February 28, 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' (EMEA/CHMP/SWP/28367/07 Rev. 1)

Comments from:

Name of organisation or individual
Biotechnology Innovation Organization (BIO)
1201 Maryland Ave, SW, Suite 900
Washington, DC 20024, USA

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).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The Biotechnology Innovation Organization (BIO) thanks the European Medicines Agency (EMA) for the opportunity to submit comments on the "Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products." BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products. In general, it is important that the guideline acknowledges and differentiates the requirements for trials conducted in high-morbidity and high-mortality disease states such as advanced stage cancers, as in such settings more flexibility should be applied, and as already recognized by regulators in other guidance documents (*e.g.,* ICH S9 guideline). Key comments included in the below include discussion of maximum doses in healthy volunteer studies (line 424); sentinel dosing (line 557-578; and no need to submit an interim report necessarily as a substantial amendment (lines 634-636). We provide further, detailed comments to the draft guideline below.	

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)*
Page 4, lines 82-83		Comment: BIO believes it would be helpful for the guideline to further specify high-morbidity and high mortality disease states such as advanced stage cancers.	
Page 4, lines 90-92		Proposed change (if any): Special attention should be given to the estimation of the exposure reached at the initial dose to be used in humans and to the subsequent dose escalations to a predefined maximum ~~dose~~ exposure.	
Page 5, line 107-109		Comment: BIO believes that further clarification is needed if the guideline intends sponsors to study bio-equivalence in a FIH study.	
Page 5, lines 109-110		Comment: BIO believes that further specification regarding how this guideline applies to high-morbidity and high mortality disease states such as advanced stage cancers will be useful.	
Page 5, line 114		Comment: The draft guideline states, "The guideline applies to all new chemical and biological IMPs." BIO requests further clarification regarding whether 'biological IMPs' include biosimilars.	
Page 6, line 158		Comment: In terms of mode action it is also important to understand the homology and conservation of the target expression and physiology amongst mammals	

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		and human to translate safety findings. Proposed change (if any): This includes the nature and intensity of the effect (e.g. extent, amplification, duration, (ir)reversibility) and other mechanistic effects of the IMP on the intended target(s) and potential off-targets. Understanding the homology and conservation of the target expression and physiology amongst mammals and human is also an important factor for safety translatability.	
Page 6, line 164		Comment: BIO believes it is currently unclear if a compound acts as an agonist whether it would require special attention similar to the examples listed. Additional clarification regarding this case would be helpful.	
Page 6, line 177		Comment: BIO believes this section should include compounds with the same MoA as well. Proposed change (if any): Previous exposure of humans to compounds that have the same, similar, or related modes of action. Additionally, please see our related comment at lines 343-344.	
Page 7, lines 178-181		Proposed change (if any): BIO suggests the following sentence at the end of this bullet For compounds with a prolonged PD effect in the efficacious dose range at single doses (often for monoclonal antibodies), a specific dedicated multiple	

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		ascending dose study may not be necessary.	
Page 7, lines 182-183		Comment: BIO notes that if the molecule targets a single specific kinase with low specificity, it is important to take into account the potential side effects at supra-pharmacology exposure activating or inhibiting other kinases. Proposed change (if any): Evidence from animal models (*e.g.,* knock-out, transgenic or humanised animals) for the potential risk of serious pharmacologically-mediated toxicity or supra-pharmacology responses including off-target activities.	
Page 7, lines 207-208		Comment: There are cases where findings are deemed of little or no relevance to humans. For example, anti0durg antibody (ADA) mediated hypersensitivity reactions to a human protein IMP in a species. BIO believes that a mention of providing justification for non-relevance should be added, and if possible a discussion of common situations/reasons a finding may be considered non-relevant to humans.	
Page 8, line 225		Comment: BIO suggests including biological products in this bullet. Proposed change (if any): Special consideration should be given to the suitability and qualification of methods to sufficiently characterise the active substance and drug or biological product.	

