KUROS

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Sent by e-mail to: sanco-pharmaceuticals@ec.europa.eu

Zurich, 11.05.2011

Re: Comments from Kuros Biosurgery AG to: REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC - CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

Dear Sir or Madam,

Kuros Biosurgery AG is hereby providing its comments to the Concept Paper on the Revision of the Clinical Trials Directive 2001/20/EC following its release for public consultation in February 2011.

- Kuros Biosurgery AG, Zürich, Liechtenstein acts as a sponsor for several clinical trials in the European Union (while Kuros Biosurgery International AG, Fürstentum, Liechtenstein acts as the legal representative).
- Kuros Biosurgery International AG, Fürstentum, Liechtenstein has been granted SME status by the EMA.
- Kuros Biosurgery allows its contribution to be made publically available on the "Clinical Trials" website.

Please do not hesitate to contact us if you have any questions.

Sincerely,

N. Falla

Nancy Falla, PhD
Head of Regulatory Affairs

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Comments of Kuros Biosurgery AG to the Concept Paper on the revision of the "Clinical Trial Directive" 2001/20/EC dated February 9, 2011

Consultation Item 1:
The idea of an EU portal distributing the documentation to the different Member States is supported by Kuros but is insufficient and unlikely to reduce the administrative costs. This portal would only be fully useful if all the countries would accept the same documentation package, i.e. if there would be no need for country specific documents, and if all the countries would accept that the documentation is submitted in English only.

Consultation Item 2:
Kuros agrees that if only a portal distributing the documentation is implemented, difficulties would remain. It is Kuros opinion that in addition to this portal, there should also be a central assessment of the documentation, a single process for the generation of questions should be defined in terms of logistics and timeframe, and there should be a single approval process.

Consultation Item 3:
Kuros is very much in favor of a single submission with a central assessment. The reasons mentioned in the concept paper for ruling this option out are not considered convincing by Kuros. The arguments presented in the position paper seem to reflect a concern of the Member States that their local authority position in the evaluation process would be weakened.

In particular:

- While ethical and site suitability assessments should remain the responsibility of the Member States, it is not clear to Kuros why "this option would insufficiently take account of … national, and local perspectives. For these aspects, a parallel, national, procedure would have to be established in any case". Indeed if a central office is established in the European Union where scientific staff representing all European countries would be permanently based and would perform the scientific and regulatory assessment of the clinical trial applications, then the national and local perspectives of the Member States would be represented.
- It is not clear to Kuros why "The sheer number of multinational clinical trials per year (approx. 1 200) would make centralised assessment very difficult. To this would add all substantial amendments of the clinical trials" since anyway these amount of procedures have to be handled currently and the present position paper describes that this represents a multiplication of individual assessments. It is also unclear to Kuros why the staff in this central office would need to be larger than if assessors would be located in all European Member States. Instead, a central

office would make the multinational review and approval process easier (e.g. like FDA who represents all 52 States).

- Regarding "The involvement of all Member States is not needed, as very few clinical trials are rolled out in more than five or six Member States." Kuros opinion is that this is a correct statement. However this issue is easily solved if the assessment is performed by the scientific staff from the concerned Member States only. For Kuros, the word "centralised" refers only to the central localization of the experts in one single European office and does not mean that all the assessors of all the Member states must be involved in the central assessment. The number of countries could just be specified in the clinical trial application. The subsequent approval would then be obtained for the selected countries only. In some countries less clinical studies are performed: these countries could either have less staff delegated in the central office, or there could be a rotation of staff such that scientific experts representing their own countries would also be allowed to assess submissions for other countries.
- It is not clear to Kuros why "a Committee structure requires frequent meetings with a robust supporting infrastructure. The costs (and, consequently, fees) involved would make this mechanism unattractive for academic researchers". It is unclear to Kuros what is the definition of "frequent meetings" is. If there is no central office and the experts remain located physically in each of the Member States then this will indeed require a robust infrastructure and possibly increased costs due to travelling, logistics... This is why a central office would facilitate communication and procedures and could help reducing fees. In addition, there could be fee reductions for Small and Medium Enterprises (SME) as already granted by EMA and for academic researchers.

