February 14, 2017

Submission of comments on 'Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products' (EMA/CHMP/SWP/28367/07 Rev. 1)

Comments from:

Name of organisation or individual
Association for Applied Human Pharmacology (AGAH), Hamburg, 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)*
	Whole document: The terms "study" and "trial" should be used according to the definitions given in the new EU regulation on clinical trials (No 536/2014)	
	Section 2: The scope of the revised guideline has been extended from first-in-human (FIH) trials to early clinical trials in general. It is unclear whether the revised guidance with its recommendations refers to all early clinical trials. Guidance that refers to FIH trials only should be clearly pointed out. Furthermore, the guideline should be more precise to differentiate between specific aspects that need to be considered for NCEs and those to be considered for biologicals.	
	Section 4: A clear differentiation between targets that have already been addressed by compounds in FIH trials and completely novel targets should be introduced. In this respect, the resulting guidance for risk stratification should be delineated more stringently.	
	Section 5: A differentiation of the nature of the IMP (whether a biological or a chemical compound) should be incorporated. Variations in quality of the IMP and the	

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	resulting actions should be addressed. Consequences of changes or modifications in the manufacturing process should be evaluated and adequately communicated.	
	Section 8: Due to the very specific clinical and pharmacological as well as methodological knowledge needed for adequate evaluation of early phase trials, it is recommended that Ethic's Committees responsible for such trials have specific experience. This experience should cover the commonly applied trial designs with special focus on adequate selection of stopping and continuation rules including adaptive designs. Thus, there should be proven knowledge in early phase trials and clinical pharmacology.	

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)*
Lines 114-116		Comment: This guideline currently considers primarily human cellular molecules as pharmacological target, but not pathogen-specific molecules, for which some aspects and consequences in this guideline do not apply. Proposed change: Please adjust the guideline accordingly.	
Lines 207-208		Comment: The need for an integrative assessment of all non-clinical data should be described more specifically. Section 4.4 should start with the following sentence: Proposed change: "A weight-of-evidence approach based on the non-clinical and emerging clinical results as well as on available information from other sources, as applicable, e.g. information on effects observed for the class of substance to be studied, should be pursued to support an integrated risk assessment. This should be continuously reviewed in an iterative process during further development."	
Lines 220-225		Comment: To this section, a sentence on changes and modifications of the manufacturing process should be added following line 225. Proposed change: "Any changes or modifications in the manufacturing process of the active substance during the non-clinical and early phase clinical development programme	

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		which might interfere with product heterogeneity, degradation profile or process-related impurities should be addressed. There should be sufficient assurance that product differences, should they occur, would not have an adverse impact on characteristics of the product, especially safety. The necessity of additional non-clinical bridging studies should be discussed based on adequate risk assessment."	
Lines 234-236		Comment: A clarification regarding the required format for the different types of documents should be provided. It is currently not clear whether "GCP" refers to the IB and whether the intention is to use the CTD format for IBs in future. GCP requirements are rather unusual in the non-clinical context. Proposed change: "… thus providing adequate information on the performed non-clinical studies to <u>support</u> a meaningful <u>risk</u> assessment, <u>which should be provided as a discussion integrating the available evidence and arriving at clear conclusions, substantiating the basis for guidance of the investigator. In addition</u>, the inclusion of a tabulated …"	
Lines 253-258		Comment: The focus of this paragraph is on the suggestion of an additional testing approach which may be considered in exceptional circumstances. This part appears to interfere with the reasoning regarding the use of relevant species in traditional toxicological studies.	

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		Proposed change: It is proposed to move this paragraph to the end of this section.	
Lines 327-328		Comment: It is rather the adverse effects at the target organs than the target organs themselves that may warrant particular monitoring in the clinical trials. Proposed change: "An evaluation as to whether the adverse effects identified in the non-clinical studies warrant particular monitoring in the CT should be undertaken."	
Lines 328-329		Comment: The approach of a more integrated assessment should be strengthened here. The following sentence should be added in line 329. Proposed change: "Additional aspects for increasing concern should be taken into consideration as appropriate, including but not limited to steepness of dose-exposure and/or dose-toxicity responses, low safety margins, non-monitorable adverse effects, toxicity without pre-monitory signs, potentially irreversible findings, non-linear PK, inconsistent/variable pharmacodynamic responses and/or systemic exposures within or between animal species, etc. (see also sections 7.3 and 7.4 below)."	
Lines 346-350		Comment: It is not clear whether a substantial amendment will be needed for any adjustment of the predefined dosing	