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Page 9, lines 237-239		Comment: Some of these disease models and alternative toxicology models may not be GLP-compliant. Additionally, it may be useful to reference ICH M3(R2) & S6(R1) in Section 6.1 as they cover alternative models. Proposed change (if any): The sponsor should confirm that all pivotal non-clinical safety studies in support of the CT application are conducted in compliance with Good Laboratory Practice (GLP). All other studies (e.g. PK and PD**,** diseases models) should be of high quality and consistent with the principles of GLP.	
Page 9, line 247-252		Comment: The use of tissue cross reactivity studies with human and animal tissues (*e.g.,* mAbs) is advocated by the draft guideline. Considering the challenges of the immunohistochemistry (IHC) method (some mAbs are not good IHC reagents, lack of adequate positive control, low sensitivity), would a weight of evidence approach for off-target binding be more suitable which could cover both in silico analysis of the target expression (mRNA, protein) in tissues and homology of the target with other human proteins, as well as other techniques such as mammalian cell surface display, other human protein arrays, ISH, ISPCR etc., lack of off-target toxicity in GLP toxicology studies, other literature data. Additionally, there is no mention of what constitutes a relevant species with regards to relative potency to humans (*e.g.,* within 10-fold of the EC50/IC50 in	

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		humans). For mAbs, a relevant species is usually defined as one in which we are able mimic the type and duration of pharmacological activity as that intended in humans. Hence even if there is a 50-fold drop in potency to human, as long as we know we can dose high enough to achieve full human relevant pharmacology (with an additional exposure margin to assess off-target effects), then the species would still be relevant. Proposed change (if any): The demonstration of relevance of the animal model(s) may include comparison with humans of: • target expression, distribution and primary structure. However, a high degree of homology does not necessarily imply comparable effects; • pharmacodynamics; • metabolism and other PK aspects; • on and off-target binding in tissue cross-reactivity studies or cell and protein arrays using human and animal tissues/cells/ proteins (e.g., for monoclonal antibodies).	
Page 9 lines 266-270		Comment: BIO suggests deleting this paragraph which does not add any specific additional information. Proposed change (if any): ~~When planning FIH/early CTs, sponsors and investigators should identify the potential factors of risk and apply appropriate risk mitigation strategies. These factors should be addressed appropriately for all FIH/early CTs in the sponsor's CTA.~~	

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Page 9, lines 282-284		Comment: This statement seems to confuse the concepts of specificity and affinity. However, the animal doses are often far higher than the human dose and consequently complete suppression of the target can be achieved in animals despite the difference in affinity. Proposed change (if any): If the therapeutic has higher affinity for the human target compared to the target in the toxicology species, this may make ~~High human-specificity of a medicinal product makes~~ the non-clinical evaluation of the risk to humans more difficult, but does not imply that there is always an increased risk in FIH/early CTs. However, in these cases, a proper discussion of the potential risks should be given to justify the conduct of a CT.	
Page 9, lines 286-287		Comment: The "Pharmacodynamics" section should reference back to the Mode of Action discussion in Section 4.1 which discusses "High risk" pharmacodynamic effects, antagonist versus agonist, the shape of the dose response curve etc. Proposed change (if any): Primary PD studies should address the mode of action related to therapeutic use and provide knowledge on the interaction of the IMP with the intended target as well as with related targets (see Section 4.1).	
Page 9, lines 288-289		Proposed change (if any): The selectivity and specificity of the IMP as well as secondary pharmacodynamics,	

