraisal.

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

Consultation item no. 17

We generally agree with the appraisal as outlined by the Commission.

As it relates to clinical trial registration and results posting, we would urge striving for global consistency with existing registration and results posting requirements that already are legislated in other ICH regions i.e. the US and the clintrials.gov database. Mandatory inclusion of trials conducted in third countries into the EudraCT database would present an additional complexity and administrative burden requiring additional resources without additional public health benefits. The European Union should rather work collaboratively with other regions to co-ordinate the transparency of Clinical Trials without unnecessary duplication of registration or differing requirements.

The Joint Industry position on the disclosure of Clinical Trial Information via Clinical Trial Registries and Databases[1] and the Joint position on the Publication of Clinical Trial Results in the Scientific Literature[2] discuss this topic and outline the Industry principles of trial registration and result publication on a global basis. IFPMA has also established a clinical trials portal since 2005[3] which allows public access to clinical trial information from companies as well as clinicaltrials.gov.
In addition, the WHO already operates an International Clinical Trials Registry Platform to ensure that a complete view of research is accessible to all those involved in health care decision making[4]. In this respect, we strongly discourage the EU to require an additional mandatory registration of third country trials within EudraCT.

1 http://clinicaltrials.ifpma.org/clinicaltrials/fileadmin/files/pdfs/EN/November_10_2009_Updated_Joint_Position_on_the_Disclosure_of_Clinical_Trial_Information_via_Clinical_Trial_Registries_and_Databases.pdf

2 http://clinicaltrials.ifpma.org/clinicaltrials/fileadmin/files/pdfs/20100610_Joint_Position_Publication_10Jun2010.pdf

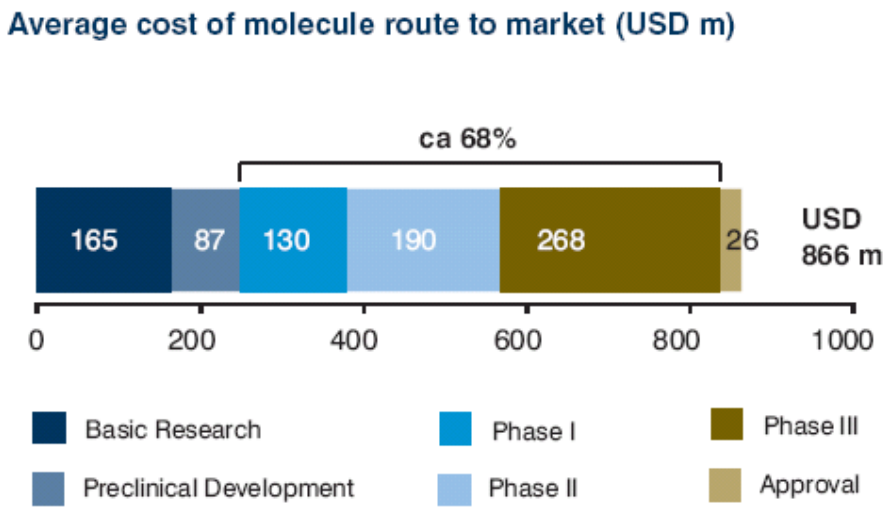
3 http://clinicaltrials.ifpma.org/clinicaltrials/no_cache/en/myportal/index.htm

4 http://www.who.int/ictrp/en/

FIGURES AND DATA

Consultation item no. 18

Clinical trials are the most expensive part of R&D.[5] As they are lengthy and costly, clinical trials constitute a very important component of the drug development process – approximately two-third (i.e., c. USD 590m) of average cost of molecule route to market is allocated to clinical trials.[6]



Source: PWC (2010), p. 9

Costs of clinical trials seem to have risen by one third between 2005 and 2007 due to increasing regulatory and other requirements.[7] Hearn et al. conclude from interviews with Directors and senior staff in 8 Clinical Trials Units (CTUs) in the UK "[…] that the EUCTD has resulted in a doubling of the cost of running non-commercial cancer clinical trials in the UK and a delay to the start of trials."[8]

As shown in the annex, the number of clinical trials is constantly decreasing in the EU. Overall, the share of the EU in clinical trials globally is diminishing. If the EU wants to stay a significant player in this area over time it has to create more favourable conditions for sponsors to place studies in the EU. There are factors (e.g. patient populations) which the EU can not influence, however, others which are very well in the power of the EU to change. Creating a more favourable, fast and uniform regulatory environment is the most important among them.

[5] EFPIA (2010), The Pharmaceutical Industry in Figures, www.efpia.org

[6] PriceWaterhouseCoopers (2010), Clinical Trials in Poland. Key Challenges

[7] See Rawlins M (2008), De testimonio: on the evidence for decisions about the use of therapeutic interventions; in: Lancet 372:2152-61, p. 2156; Collier R (2009), Rapidly rising clinical trial costs worry researchers; in: CMAJ 180(3):277-278

[8] Hearn J, Sullivan R (2007), The impact of the 'Clinical Trials' directive on the cost and conduct of non-commercial cancer trials in the UK; European Journal of Cancer 43:8-13, p. 8

Country trends in participation in clinical trials – 2008

Rank	Country	Number of sites	Share by sites (%)	Growth (%)	Site density (no. of sites per 1 m population)
1	USA	36,281	48.7	-6.5	117.4
2	Germany	4,214	5.7	11.7	51.5
3	France	3,226	4.3	-4.0	49.3
4	Canada	3,032	4.1	-12.0	89.0
5	Spain	2,076	2.8	14.9	45.1
6	Italy	2,039	2.7	8.1	33.9
7	Japan	2,002	2.7	10.3	15.7
8	UK	1,753	2.4	-9.9	28.3
9	Netherlands	1,394	1.9	2.1	84.0
10	**Poland**	**1,176**	**1.6**	**17.2**	**30.8**
11	Australia	1,131	1.5	8.1	50.9
12	Russia	1,084	1.5	33.0	7.6
13	Belgium	986	1.3	-9.4	91.1
14	Czech Rep	799	1.1	24.6	76.0
15	Argentina	757	1.0	26.9	18.9
16	India	757	1.0	19.6	0.6
17	Brazil	754	1.0	16.0	3.9
18	Sweden	739	1.0	-8.6	79.1
19	Mexico	683	0.9	22.1	6.1
20	Hungary	622	0.8	22.2	62.1
23	China	533	0.7	47.0	0.4
26	Ukraine	440	0.6	31.0	9.6
31	Romania	354	0.5	19.4	15.9
35	Slovakia	246	0.3	27.7	45.7
37	Bulgaria	215	0.3	12.7	28.4
42	Lithuania	146	0.2	30.2	43.7
50	Estonia	83	0.1	34.6	61.9

Note: Trial density is the number of recruiting sites divided by country population in millions.
Source: Datamonitor

CEE/SEE/CIS