European Medicines Agency

SUBMISSION OF COMMENTS ON The Requirements for First-in-Human Clinical Trials for Potential High Risk Medicinal Products
EMEA/CHMP/SWP/28367/2007

COMMENTS FROM The Biotechnology Industry Organization/Sara Radcliffe, Vice President, Science and Regulatory Affairs

GENERAL COMMENTS

The Biotechnology Industry Organization (BIO) submits these comments on the European Medicines Agency's (EMEA's) draft guideline *The Requirements for First-in-Human Clinical Trials for Potential High Risk Medicinal Products.* BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and 31 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. Our members invest heavily in the research and development of biotechnology and pharmaceutical products in the European Union (EU) and elsewhere, and employ thousands of highly skilled persons in the EU. We appreciate the opportunity to submit comments on the draft guideline.

The draft guideline highlights some of the key points to consider when taking Investigational Medicinal Products (IMPs) that "have a potential for high risk in first-in-man administration" (p. 1) into clinical testing. We agree that some new IMPs can be classified as highly novel molecules which show a high degree of species specificity and for which there is little or no prior knowledge of the risk/benefit ratio in humans. These molecules require special attention in defining and communicating the risk management strategy. However, the appropriate requirements for entering first-in-human (FIH) clinical trials may not be equally applicable to all such IMPs, and many of the most important requirements will be equally applicable to both "high-risk" and non-high-risk products. Consideration should be given to re-focusing the guideline to a 'points to consider' document on risk management strategies and dose-setting for all FIH clinical trials. The emphasis of the guideline should be more focused on risk mitigation strategies through the integrated analysis of all pre-clinical data and the appropriate design of clinical trials. This would remove the need for a definition of "high risk", while still addressing appropriate risk management strategies.

Two key areas need to be covered by the guideline:

1. The dose/concentration-response relationship for toxicity and pharmacology.
   Preclinical data are used to characterise the mechanism of action and the shape and steepness of both the toxicological AND pharmacological dose/concentration-response relationships; these data are normally generated for all potential candidate drugs (see Figure 1). We note that the suggestions provided in the guideline to characterise concentration-response relationships should be seen as suggestions, and not as an exhaustive or mandatory checklist of endpoints.
2. Risk management in relation to the risk profile of the IMP
   Using all the available data, the sponsor should justify the design of the clinical study (starting dose, dose escalation, therapeutic intention, clinical population etc) based on the risk profile of the IMP. Depending on the risk profile of the IMP, the therapeutic intention and clinical population, the

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starting dose may be set above the Minimal Anticipated Biological Effect Level (MABEL), at the MABEL or at some fraction of the MABEL. Such dose decisions will reflect not only the predicted MABEL itself but also the known toxicity profile and predicted No Observed Adverse Effect Level (NOAEL). Adverse effects must also be defined as acceptable and unacceptable depending on the indication and patient population. Figure 1 illustrates an IMP with a clear delineation between maximization of pharmacological activity and the advent of unacceptable toxicity. However, in some cases pharmacological activity may be increasing when unacceptable toxicity occurs. Likewise, uncertainty in the probability of an adverse event resides within each dose level with the probability likely increasing as the doses increase. For an IMP with high uncertainty in the probability of an unacceptable toxicity, lower initial doses – at or below the MABEL – are warranted. Thus, limitations of the preclinical animal species / models for predicting human safety should be addressed.

MAJOR COMMENTS (cont.)

Where there is limited confidence in the predictive value of the available preclinical data, even more attention than usual must be paid to risk mitigation strategies during the design of the clinical trial e.g. there should be a cautious choice of clinical population, starting dose and dose escalation scheme. Information may be given a higher weight in the determination of the starting dose if it is not only supported by strong interspecies correlation but also by a high level of confidence in the underlying data. In association with the nonhuman data package, safety margins (risk) should be tempered by the therapeutic intent and clinical population; for example, higher risk in oncology may justify a starting dose above the MABEL. In contrast, when an IMP has a novel mechanism of action and there is little or no prior knowledge about the target a more conservative approach may be justified, with a starting dose based on the MABEL or a fraction of the MABEL (to be justified by the Sponsor - see Figure 2). This general approach recognises the need to assess potential toxicities associated with the pharmacology in addition to adverse effects that are not related to primary pharmacology.

It should be recognised that it may not be possible or appropriate to generate data to cover all the points addressed in the draft guideline in the section Preclinical Requirements. Rather, the sponsor should justify on a case-by-case basis which data are appropriate for the purpose of characterising the dose/concentration-response relationship. Likewise in relation to the section on clinical requirements, the sponsor should justify the design of the FIH clinical study based on the risk-profile of the IMP and should address the points to consider in the Investigational Medical Product Dossier (IMPD).

Below is a list of comments on the guideline. If the guideline is re-focussed as described above, those comments made in relation to “high risk” definition become less relevant.