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		defined as effects of the IMP on proteins other than the desired therapeutic targets, should be critically evaluated and documented. ~~This might also include effects on other downstream or physiologically integrated endpoints.~~	
Page 10, lines 291-292		Comment: BIO suggests that the tern "material" could be clarified (drug vs. tissue). Proposed change (if any): The primary and secondary PD should be conducted in vitro, using animal and human-derived ~~material~~ tissue and in vivo using animal models, as relevant.	
Page 10, lines 292-295		Comment: A series of assays and studies are described, with the implication they should all be conducted. BIO recommends EMA clarify that these are to be done when deemed relevant. Proposed change (if any): Relevant studies can ~~These studies should~~ include target interactions preferably linked to functional response, e.g. receptor binding and occupancy, inhibition of enzymes, duration and (ir)reversibility of effect, dose-response relationships and physiological turn-over of the target.	
Page 10, lines 314-316		Comment: BIO finds this portion of the draft guideline text to be insufficient and unclear. As such, we suggest adding additional text. Proposed change (if any): Additional studies to	

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		investigate effects in these and other organ systems should be conducted on a case-by-case basis where there is a cause for concern, e.g. in case of low selectivity of the IMP for its primary target**,** or where potentially important off-target effects may be a consideration.	
Page 11, lines 329-332		Comment: If animals were to have serious adverse events (AEs) after dosing with a mAb, and this was due to ADA, the approach to human dosing should be based upon the translatability of the finding. This will depend upon the nature of the IMP (human/humanized IgG mAb or Fab) and any potential role of the target in the proposed ADA-related mechanism of toxicity. As such, we suggest including assessment of translatability to the guideline. Proposed change (if any): If mortalities and/or serious toxicity are observed in non-clinical studies, an evaluation of putative mechanism of toxicity and/or cause of death is expected to be addressed (e.g. consideration of histopathological examination of deceased animals, which is certainly necessary in pivotal studies and should also be considered for dose range finding studies). The translatability of any mortalities/serious toxicities to humans should be assessed.	
Page 11, lines 343-344		Comment: The definition of "mode of action" may be unclear. The intent is to enable the Sponsor to utilize data from other compounds that engage the same	

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		target in the same manner. Proposed change (if any): Experience, both non-clinical and clinical, with molecules that bind to the target in the same manner ~~having a similar mode of action~~ can also be useful.	
Page 11, lines 364-369		Comment: BIO believes it would be useful to clearly show how MABEL, PAC and ATD differ. For example, what does minimal mean? BIO suggests re-defining this term by replacing "anticipated" with "acceptable". Using "acceptable" would link this term to the risk-assessment. Additionally, some guidance on "Biological Effect" would also be helpful (*i.e.,* any biological effect or a biological effect that may result in an AE). Together this would ensure that the MABEL dose addresses safety and not just any biological effect. Proposed change (of any): Exposure showing PD effects in the non-clinical pharmacology studies, including ex vivo and in vitro studies in human tissues if feasible, should also be determined and these data should be used to determine the minimal acceptable ~~anticipated~~ biological effect level (MABEL) in humans and an estimation of the pharmacologically active dose (PAD) and/or anticipated therapeutic dose range (ATD) in humans.	
Page 11, line 364-367		Comment: Anticipated therapeutic dose range (ATD) appears to be a new term that is not in common use. BIO asks EMA to define and discuss the term in more	

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		detail. This also introduces a new element, not just estimating the starting dose but also providing a full exposure-response relationship estimate for humans. Finally, the use of "therapeutic" in this sense seems to imply some prior knowledge of the level of target engagement/PD that is required for clinical efficacy.	
Page 11-12, line 369-373		Comment: The description in the paragraph is referring to the calculation of the starting dose. The three methods mentioned: MABEL, PAD and ATD do not necessarily incorporate target binding or receptor occupancy. It is rather a PKPD approach that can take into account multiple parameters. Therefore, this sentence could be clarified to state that the predicted target occupancy or amount of target binding should be calculated at the dose levels proposed as starting doses. Proposed change (if any): In addition, the starting dose propositions based on MABEL, PAD and/or ATD should consider the predicted target binding and target occupancy studies in vitro in target cells from human and the relevant animal species and exposures at pharmacological doses in the relevant animal species. Whenever possible, all relevant data should be integrated in a suitable modelling approach for the determination of the MABEL, PAD and/or ATD.	
Page 12, lines 383-385		Comment: The guideline is advocating to use the lower of the NOAEL and the MABEL (hence for biologics this will almost always be the MABEL) as a starting dose, unless providing justification for not using it. It is stated	

