FUEHRING Stefan (ENTR)

From: ENTR /F/2 PHARMACEUTICALS
Sent: lundi 11 janvier 2010 10:03
To: FUEHRING Stefan (ENTR)
Subject: FW: Assessment of the functioning of the Clinical Trials Directive

A/613

FROM:
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Dear Sir/Madam

Please find enclosed my comments and reply to the public consultation of DG ENTR.
Sincerely
Fatima Cardoso

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?

In the large centers from western countries there was very little improvement in patient protection since this was already a major concern. There was however a huge increase in the paperwork, time required and costs which led to a decrease in the number of studies opened and in the number of patients included, especially in academic trials.
I am not aware of studies showing the benefits of the Clinical Trials Directive but there are many studies showing the negative consequences of this Directive specially increased time and cost for trial approval, important decrease in academic-led trials and important decrease in trials opened in Europe overall; this has had negative impact for European patients with less access to clinical trials and new treatments.

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

Yes this is accurate with the exception of the conclusion that “with the exception of one Member State, there has been no decrease in clinical research activity in the EU”. There are several publications contradicting this statement and showing a clear decrease of clinical research in Europe especially regarding academic-led research. Even by using the data presented in the graphics of the first pages of this report we can clearly see a huge decrease in number of patients included in clinical trials in Europe. One explanation may be related to the fact that, because trials take so long to be open in Europe, the active part of the trial in European centers is quite shortened and hence fewer patients are included.

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

Yes this is an accurate description; I would say that “double” would be an accurate assessment of the impact, at least.
Important examples are a) academic trials for several reasons but particularly the problem of insurance for multinational academic trials; b) another important example are trials non-drug related such as radiotherapy and surgery trials, for which there is no support from pharmaceutic industry and no support either from other sources at an European level.
It is also urgent and indispensible to solve the problem of the cost of drugs given in control arms of academic trials since, if given according to reimbursement guidelines, should not be paid by the study sponsor.

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?

Option A: this is the better option; it is similar to the current situation in countries such as Belgium that have chosen to not to have a central national ethics committee (EC) but where a local EC acts as central for a particularly study; this avoids an overload of a central body and hence fewer delays in the approval process.
Nevertheless, clear guidelines on how to evaluate the different type of trials must be put in place since, although this option can allow a faster procedure, it can also lead to important differences in trial assessment.
Another foreseen issue relates to the very different laws in individual countries related to collection and transport of biological material. Translational research is nowadays an intrinsic part of a clinical trial and collection of biological material is indispensible; additionally it is indispensible to share this material and centralise its analyses to increase quality and decrease costs and quantity of material used.

Option B: it is too centralized with a big potential to lead to important delays in the assessment and approval process. We already have the example of countries 9for example Portugal) that have implemented a central EC or approval body where the time for trial evaluation and approval is much higher and many times beyond acceptable levels. If this option is chosen then this “central body” must be extremely well staffed both in terms of number of members and in terms of available expertises and member states, and once again clear guidelines for the assessment process must be implemented.

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?

Option 3.4.1 is too centralized and the same comments as above (item 4) apply.

Option 3.4.2 is the preferred one: one member state could function as the reference one for a specific trial for all issues including regulatory and ethical approval. For different trials there would be different reference members, de-centralizing the procedure which would speed up the process. However, as said also for item 4, guidelines are indispensible to assure a uniform way of evaluating trials; it is also indispensible to take into consideration and legislate regarding issues about collection and transport between countries of biological material collected in the context of a clinical trial (please see also comment given in item 4).

What is described in option 3.4.3 is indispensible whichever decision is taken.

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

Yes this is an accurate description.
In the definition of “clinical trials” there are at least 3 specific cases that need to be defined and included since they are specific cases that perhaps need specific legislation: a) translational research trials and b) “strategy trials” (i.e. trials using already approved treatments where the question relates to a strategy of management and not to a specific treatment) and c) trials using approved treatments being evaluated in different settings. For cases b) and c) the risk for the patient is clearly inferior than in a phase 1 trial and therefore requirements for insurance, SUSAR reporting, monitoring, etc should be different.

Consultation item n°7: Is this an accurate description? Can you quantify the impacts?

Are there other examples for consequences?

Yes this is an accurate description. There are additional huge difficulties for multinational trials with collection of biological material. Cancer treatment is fast moving towards personalisation and each cancer type classified into several subtypes for which separate trials must be run. Addressing important questions in large numbers of subpopulations of patients can only be done through multinational trials.

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?

Option 4.3.1 would take too long and could still lead to different interpretations and implementation in each member state. Therefore option 4.3.2 is preferable.
The Regulation should address all issues and special cases described above (academic trials, non-drug related trials, strategy trials, translational research, collection and transport of biological material, multinational trials…) and be very clear in terms of guidelines for assessment and approval of trials.

