29 September 2019

Submission of comments on ''ICH guideline E8 (R1) on general considerations for clinical studies - step b' (EMA/CHMP/ICH/544570/1998)

Comments from:

Name of organisation or individual
Joint comments of Arbeitsgemeinschaft Angewandte Humanpharmakologie (AGAH), Germany, and Deutsche Gesellschaft für experimentelle und klinische Pharmakologie und Toxikologie (DGPT), Germany

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Emphasis of Clinical Development Plan before the beginning of development is encouraged. In order to optimise the clinical trials, to allow adequate planning of resources and to set-up reliable planning procedures a clinical development plan should be drafted the latest after meaningful results from proof-of-concept trials are available. In those cases when enough knowledge about mechanism of action is already deduced from animal experiments and from other similar compounds the clinical development plan can already be drafted prior to first-into-human trials.	
	It is recommended to explain the term "quality by design" already in the first paragraph, as this term is not broadly known to those who perform clinical trials.	
	Minimal interventional studies should be actively addressed including adapted ICF procedure	
	This document is designed exclusively to cover studies carried out for the purposes of obtaining and maintaining marketing authorization by pharmaceutical companies. It does not address studies conducted by independent researchers, but it would also be binding for such studies. This causes major and unnecessary obstacles for independent research which provides an essential contribution to the understanding and appropriate use of many drugs. It is in the best interest	

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	of patients, the public and the researchers to separately address this issue in the document.	
	In early phase clinical trials alternative study designs become more and more important. Especially in First-in-Human trials it is common to work with adaptive designs in regards to dosing steps and sample size per dosing group where interim decisions are based on safety, tolerability and pharmacokinetics. Not only in oncology, studies with adaptive design including healthy subjects and patients are of increasing relevance. Several reasons like acceleration of development process but also reduction of drug exposure for healthy subjects and early detection of efficacy-related effects including adequate surrogate endpoints are of increasing relevance for modern drug development. Thus, today separation of phase 1 and phase 2 trials is no longer the only practical option. Such trials should be actively mentioned as option and the necessity of adequately defined decision procedures should be addressed.	
	The draft guideline addresses the integration of quality into clinical studies, considering the diversity of clinical study designs and data sources used. Besides individual studies, meta-analyses have been used to provide a comprehensive overview of study outcomes. Furthermore, pharmacometric methodologies, such as modelling and simulations, have become an integral	

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	part of modern drug discovery and development to quantify the relationships between the dose of an administered drug, its exposure, and its clinical efficacy and safety in individual patients and in certain populations. This methodology has been used successfully to identify the most appropriate dosing regimen of a medicine, by describing variability between individuals that may be associated with lack of efficacy in certain patients or with toxicity in others. Reference to meta-analyses, pharmacometric methodologies and other in silico investigations should therefore be included in in the general principles to consider in planning a drug development programme (Section 4) and in the Annex.	
	Several bullet points in Annex 1 are not actively addressed in the main body of the guideline, here it is recommended to care for completeness (general comment), the "missing" terms should be specified (see also specific comments); Safety pharmacology is missing in Appendix 1 as well as in main text, Pharmacoeconomic and effectiveness studies are mentioned in the Annex, but not discussed in the text.	
	Patient-reported outcomes (PROs) can be important clinical study endpoints for regulatory approval studies, including effectiveness studies. These have been mentioned in Annex 1, but their relevance and proper planning of validation studies should also be addressed in the text, for example following the paragraph on validation of biomarkers (lines 237-239) and/or in the	

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	context of the discussion of patient involvement which is especially important for development, validation and application of PROs.	
	Following Regulation (EU) 2017/745 (MDR) combination products such as integrals are regulated by Directive 2001/83/EC or Regulation (EC) 726/2004 as medicinal products. The draft ICH E8 has no reference to combination products at all. As those products are a significant part of medical applications they should be considered in this guideline as well.	
	Due to the growing importance of companion diagnostic devices it is considered meaningful to address the specificities of device development, validation and its interference with clinical trials and clinical development programs.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
21 - 22		Comment: "Provide a guide to the ICH efficacy documents to facilitate user's access…". Mentioning the ICH safety seems to have been forgotten. Proposed change: "Provide a guide to the ICH efficacy and safety documents to facilitate user's access	
77 - 85		Comment: Section 2.3 Patient Input to Study Design: Great care should be applied when writing "Patients' views can be requested on all phases of drug development". Patients with the disease condition in question do always have a bias, this might be an ethical problem: for example the demand to achieve therapeutic progress may expedite inadequately early phase trials without balanced assessment of risk-benefit for the participating subjects. Therefore a re-wording with reduced importance in early phase healthy subject trials is recommended.	
114 - 116		Comment: thorough discussion of patient population at planning and feasibility stage is vital Proposed change (if any): add in line 115 - " thorough discussion of patient population with investigators and/or pre-screening during feasibility.	
209 - 211		Comment: should be added: "To this end, criteria for such adaptations and/or interim decisions, the involved parties to make such decisions, and the need to approval by authorities	

