SUBMISSION OF COMMENTS ON

DETAILED GUIDANCE FOR THE REQUEST FOR AUTHORISATION OF A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES, NOTIFICATION OF SUBSTANTIAL AMENDMENTS AND DECLARATION OF THE END OF THE TRIAL

Please submit comments in editable document format (e.g. MS Word).

COMMENTS FROM WYETH Pharmaceuticals / Global Regulatory Affairs

1. GENERAL COMMENTS

Organisation	General Comment	Response from EMEA/EC [*to be completed by EMEA/EC*]
Wyeth	**Comments:** 1.1 Legal Basis (paragraph 2): "In this respect, Directive 2001/20/EC is exhaustive, i.e. the harmonisation is not based on minimum requirements, and Member States are not allowed to "add on" the Community rules." The addition of the sentence is welcome, as this clearly states that the provisions of Directive 2001/20/EC should have been implemented in a uniform manner across all EU Member States and that no additional Member State requirements are allowed. However, in practice this does not reflect the current situation today some 5 years after the implementation of the Directive, whereby some Member States have additional requirements which go beyond those laid out in Directive 2001/20/EC. Wyeth would like to emphasize that further efforts should be made by the Commission to ensure harmonization of requirements for CTAs across EU Member States.	

2. SPECIFIC COMMENTS ON TEXT

Line No + Para-graph No	Organisation	Comment, Rationale and Proposed Changes *If changes to the wording are suggested, they should be highlighted*	Response from EMEA/EC **[***to be completed by EMEA?EC***]**
2.2 Covering Letter (page 10, 2nd paragraph)	**Wyeth**	**Comments:** The second paragraph page 10 on SUSARS is unclear : "The applicant shall set out precisely in the cover letter where the reference information is contained as regards the assessment whether an adverse reaction is a suspected unexpected serious adverse reaction ("**SUSAR**") as defined in Directive 2001/20/EC and implementing Community guidelines." **Proposed change (if any):** We propose that the following sentence is re-worded for clarity and example sources of the reference safety information included, as follows: "The applicant shall set out precisely in the cover letter where the reference **safety** information **(e.g. current Investigator's Brochure or SmPC for marketed products)** is contained as regards the assessment whether an adverse reaction is a suspected unexpected serious adverse reaction ("**SUSAR**") as defined in Directive 2001/20/EC and implementing Community guidelines **(see also section 2.6)."**	

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Section 2.8.3 *Possibility to refer to the SmPC* *(page 18)*	**Wyeth**	**Comments:** 2.8.3: The title of this section needs correcting – currently reads "*2.8.3 Possibility to refer to the Possibility to refer to the SmPC*". The first sentence of this section allows for the possibility to submit the current version of the SmPC as the IMPD if an IMP has a marketing authorisation in any Member State or an ICH country and is being used in the same form, for the same indications, and with a dosing regimen covered by the SmPC. This sentence requires revision, as the SmPC would not typically be the approved labelling/ prescribing information in ICH countries outside of the EEA, e.g. for a product with a marketing authorisation in the US but which is not yet approved in the EEA, the US Prescribing Information (and not an SmPC) would be available. In addition, the possibility to use an IMP (for example, as a comparator) in a clinical trial which does not yet have a marketing authorisation in an any EU/EEA Member State but is authorised in an ICH country is welcome, however, it is uncertain whether this would be accepted in all EU Member States. **Proposed change (if any):** It is proposed that the title and the first sentence of section 2.8.3 is revised as follows: 2.8.3 Possibility to refer to the SmPC **or other approved prescribing information** The sponsor may submit the current version of the SmPC **or other approved prescribing information (for ICH countries outside of the EEA)** as the IMPD if an IMP has a marketing authorisation in any Member State or an ICH country and is being used in the same form, for the same indications and with a dosing regimen covered by the SmPC **or other approved prescribing information (for ICH countries outside of the EEA).**	

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Section 2.8.5 Overview (page 20, Table 1)	**Wyeth**	**Comments:** Column 1, row 2 - *"The IMP has a MA in any EU Member State **or ICH country**..."* The EUDRACT website and user manual will need to be revised accordingly. The current form does not facilitate entry of information on a non-EU source of an IMP. The European Commission should consider amending D.2.1.1.3: 'MA number of the form (if MA granted by an EU, EEA, ICH or MRA State).' The drop-down list of countries in D.2.1.2 section of the form should be extended to accommodate the additional countries. D.2.1.2.1 and .2 sections of the form should also be amended to refer to 'EU' Member State for clarity. The form should also be altered to facilitate several sources of comparators from both within and outside the EU.	

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Section 2.8.5 Overview (page 20, Table 1)	**Wyeth**	**Comments:** Column 1, row 5 *"The IMP has a previous CTA in the Member State concerned and has not been modified.* - *no new data available since CTA* - ***new data available since CTA**** - *different conditions of use"* *Additional clarity on how to handle new data would be appreciated. If new data has been added to the original CTA by non-substantial amendment or substantial amendment, is it necessary to provide the new data? One would presume that it is not necessary as the Member State will have access to the data either as a result of submission or inspection. Please include additional clarity in the document to confirm that it is not necessary to provide the new data. **Proposed change (if any):** It is proposed to revise the table as follows: *"The IMP has a previous CTA in the Member State concerned and has not been modified.* - *no new data available since* ***last amendment to*** *CTA* - *new data available since* ***last amendment to*** *CTA* - *different conditions of use"*	
Section 2.8.5 Overview (page 20, Table 1)	**Wyeth**	**Comments:** Column 1, row 7 *"The IMP is a placebo and the placebo has the* ***same composition****, is manufactured by the* ***same manufacturer*** *and is not sterile"* Additional clarity would be appreciated on "same composition" and "same manufacturer" and how this is being defined (e.g., what is the reference for assessing sameness).	