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		(line 386) that the starting dose should have no PD response (at least in healthy volunteers). This is overly conservative for highly specific biologics (especially for antagonists against soluble targets) and depends on the pharmacological pathway that is being targeted and if the molecule is considered a high risk molecule (*i.e.,* all the considerations assessed in sections 4.1-4.4). The concept of duration of PD response should be included *i.e.,* that it may be acceptable (dependent on risk) to have a PD response at the starting dose but only for a short duration, dependent on perceived risk. Molecules are risk-classified (high vs low) based on the considerations laid out in section 4.1-4.4). For lower risk biologics a MABEL approach may not be needed (this would be the 'justification' but what these examples of justifications might be should be clarified in the guidance-again referencing back to the text in section 4.1-4.4). Otherwise it is possible that readers will think that the MABEL should be used for all mAbs. Proposed change (if any): For molecules associated with a certain level of risk triggering the use of the MABEL, when the methods of calculation based of NOAEL or MABEL give different estimations of the starting dose for humans, the lowest value should be used; ~~justified.~~ ~~Justification for not using the MABEL may entail the molecule being considered having a low safety risk based on the pharmacological risk considerations described in section 4.1 to 4.4.~~ Justification should be included in the IB and CT protocol.	

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Page 12, lines 386-387		Comment: The starting dose in healthy volunteers should not necessarily result in an exposure that is below that which we would expect to produce a PD response. Classes of drugs which already have a reasonably well established dose-response and/or toxicology response do not need to follow this path. Proposed change (if any): In healthy volunteers, for novel molecules against novel targets, the starting dose should ideally result in an exposure to a subject that is below that which would be expected to produce a PD response. However for well-defined classes of drugs against targets/pathways for which there is already a reasonably well established dose/exposure/PD/toxicology, a PD response of limited magnitude and duration could be acceptable.	
Page 12, line 390-391		Proposed change (if any): The choice of subsequent dose levels should include some estimate of the potential nature and duration of PD effects and exposure levels to be achieved as well as adverse effects seen (if any).	
Page 12, line 399-402		Comment: If doses are planned and not fixed in the protocol why would there be a need for protocol amendment? As long as there are exposure based stopping criteria and limited steps in between dose escalation, flexibility is there not to have a protocol amendment. Proposed change (if any): If emerging clinical data	

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		reveal significant differences from non-clinical or modelling and simulation data, a substantial amendment may be required to adjust the study design/conduct (the adjustment in relation to the planned dose levels) ~~unless this possibility was~~ should have been discussed including predefined decision criteria and approved in the protocol.	
Page 12-13, lines 405-433		Comment: This section is problematic for immunotherapy biologics in particular. A maximum dose set based on serum levels determined in human PK studies would not necessarily reflect tumor concentrations of the drug, when in many cases the effects are expected to be mediated by activity on tumor infiltrating immune cells, or targets preferentially expressed in the tumor microenvironment. It is therefore difficult to set a maximum dose based on these factors, and the highest dose studied will generally need to be based on a combination of PD hypotheses, clinical safety from previous doses tested, and emerging clinical activity since these trials are conducted in patients. While this is briefly touched on in section 7.7 (lines 453-469), further discussion in the guideline of these situations may be helpful.	
Page 12 line 406-408		Proposed change (if any): The design of FIH or early CTs often aims to determine a dose or exposure-response curve for the most relevant pharmacological effect(s), and includes a maximum predefined dose or exposure ~~margin~~.	