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		and/or Institutional Review Board/Ethics Committees should be actively addressed.	
243 - 246		Comment: Safety pharmacology is missing, core battery of safety pharmacology studies generally should be conducted before human exposure.	
244		Comment: please add immunogenicity	
258		Comment: Non-clinical safety information should be adequate to assess potential risk for participants of human trials	
269 - 270		Comment: Section 4.2 addresses Quality and Formulations of Investigational Medicinal Products. The reference to age-appropriate formulations only mentions paediatric populations. It is suggested to include age-appropriate formulations in elderly populations as well. Proposed change (if any): Age-appropriate formulation development is a consideration when clinical studies are anticipated in paediatric populations (ICH E11) and in the elderly (ICH E7).	
308 - 309		Comment: Reference to food interaction studies should not focus on modified release formulations only. Instead food interaction studies are already needed at the early stage focusing on the drug compound properties. Later in clinical development when more sophisticated oral formulations are developed, formulation specific food interaction studies may also be needed. Proposed change: Food interaction needs to be adequately addressed already during early development. Extent of food interaction as well as in certain cases interaction with specific	

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		food components may be necessary. Furthermore, in case of modified release formulations intended for oral administration food interaction studies may become necessary which investigate robustness of the formulation when co-administered with food. In case of certain sensitive ingredients food-component related interaction studies may become necessary.	
321 - 330		Comment: role of biomarker should be added	
345		Comment: please add: "as well adequate basis for benefit/risk assessment	
361 - 371		Comment: Non-interventional studies are not governed by ICH-GCP. It should be made clear in section 4.3.3 that post approval studies are only mentioned to complete the picture.	
after 406		Comment: A new section 4.3.6 should be added here, such as: 4.3.6 Research-Driven Clinical Studies. Beyond studies conducted for the purposes of obtaining and maintaining marketing authorization by pharmaceutical companies, studies conducted by independent researchers are important to close initial and emerging knowledge gaps at later stages of the life cycle of a drug. These studies are often referred to as investigator-initiated trials (IIT). Objectives, design and conductance of such studies may differ considerably from those supported by the owners of the marketing authorization, also related to the limitation of respective resources and the need to provide information on drug effects in "real-world" patients. Peculiarities in study designs, including the process to obtain informed consent, should be justified by the relevance of the data to be acquired by such studies.	
after 490		Comment: Minimal intervention studies Proposed change: It should be added: Minimal interventional studies may be categorized as observational studies if both	

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		the intervention itself and related the risk and effort for participants in the study is minimal.	
493 - 494		Comment: Standard of care should be highlighted, which can also be non-chemical treatment Proposed change (if any): For example, comparisons may be made with placebo, no treatment, standard-of-care (with or without medication), active controls or different doses of the drug under investigation.	
499		Comment: It should be clearly emphasized that internal control is preferred compared to historical control	
505		Comment: Internal control is defined by the protocol in the same way the test group is. The data generated is more robust than data obtained from external controls that are not defined by the same protocol. Proposed change (if any): Add: Use of internal control is to be preferred to external control.	
586 - 590		Comment: Steering of recruitment should be considered to avoid bias Proposed change (if any): add "balanced recruitment between sites, regions and countries should be considered to avoid bias through over-recruiting investigational sites" to section	
591 - 624		Comment: Section 5.1.6 mentions the elements required for a statistical analysis plan, including analysis populations (line 608). It is suggested to include a definition of the relevant analysis populations in this section, in the context of the quality aspect in clinical studies.	
595 - 598		Comment: there are several cases where the SAP in a blinded study should be finalised earlier than the unblinding process (e.g. after 1/3 patients recruited) and for open	

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		studies it is not common to have the SAP finalised before the conduct of the trial Proposed change (if any): The SAP should be finalised early enough to avoid inadequate interference with the study outcome	
678 - 684		Comment: Updated Training should also occur in case of new information or if a protocol amendment is available	
696 - 721		Comment: Section 6.2 addresses the need for clear criteria for stopping study treatment, and Section 6.3 the role of a DMC to determine whether to continue, modify, or terminate a study. Since studies may be terminated without involvement of a DMC, it is suggested to include a reference to the need for clear criteria for study termination also in Section 6.2.	
708 - 712		Comment: withdrawal criteria should be defined based on all clinical or non-clinical information of the study drug	
713 - 721		Comment: there is a commenting process for Questions to be answered upon DMCs currently running. This process showed that the terminology to be used for the different types of DMCs is unclear and requires specification especially when DMCs in early phase trials are to be differentiated against DMCs in later phases. AGAH has already commented here. It is strongly recommended to harmonise terminology between guidelines.	
733 - 772		Comment: Section 7 describes the need for proactive, cross-functional discussions and decision making at the time of study planning. Such discussions involve study investigators and study teams, as appropriate. In the context of the prerequisite non-clinical studies, and where applicable, clinical studies to support the study being designed, reference should be made to the Investigator Brochure as critical document summarising the relevant information. It is	

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		therefore suggested that the requirement of a comprehensive and updated Investigational Drug Brochure should be included in the considerations provided in this Section.	
777 f table		Comment: Safety pharmacology is missing under non-clinical testing…..	

Please add more rows if needed.