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Section 3.3.1. ***Amendments as regards the clinical trials protocol*** (page 23, 6th bullet point of section 3.3.1)	**Wyeth**	**Comments:** "*With regard to the protocol, the following is a non-exhaustive list of amendments which are typically "substantial":* • … • *Addition of clinical trials sites."* Whilst it can be agreed that the addition of clinical trial sites can be viewed as a 'substantial' amendment, we recommend additional text to clarify that this information should be notified to the competent authority (CA) for information only, as the ethics committee will be responsible for assessing this information. Indeed, although the revised guideline lists a number of examples of amendments that might be considered 'substantial' based on the criteria listed in section 3.3, it would also be helpful if guidance were also included as to which types of substantial amendments should be assessed primarily by the CAs and which substantial amendments should be assessed primarily by the ethics committees, and which types may require assessment by both the CAs and ethics committees, consistent with the guidance provided in section 3.4.	
Section 3.3.1 ***Amendments as regards the clinical trials protocol*** (page 23)	**Wyeth**	**Comments:** To enhance the efficiency and competitiveness of the EU trials system, we recommend a reduction in the number of amendments considered "substantial," especially in early phase clinical research. The fundamental purpose of regulatory oversight of clinical trial research is to ensure that risks and benefits for trial participants and society are appropriately balanced. It is possible to achieve this, while at the same time maintaining an efficient, practical, and globally competitive clinical trials system in the EU, by reducing the number of trial amendments that are considered "substantial" for early-phase (pre-Confirmatory) clinical trials.	

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		In general, the number of amendments that are considered "substantial" for early phase trials are more than is necessary, and in our experience this has reduced the efficiency with which clinical trials can be conducted in the EU. This is because the definition of a "substantial amendment" under the Guidelines appears to be based on considerations that apply to later-phase (such as Confirmatory) trials. In general, changes to statistical methodology, stratification, or sample size of pre-Confirmatory trials could be more efficiently implemented if they were treated as non-substantial amendments. Specifically, a change to the statistical analysis plan, method of stratification, etc. in a Phase 1 or Phase 2 (exploratory) trial will not compromise the scientific value of the trial; in fact, such changes are usually driven by accruing data and are intended to improve the value of these exploratory trials. In addition, in exploratory efficacy (Phase 2) trials, it is often very valuable (given the exploratory nature of such trials) to adjust sample sizes based on analysis of accruing interim data. These types of trial amendments can be effected immediately in the US* with submission of the amended protocol to the INC, and with a simple notification to Health Canada**, while both apparently require a substantial amendment in the EU; this has complicated the conduct of global exploratory-phase trials in the EU. Furthermore, in Phase 1 trials it is often valuable to add additional cohorts that are bracketed by the upper and lower doses proposed in the original protocol based on accruing data (for example, the original called for 100 and 300 mg, and a decision is made based on emerging PK data to add a 200 mg dose). Such changes do not affect the overall risk-benefit profile of the trial and therefore should be classified as non-substantial. Another aspect that has been difficult from an operational viewpoint are situations in which additional safety monitoring or measures are considered as valuable, and the Sponsor decides to add them to the protocol. While it is possible to add such measures immediately under an urgent safety measure, many such amendments are motivated by the precautionary principle and are not driven by specific, serious safety issues that rise to the level of concern for which the urgent safety measure procedures	

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		were intended. Adding such measures under a substantial amendment only delays the implementation of such precautionary measures and complicates the conduct of global trials. Additional methods of testing can also become available during the conduct of a trial and it would be valuable if such testing measures could be added to all trial sites globally at the same time. A final issue worth noting is the addition of tests (such as additional biomarkers). These typically do not require more blood draws, and when they do the safety implications are minimal. It would make sense if sponsors were able to implement such changes immediately. Given the above, we believe it would enhance the efficiency and competitiveness of the EU trials system if the definition for what is a "substantial amendment" were to exclude the following: **Proposed change (if any):** It is proposed to add the following points to the list of not "substantial" amendments (page 23): "With regard to the protocol, the following is a non-exhaustive list of amendments which are typically *not "substantial*": **• a change in the way the data on *exploratory* studies is analyzed or changes to the randomization scheme in *exploratory* studies *(it is understood that changes to the analysis of Confirmatory trials are of more impact).*** **• addition of an extra cohort within the dose range covered by the approved protocol in *exploratory* studies** **• addition (but not subtraction) of safety measures or new tests to any phase of protocol that are being added as a precautionary measure and which do not warrant treatment as an urgent safety measure.**	

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		• Sample size adjustments within 50-150% of the original sample size for *exploratory* studies. *** refer to the USA 21.CFR.312.30 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.30)** **** refer to Health Canada Food & Drug Regulations-Amendment (Schedule No. 1024) Clinical Trial Framework** **http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/reg/1024-eng.php**	
Section 3.3.1. ***Amendments as regards the clinical trials protocol*** (page 24, 2nd bullet point)	**Wyeth**	**Comment:** With regard to the protocol, the following is a non-exhaustive list of amendments which are typically *not* "substantial": • … • Limited lengthening of the trial time. We request additional clarification regarding "limiting lengthening of the trial time". For example, 3 months increase in the duration of a long-term trial which was originally planned to take 2 or 3 years to complete might be considered "limited", whereas a 3 month increase in the duration of a short-term trial originally planned to complete in 6 months might not be considered "limited". We propose that "limited lengthening of the trial time" be defined as an increase of ≤30% in the overall duration of the trial.	

Please feel free to add more rows if needed.