In my opinion, the different transposition of the Directive to national laws is a bigger problem.

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

Please see comment to item 6. The risk in a trial using already approved drugs is very different from a phase 1 trial. This could be addressed by clearly defining specific cases such as the ones described in my comment to item 6.

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

Yes, I agree.
Some examples of “Requirements not always adapted to the practical circumstances” are “international registries” such as the ones ongoing in the field of breast cancer (pregnancy and breast cancer and male breast cancer). These are non-therapeutic studies but with collection of biological materials (blood, tumour and placenta). The risk for the patients is almost non existent (only associated with the collection of biological material that would be collected as part of current practice also) and yet in some member states expensive insurance is demanded.

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?

A revision of guidelines, albeit necessary, is insufficient to address this problem in a satisfactory way since issues of insurance, monitoring, single sponsor, reporting are a crucial component of the existent problems and need to be addressed.

The rules for safety reporting, for labelling of the IMP and for reporting of SUSARs need to be revised. There should be a mechanism to submit the SUSAR only once at a national level (in the present situation every study using a certain drug must report all SUSAR from all trials using that drug which means that the same SUSAR is reported several times increasing exponentially the work of ethics committees and regulatory authorities that need to revise them all); the safety reporting can and should be simplified specially for already approved drugs (in phase 3 trials there is generally no need to report all SAE from already approved drugs used in the control arm). Labelling requirements should be the same in all member states.

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?

This would be a better option and should address issues described above such as insurance, monitoring, single sponsor, reporting, and collection and transport of biological material in the context

of a multinational clinical trial.

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

In principle I agree but it depends on the definition of "academic trial". Additionally, the definition of "academic trial" must the same in all member states otherwise a multinational trial could eventually be considered differently by different member states, which would lead to huge problems. For example the MINDACT trial, partially funded by the EU under the Framework VI Programme, would not be possible if classified as academic in some countries and non-academic in others.

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?

I am not qualified to answer this question, except to say that it is essential to consult the experts in this area as well as patients/parents associations.

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?

I do not have enough expertise in this field to answer this question, except to say that it is essential to consult the experts in this area as well as patients associations, and also to look for the examples of some good trials already run in this field.

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

Europe, and to a lesser extent also the US, are loosing some of their leading position in clinical research. Countries such as India, China and some African countries are big enough to run large trials exclusively in their territory, and the cost and complexity of the activation process is substantially inferior, which makes them attractive to the Pharmaceutic Industry. However, at least for the moment, the quality of the data and particularly the capacity to collect and the quality of biological material are clearly inferior. Facilitating large multinational high quality trials with translational research components can be a strong and attractive point for Europe to keep a leadership position in cancer clinical research.

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

Regarding the options proposed I have 3 comments: "Self-regulation by EU-based sponsors" does not seem feasible or reliable. "Strengthening a culture of transparency" is of course important but registering a trial does not by itself insure that it is conducted correctly. "Strengthening scrutiny of clinical trials results of which are submitted to the EU, or which are financed in the EU" is crucial but does not solve the problem of trials that are exclusively run in 3rd countries.

Additional options are a) facilitating high quality trials as described above; b) Demand that all registration trials must be run in at least one EU member state if the approval of IMP is to be given for Europe.

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?

As mentioned throughout my comments it is essential to include issues of translational research and transport and sharing among countries of biological material collected in the context of multinational clinical trials or projects.
SME involvement is important but raises issues of ownership of knowledge and property rights that if not well clarified significantly hinder sharing of knowledge and resources among investigators.

From: jan-willem.van-de-loo@ec.europa.eu [mailto:jan-willem.van-de-loo@ec.europa.eu]

Sent: 18 November 2009 17:43
To: Piccart Martine
Cc: Cardoso Fatima; Meirsman Livia; Straehle Carolyn
Subject: Assessment of the functioning of the Clinical Trials Directive

Dear Prof Piccart and coworkers,
Assessment of the functioning of the Clinical Trials Directive until 8 January 2010.
In its Communication of 10 December 2008 to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on "Safe, Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector", the Commission announced that an assessment would be made of the application of the Clinical Trials Directive.This assessment would consider, in particular, various options for improving the functioning of the Clinical Trials Directive with a view to making legislative proposals, if appropriate, while taking the global dimension of clinical trials into account.

The public consultation of DG ENTR is available at:
http://ec.europa.eu/enterprise/pharmaceuticals/clinicaltrials/clinicaltrials_en.htm
and the consultation document is at:
http://ec.europa.eu/enterprise/pharmaceuticals/clinicaltrials/docs/2009_10_09_public-consultation-paper.pdf
Best regards,
Jan van de Loo

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