EORTC
European Organisation for Research and Treatment of Cancer
AISBL International Non-Profit Association under Belgian law IVZW

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EORTC comments on the draft version 3 of the Guidance for the request for authorization of a clinical trial on a medicinal product for human use 7th of September 2009

Page	Article	Comment
In general		It is not clear if annexes are supposed to be updated at the same time (annex I, annex II and annex III); we expect annex I will be updated to be in line with the EudraCT data base. We would like to make one comment on Annex I: to eliminate the difference between CTA form for CAs and ECs (the only field of difference is the address of EC provided to CA and address to CA provided to EC) as management of 2 different pdf increase the bureaucracy without any added value. We would also like to know by which mechanism we could provide comments to the last version of the Annex I (the one to be used with the version 8 of EudraCT)
In general		We would suggest to propose the use of EudraLink for the submissions of dossiers for all member states
In general		We regret the disappearance of the table of documents required by different countries and would have preferred its modification in the sense of harmonization.
In general		This revision may have been an occasion to further move towards harmonization of formats and requirements, however it seems to us that current proposal focalizes on the clarification of issues not specified before and do not really address the harmonization problem
7	2.1.2.	We welcome the clarification of the fact that validation is part of 60 days period. However, the tacit authorization is still problematic. Authorities may have delays in their process and therefore the grounds of non-acceptance sometimes arrive few days after the expiration of the waiting period for the tacit approval. We would recommend to all member states to at least, as done by Austria, to post confirmations of absence of grounds on non-acceptance on their web site at the date of tacit approval.
8	2.1.4.2	We welcome clarification on amendments during the initial evaluation of the trial.
8	2.1.4.3	The clarification on the process of withdrawals is welcome; however the pertinence of phone contact as pre-step is not clear for us, particularly given the speed of modern means such as e-mail or fax and the possibility to

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		trace it.
9	2.1.6	The text proposed will further stimulate the use of national languages which is prohibiting for international research. We would advise to rather encourage the use of English at least for the CTA form and cover letter, but also for replies (for your information, Belgian authorities add on their communications unofficial English translation on top of the text in the national language; provided important part of the communication are standard letters this seems very feasible to us)
10	2.3	Is there a possibility to give a room for correction of the information given during the request of the EudraCT number?
11	2.4, point d	Our first general proposal will already minimize the possibility of divergences; However, it is a matter of fact that some ECies do not require the Annex I, but their form instead and given questions might be formulates slightly differently, the information they get might be interpreted in a different way; this further emphasize the need to harmonize forms, including EC forms
13	2.6 second paragraph	The text imposes the need for an IB within the request for authorization which is in contradiction with the simplified IMPD dossiers which only have an SmPC. We propose to put instead: "…has to be accompanied with an IB or SmPC or both, as applicable" which is more consistent with the rest of the guideline
15	2.7.1	In addition to description of what is required for drugs without MA, it shall be added <u>what is not required for those with MA.</u> We would propose that it is clearly stipulated that no QP declaration or manufacturer's authorization is needed for drugs with MA and manufactured at facilities covered/described in this MA (in other words supplied through the same chain as commercial supply)
18	2.8.3.	Duplicate word in the title We welcome this section which clarify several issues crucial for many trials conducted by non-commercial sponsors (e.i. trials on generics)
22	3.2	It would be very helpful to introduce a notion of administrative substantial amendment: in terms of common sense, when one CRO responsible for the drug release is replaced by another one (both officially registered) or when they change the address – it is a substantial amendment because this information is in the CTA form. However, there is no real room for approval as

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		such – it is rather an approval by acknowledgement. The delay of 35 days is therefore too long for this. We suggest either to consider these changes as non-substantial or to request their approval immediately upon reception of a valid request for amendment (within the timelines of validation)
23	3.3.	We do appreciate the effort made to clarify the issue of classification of amendments. However, we do regret this list is heavily incomplete as compared to lists developed by authorities in some MSs, such as France & Belgium. This will lead to further divergences in interpretation.
	3.3.1	We welcome the clarification on the fact that adding, deleting exploratory tertiary end-point is not substantial. We would like to add that the fact to increase the duration of the trial (without changing the number of events/patients) should not be substantial.
24	3.3.3. Bullet4	Changes of internal organization of the sponsor may be the change of the name of the applicant. From the text proposed we understand this is a non substantial change. However, up to now any change to the xml file or CTA form is considered by most MSs as substantial. Therefore, we suggest to put clearly that "any change to CTA form or xml file shall not be considered necessarily as substantial"
25	3.4 §4	This is an additional step which we do not see the use of. Both CA and EC receive the amendment – for approval or information as applicable. Similarly to the initial application, it shall be the responsibility of the sponsor to start only provided appropriate approvals has been obtained. The only pertinent information which may be required is in the framework of negative output. Indeed it is relevant to require informing the body to which the amendment was sent for information only that the body responsible for approval has definitely rejected the amendment.
27	3.6	Same remark as for implicit initial approval
28	3.8	We would suggest to clearly state that the halt foreseen in the protocol (stop of recruitment for IDMC or between 2 phases of the same protocol if foreseen upfront) is not a temporary halt of the trial in this context and do not need to be notified
	Section 3 in general	Is there a room for urgent amendment for reasons different from urgent safety measures? Example – there is a significant change in labels due to acquisition of one company by another or a change in the manufacturing site (for drugs with MA), but there is an urgency in drug

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		supply because of expiry or unforeseen boost in recruitment.
31	4.2.1&4.2.2	It is not clear if deadlines are the same for EC
31	4.4	This section needs further clarification. The status of amendments which may happen after the end of the trial is still unclear. Aside the explanation about the requirement for the sponsor to notify any change to the ratio risk/benefit after the end of the trial, we would recommend to add that any other change to the protocol or trial does not need to be notified to either authorities or ethical committees (examples: change in intensity of the long term follow-up without any increase of risk for the patient, change, re-formulation of secondary endpoints, changes of PIs during the long term follow-up etc). Moreover, in some maintenance trials with a drug with MA, primary endpoints may already be achieved and trial finished and published – but patients still receive the treatment in their best interest (it is also sometimes likely they would receive it outside the trial). What are guidelines in case of a trial with patients still on treatment after the end of the trial? Is this treatment still under the responsibility of the sponsor or is this “off protocol”?