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Page 12, lines 409-411		Proposed change (if any): A maximum dose ~~or~~ based on a maximum exposure, which should not be exceeded in the study without approval of a substantial amendment, should be pre-defined and justified in the protocol for the full CT and/or each Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products study part.	
Page 13, lines 424-425		Comment: This portion of the draft guideline does not reflect current practice. Healthy volunteer studies are preferred to evaluate supra-therapeutic doses where no particular safety concerns exist, to establish a safety margin prior to exposing the IMP to patients. This is justified often since patients can experience more variable exposures (*e.g.,* DDIs for low molecular weight compounds). In addition the recent update of ICH E14 guideline allows the use of the FIH study to determine QTc prolongation, which is typically investigated at supra-therapeutic doses. Finally, for a biologic the estimation of the therapeutic dose and therapeutic dose range can be difficult prior to the first in human study since the dose frequency is important in defining the dose. Proposed change (if any): ~~In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified.~~	

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Page 13, lines 426-428		Comment: This section of the draft guideline does not take into account the duration of effect. It implies, although does not state, that the complete inhibition would be at the end of the dose interval. In this scenario, no dose escalation would take place above the therapeutic dose and hence the tolerability of supratherapeutic doses will not be established in healthy volunteers.	
Page 13, lines 426-428		Comment: Similar to our comments in lines above 424-425, BIO believes that further clarification is needed if FIH maximum single ascending dose (SAD) is a dose that causes complete inhibition. Moreover this statement is complicated by whether this is to be evaluated on a target occupancy biomarker or more functional biomarker, and the relationship of the functional biomarker with clinical efficacy. Proposed change (if any): Target saturation should be taken into account, e.g. if the intended therapeutic effect is linked to enzyme inhibition, then the ~~maximum dose~~ anticipated therapeutic dose range (ATD) should consider when near complete occupancy and/or functional inhibition is achieved and little ~~no~~ further therapeutic effect is to be expected by increasing the dose (depending on the correlation between the functional endpoint and clinical efficacy).	
Page 13, lines 429-433		Comment: There are several published papers about maximum tolerated dose (MTD) and they all discuss the critical definition of the criteria for MTD. MTD is to be	

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		defined by acceptable criteria. It is agreed that investigating the MTD in healthy subjects should no longer be an objective, although the maximum dose to be investigated in healthy subjects can be above the efficacious dose range (see previous comment). Proposed change (if any): For trials or trial parts that include patients, the maximum tolerated dose (MTD) (if applicable) should be clearly defined by acceptable criteria and not be exceeded once it has been determined.	
Page 13, lines 432-433		Proposed change (if any): A trial design using a MTD approach is ~~considered to be unethical~~ not recommended for healthy volunteers unless properly justified.	
Page 13, lines 444		Comment: As a worst case, it appears important to refer to steady-state exposure, not just multiple dose PK. Additionally, BIO asks EMA to please specify that AUC0-t is AUC0-tau, where tau is the dosing interval. Proposed change (if any): The chosen dose, as well as expected steady-state exposure after multiple dosing (Cmax and AUC0-tau), should have been covered during preceding SAD parts/trials.	
Page 13, lines 445-447		Comment: This scenario should be accounted for in the protocol via flexible wording to enable dose adjustment without having to go through a substantial amendment.	

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		Proposed change (if any): The chosen dose, as well as expected exposure after multiple dosing (Cmax and AUC0-tau), should have been covered during preceding SAD parts/trials. If, however, emerging clinical data following multiple dosing suggests tolerance to adverse effects seen in a SAD part of a study whilst exposure remains below the predefined exposure threshold, ~~a substantial amendment to the protocol to cover~~ higher doses in a MAD part can be considered (this scenario should have been described and approved in the protocol).	
Page 14, lines 451-452		Comment: BIO suggests including examples of the durations for slow infusion and slow bolus as these would be helpful to sponsors.	
Page 14, lines 453-469		Comment: BIO believes it would be helpful to provide guidance for studies in patients where the drug is administered by the intravitreal or similar routes. In such circumstances, it is not readily possible to relate systemic exposure to drug with toxicities at the site of administration, often due to the low systemic exposure to drug. The same challenge will apply to studies in healthy volunteers where the drug is administered by the ocular topical, dermal, inhalation route.	
Page 14, lines 462-463		Comment: BIO believes this approach is very conservative and would not be necessary in some situations. As such, we propose that it is limited to	