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		selection. A substantial amendment should only be necessary when the dose is increased above the predefined selection. The two sentences should be merged as follows. Proposed change: "Substantial amendments will also be needed where the pre-defined dosing selection will be augmented (increase in predefined dose increments, higher than pre-defined maximum dose) and also where dose escalation has reached a pre-defined maximum exposure and … is warranted."	
Line 366		Comment: In the previous guideline, the MABEL approach was only requested for IMPs for which factors influencing risks according to section 4.1 have been identified (e.g. biologics). In the current revision, this differentiation is not mentioned with respect to the determination of MABEL. Proposed change: A specification for the applicability of MABEL should be added in section 7.2.	
Lines 372-375		The guideline does not consider pathogen-specific molecules, for which e.g. a MABEL cannot be calculated. Proposed change: Please adjust the guideline accordingly.	
Lines 383-385		Comment: In the way it is described now, MABEL would determine the starting dose of many NMEs. This is too conservative and does not allow a differentiation between NMEs with different risk potential. The use of MABEL should be	

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		reserved for those compounds for which the mode of action/nature of target/relevance of animal species revealed an increased risk. Proposed change: Remove the bracket term in line 383	
Lines 398-399		Comment: Non-linear PK can result in a lower or higher than dose proportional increase of exposure. Proposed change: Specify that smaller dose increments should be considered in case of higher than dose proportional increase of exposure.	
Line 400		Comment: Substantial amendments should be required only if a dose adjustment exceeds the originally approved dose range (i.e. PK increases lower than dose-proportional). Risk-based reduction of originally planned dose steps should be possible without a substantial amendment. Proposed change: Specify the need for a substantial amendment	
Lines 402-403		Comment: Skipping of a dose may be acceptable without a substantial amendment if conditions pre-defined in the protocol are met, e.g. an unexpected shallow dose-exposure or exposure-response relationship.	

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		Proposed change: At the end of the sentence in line 404, it should be added "unless pre-specified in the protocol".	
Lines 424-428		Comment: The main objective of early clinical trials is to investigate the safety and tolerability of an IMP under well controlled conditions. These trials are usually the only ones where detailed data for exposures above the expected human therapeutic dose are collected and thus inform dose-exposure-response models for safety/tolerability endpoints, especially those which are assumed to be mode of action related. The maximum dose / exposure in FIH trials needs to cover the uncertainties of the predicted therapeutic dose / exposure and has to provide a sufficient safety margin with respect to clinical drug-drug-interactions (DDI) and thorough QT investigations. Furthermore, it has to cover variability in exposures for long-term clinical trials in larger patient populations which cannot be as strictly controlled as early clinical trials. Following the guideline's current wording might put patients at later trial stages at higher risk. Proposed change: Lines 424 and 425 should be deleted. The target saturation aspect should be included in lines 411 – 412: "This justification should be based on all available non-clinical and clinical data, including PD (e.g. target saturation), PK, findings in toxicity studies…".	
Line 449		Comment: The IMP administration should be characterised	

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		and justified not only by route but also by rate. Proposed change: The choice of route and rate of IMP administration for dosing in humans should be justified based on the non-clinical data.	
Lines 462-463		Comment: The reason for this requirement is unclear and is not common and established practice. If the PK of an IMP is considered to be substantially different in patients compared to healthy subjects, then the data from healthy subjects are not predictive and all clinical trial should be performed in patients only. If the PK is expected to be similar in patients, then multiple dose administration may be done right away. Proposed change: Lines 462 and 463 should be deleted.	
Line 481		Comment: The half-life of a compound is not an aspect of a trial that can be designed. If the wash-out time was meant, the wording should be adapted as follows. Proposed change: "wash-out time for the same subjects participating in multiple IMP administration periods considering the half-life of the IMP"	
Line 513		Comment: For this paragraph, a reference should be made to section 7.5.	

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		Proposed change: Add a reference to section 7.5.	
Line 518		Comment: Food interaction (FI) trials are usually conducted with single dose administration. Proposed change: Delete "FI"	
Lines 521-541		Comment: The factors for the choice of trial subjects do not include gender and age as selection factors. In addition, it is not mentioned to consider how ill a patient may be or how healthy he/she needs to be to participate in the trial. Proposed change: Add gender and age as factors and ask for consideration of the general health status of a patient.	
Lines 542-543		Comment: Single safety laboratory parameters outside the reference range are the rule rather than the exception even in trials with healthy subjects. This is acceptable as long as this is clinically insignificant and does not compromise interpretation of trial results [Reference: Breithaupt-Groegler K, Coch C, Coenen M et al. Who is a 'healthy subject'? -consensus results on pivotal eligibility criteria for clinical trials. Eur J Clin Pharmacol (2017). doi:10.1007/s00228-016-2189-8]. Proposed change: Replace the sentence by "The key inclusion and exclusion criteria for trials involving healthy subjects must be clearly defined and should be appropriate for the chosen population and the type of the trial."	