In conclusion, Kuros does not agree with the rationales for ruling out this option presented in this position paper.

Consultation Item 4 and 5:

Kuros agrees with the "catalogue": the assessment should apply to initial authorisation and to substantial amendments and should only cover the risk-benefit assessment, as well as aspects related to quality of the medicines and their labelling. Only ethical and site suitability assessments could remain outside the CAP.

Consultation Item 6:

A combination of both options 1 (Member State could opt out) and option 2 (majority vote) are preferred. In addition, the Sponsor should be allowed to withdraw the application from certain Member States without impacting the assessment from other Member States in the context of a centralized process. The sponsor must also be allowed to add more countries while the study is ongoing covered by the initial CAP since this is a frequent need.

Consultation Item 7:
The CAP should be mandatory for all clinical trials if a central European Office is established as proposed by Kuros in the previous Consultation Items. This mandatory procedure is necessary in order to avoid duplication of the scientific evaluation staff. The number of countries could just be specified in the clinical trial application.

If a there is no central office and the experts remain located physically in each of the Member States, then the CAP should be optional, and there should be clear advantages for the industry to use this procedure otherwise the companies will continue to submit the clinical trial applications as they do presently.

Consultation Item 8:
It is Kuros opinion that the concept of type A trials (e.g. for marketed products used in the context of the approved indications) is good however they would have to be assessed with equal priority to non-type A trials.

Consultation Item 9:
Kuros agrees that it is better to come up with harmonised and proportionate requirements which would apply to *all* clinical trials falling within the scope of the present Clinical Trials Directive.

Consultation Item 10:
Kuros is in favor of harmonised and proportionate requirements for clinical trials which would apply independently of the nature of the sponsor ('commercial' or 'academic/non-commercial'). As mentioned in the Concept Paper, it is indeed difficult to understand why certain rules to protect the safety and the rights of participants and the reliability and robustness of data should apply to some types of sponsor and not to others.

Consultation item 11:
Kuros agrees with the preliminary appraisal. There should be greater harmonisation of the contents of the submissions and ICH guidelines should be taken into account.

Consultation item 12:
Besides the harmonisation of the contents of the periodic safety submissions it would greatly reduce the administrative work of the sponsor and contribute to improving the compliance if frequency for periodic safety reporting would be harmonised across all EU countries.

Consultation item 13:
Kuros does not agree with the proposal to introduce the notion of "auxiliary medicinal products". Indeed, before the clinical trial it is not possible to establish a precise list of which additional treatments the patients will require (e.g. a rescue treatment). We presume that this proposal is motivated by the concern to limit risks of drug-drug

interactions. It is up to the sponsor to evaluate any potential interactions of IMPs with "non-IMPs" and study them in appropriate clinical studies.

Consultation item 14:
Kuros is of the opinion that the insurance/indemnification should remain as it is currently covered for the clinical studies, since the Sponsors have a better knowledge of their products to ensure appropriate insurance and indemnification.

Consultation item 15:
Kuros is in favor of a single sponsor. Allowing multiple sponsors might lead to contract problems when defining responsibilities, and therefore might complicate clinical trials.

Consultation Item 16:
Kuros is in favor of an amendment to allow emergency clinical trials in line with what is already done in the USA.

Consultation item 17:
It is indeed good to build capacity in third countries in order to ensure that the standards are followed. It is however unclear to Kuros how capacity building in third countries will be further support compared to what is currently in place: a more detailed proposal would have to be made available for consultation.
Kuros would appreciate that the clinical trials in third countries and intended to be used to support registrations in the European Union would be registered in the EU clinical trials database since this would enhance the transparency.

Consultation item 18:
It is difficult for Kuros to comment on the Annex listing the key figures. The Competent Authorities are probably more able to provide comments since they possess the actual data.