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		specific situations. Additionally, we note that if supratherapeutic doses cannot be administered to healthy volunteers, then subtherapeutic doses will have to be evaluated in studies in patients. Administering single doses to patients may make clinical trial recruitment challenging since the patients will derive no therapeutic benefit from the administration of a single dose. Proposed change (if any): In some particular circumstances (i.e., major difference expected in exposure between patients and healthy volunteers, or for molecules with a narrow therapeutic index) when moving from healthy volunteers to patients, consideration should be given to reverting to a single dose design (with dose escalation as appropriate) in the first patient cohort.	
Page 16, line 538		Comment: The predicted therapeutic window should be clearly defined, along with all of its synonyms (therapeutic index) and related items (*e.g.,* safety margin). In determining whether to evaluate a compound in healthy volunteers or patients, the safety margin should be taken into account (*i.e.* the ratio of exposure at the animal NOAEL to the predicted exposure in man at each dose level). If the highest dose in healthy volunteers should not be higher than the predicted efficacious dose/exposure, then the ratio at this dose level will be the therapeutic window.	
Page 17, lines		Comment: For the first SAD cohort sentinel dosing may	

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557-578		be appropriate dependent on the risks as described in section 4, but not necessarily for all cohorts. This also seems to be implied in lines 590-593. Proposed change (if any): Sentinel dosing in the first single dose cohort should be discussed. If warranted, it should be also justified how many cohorts may use this sentinel dosing. Relevance of sentinel dosing in the multiple dose studies may be a point of discussion when warranted.	
Page 17, lines 565-566		Comment: At the time of designing the FIH clinical trial it is not possible to predict the variability in exposure or PD response in man. It is most often assumed that the variability in man will be similar to that in animals. PD data are reported and interpreted differently to PK data (*i.e.,* Cmax and AUC are calculated for PK but Emax and AUEC are not routinely reported). For PD data, duration of effect is more commonly used. It is not clear how the sample size relates to the decision to progress to the next dose cohort.	
Page 17, lines 567-568		Proposed change (if any): A planned maximum number of cohorts that will be dosed and the corresponding doses with the expected exposure for each cohort should be stated in the protocol.	
Page 17, lines 579-581		Comment: The requisite time between dosing successive subjects within a cohort should focus on	

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		serious adverse reactions rather than any or all adverse events (this is made clearer in line 587). As such, we suggest adding language similar to that in line 587 to make this focus clear.	
Page 17, lines 581-582		Comment: The statement as written did not take into account the toxicology data that have been generated and focuses solely on PK and PD.	
Page 17, lines 584-586		Comment: BIO suggests clarifying "review of all data". Proposed change (if any): At the end of the observation period there should be a clearly defined review of all data in the same manner as the precautions applied between cohorts (see section 8.2.7) before allowing dosing of further subjects in the cohort, ~~in the same manner as the precautions applied between cohorts~~.	
Page 17, lines 594		Comment: For placebo control studies it should be specified whether the sponsor (or selected team members) could be unblinded for an efficient ongoing review of the results between cohorts and/or parts of the study.	
Page 17, lines 595-601		Comment: BIO notes this is the first mention of the duration over which safety data should be collected for use in the dose escalation decision. It would be useful to introduce this concept in Section 7.3 (dose escalation). It would also be good to note that for a biologic (*e.g.,* IgG mAb) the timeframes for collection of safety data	