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Lines 584-586		Comment: It is not clear whether only the data to be reviewed or also the decision making group needs to be the same for the decision to continue dosing after the first subjects of a cohort as for the decision to move to the next cohort. There should be the option that the decision to continue within a cohort is taken by a defined but smaller expert group. In addition "all data" appears too general, the data should be relevant for decision making in an N=1 situation as after the first dose group of a dosing period. Proposed change: "At the end of the observation period, there should be a review of clearly defined data before allowing dosing of further subjects in the cohort, following similar precautions as applied between cohorts…"	
Lines 590-593		Comment: It is not clear what is meant by "at later stages of study design". Staggering IMP administration in early dose escalation trials such as FIH is best practice and should not be limited to initial dose levels only. Statements made in lines 575-589 should refer to all stages that involve dose escalation parts in early clinical trials. Proposed change: Delete lines 590 – 593.	
Line 596		Comment: The availability of PK data before drug administration in the next cohort can be ambiguous since it	

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		may refer to timely or biological availability. At lower doses, the consideration of PK data from the previous cohort may not be scientifically necessary. Thus a justification of PK data for cohort decisions should be introduced. Proposed change: "… and PK data, where justified, or possible AEs from those participants…".	
Lines 641-644		Comment: The requirement that all planned trial visits have to be completed for a subject to be considered evaluable for dose escalation decisions is neither needed to ensure the safety of trial subjects nor will it in many instances be feasible. In order to ensure the safety of trial subjects, it is sufficient and well established standard practice to cover the period of highest risk / peak effect which has to be defined case-by-case based on the individual characteristics of the IMP (e.g. expected AE profile based on non-clinical data, expected PK and PD profile). In contrast, the timing of the last trial visit of a subject will focus on full characterisation of PK (e.g. 5-10 half-lives), PD and, if applicable, for biologics additional aspects such as ADA formation. Waiting for completion of all planned trial visits which in some instances may last for weeks and months is not reasonable / feasible. Proposed change: Delete the requirement, that all planned trial visits have to be completed for a subject to be considered evaluable. Instead allow the case-by-case definition of	

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		appropriate minimum requirements regarding observation period and data to be available in order to qualify a subject as evaluable.	
Line 650		Comment: The data review should include all data of the predefined parameters to be considered for review. Exploratory data which may be recorded during the trial may not be needed for the review. Proposed change: Change "All data" to "All predefined data"	
Lines 654-656		Comment: A substantial amendment should not be needed for every case that dosing is re-started after a temporary hold, e.g. after full evaluation of an AE initially considered as an ADR. It should only be needed for the cases that constitute substantial changes to the pre-defined conditions of the protocol. Proposed change: "… after full evaluation of available data and the approval of a substantial amendment, <u>if applicable</u>."	
Lines 675-676		Comment: The stopping rule "Severe non serious ADRs in two subjects of the same cohort" only considers intensity of the adverse reaction but does not consider the cohort size. Proposed change: Change the respective stopping rule to "moderate or severe non-serious ARs in ≥50% of subjects in	

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		the same cohort"	
Lines 683-685		Comment: The dose stopping criterion based on the clinical exposure equivalent to the exposure at NOAEL in the most-sensitive species practically limits the dose escalation to the safety factor applied for the MRSD if this is based on the PK approach with exposure equivalence at NO(A)EL. For a compound with a narrow therapeutic range, this criterion may preclude dosing to the therapeutic range even if there is no clinically detectable limitation of safety and tolerability. Under these circumstances, it may be required and reasonable to exceed NOAEL exposures in early clinical trials. Important aspects are among others relevance of non-clinical findings for humans as well as frequency, severity, monitorability and reversibility of these findings. Proposed change: Delete lines 683-685.	
Lines 726-727		Comment: The requirement for independency of a decision making group should not exclude the participation of the investigator which may be implied by the current wording. The responsibility of the investigator for the trial subjects should be taken into account and considered for decision making in the trial. Proposed change: "The decision making group should also include members sufficiently independent from IMP	

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		administration and safety monitoring.”	

Please add more rows if needed.