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		should be longer than 48 hours. This is especially the case where an IgG mAb is administered subcutaneously and the serum Tmax may not occur until ~ 10 days post-dose.	
Page 18, lines 612-616		Comment: BIO believes that this section may benefit from further clarification. In instances where there is dissociation between PK and PD, PK/PD models are of great use to first characterize in a mechanism-based way. If such models can be developed early on and validated from preclinical PK/PD, such tools are the most reliable way to model single dose human PD and use simulation to project multiple dose PK (hence select MAD doses in the most rational way). There may be cases where the disconnection is unexpected as it was not seen in preclinical species and thus cannot be adequately characterized as the underlying cause is not understood. As such, BIO suggests changing the text to signs of poorly characterized and/or unexpected dissociation. Proposed change (if any): In specific situations where PK, PK/PD models are of limited value (e.g. poorly characterized and/or signs of dissociation between PK and PD profiles and potential toxicities due to off-target effects at the administered human doses) dose escalation schemes and progression to further study parts need to be more cautious (e.g. consider a slower progression of the dose escalation scheme).	
Page 18, lines		Proposed change (if any): For studies with multiple	

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634-636		parts, consideration may be given to submitting an interim report to the competent authorities for review as a substantial amendment prior to the start of further dosing phases. In case the results of a completed part are leading to a substantial change to the design in the subsequent part of the study, then a substantial amendment should be submitted for review prior to the next part. Otherwise, when interim results are provided for review without substantial change of subsequent design, we propose that these should be provided as a notification in parallel to the start of the next study part.	
Page 18, lines 641-642		Comment: "Evaluable" subjects should be defined and it is expected that these are subjects who have completed all planned study visits. For an NCE, the subjects are most commonly domiciled for several days and all assessments are completed under on Visit. For biologics, there may be a period of confinement of several days but the healthy volunteers are subsequently discharged. Subjects many then return for several visits in order to collect PK and PD samples. If a subject misses one such visit, there will still be adequate data to provide sufficient PK and PD data for the dose escalation decision. If PK and PD data are not part of the dose escalation decision then the statement as originally written is likely to be appropriate Additionally, there will be study visits that occur after the last visit that provides data for the dose escalation	

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		decision. Therefore, the statement "all planned study visits" is inappropriate.	
Page 19, lines 643-644		Comment: The terminology "data collection" is unclear. This may include analysis of all samples collected. As such, we ask EMA to clarify what is meant by "data collection" as we believe additional specifics would be helpful.	
Page 19, lines 673-676		Comment: The definition of 'possibly related' should be cross-referred to ICH E2A, Section A.1, page 7. Proposed change: Possibly related means that there are facts (evidence) or arguments to suggest a causal relationship.	
Page 20, lines 686-688		Comment: BIO believes that this wording is very restrictive and has the potential to lead to study halt on the basis of an outlier. Proposed change (if any): For an individual to be dose-escalated, comparisons of the non-clinical (average) and clinical exposure should be based on the ~~maximum~~ observed clinical exposure in ~~an~~ that individual subject within a cohort and not the mean (average) clinical exposure in ~~a~~ the cohort. For a new cohort to be dose-escalated, comparisons of the non-clinical (average) and clinical exposure should be based on the 90th percentile clinical exposure within the cohort and not mean (average) clinical exposure in	

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		that cohort. An alternative is also to calculate the probability to have subjects in the next cohort exceeding the exposure threshold.	
Page 20, lines 692-693		Comment: It is unclear as to how "chemical structure and others compounds in class or other classes" relates to the use of PD as a stopping rule. Proposed change (if any): Additional stopping rules should also be based on what is known about the PD of the drug (e.g. mode of action, data from human or animal knockouts, regeneration of the target and others compounds that interact with the target in a similar manner ~~chemical structure and others compounds in class or other classes~~).	
Page 21,lines 740-742		Comment: For studies in healthy volunteers, it is feasible to conduct studies at a single site. However, for studies in patients it may not be feasible to conduct the study at a single site in a reasonable timeframe due to the scarcity of the patients.	

Please add more rows if needed.