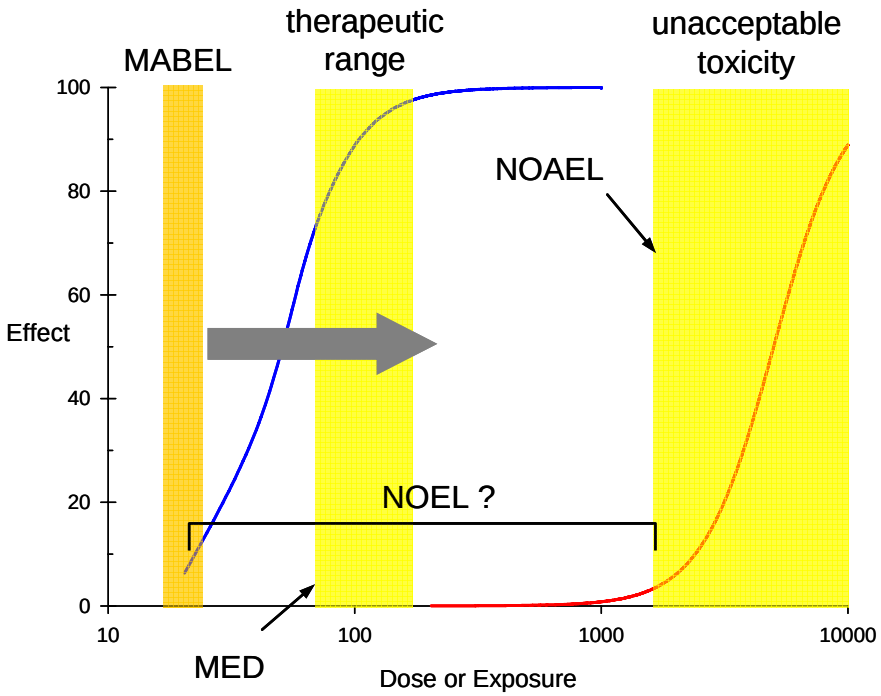

Figure 1: Schematic representation of MABEL as a starting point to explore the therapeutic range and either the dose or exposure associated with toxicity.

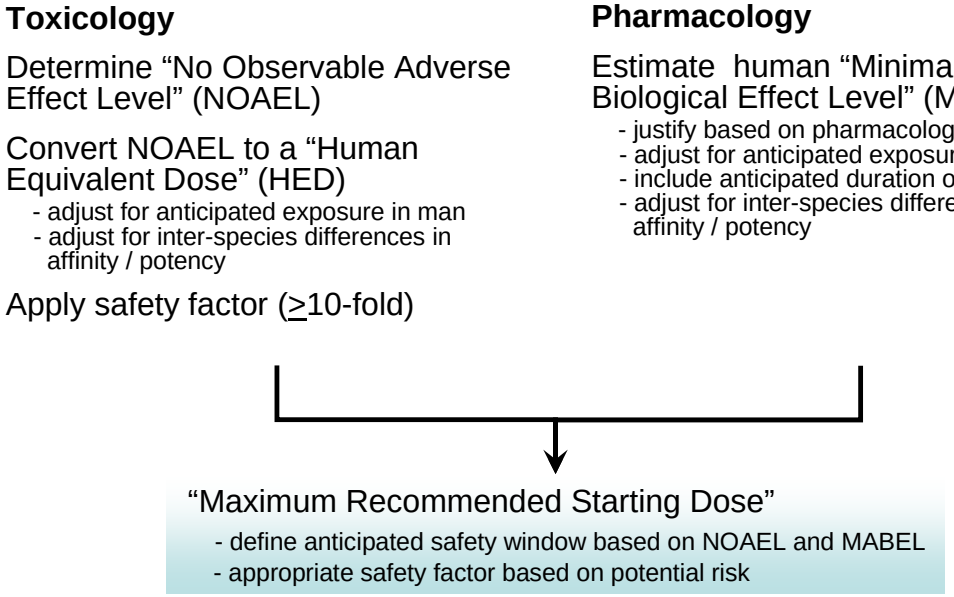

Figure 2: Schematic of dose selection for first-in-human studies
The Minimal Anticipated Biological Effect level (MABEL) focuses on the pharmacology of the IMP, its mechanism of action and inter-species differences. In contrast, the No Observable Adverse Effect Level (NOAEL) helps to define the expected safety window for the IMP. The maximum recommended starting dose should be selected based on the anticipated safety window.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
	The guideline uses mixed terminology to refer to an IMP – e.g. line 24 & 63 "medicinal products". The term is clearly defined in lines 16 and 17 and avoids the need for distinction between a biological and a small molecule/chemical. It is recommended that the term IMP be used throughout for clarity.	
	The document does not particularly address oncology FIH trials where many compounds are higher risk and the FIH dose selected is based typically on the SD10 i.e., 1/10 dose (based on surface area) that causes severe toxicity or death in 10% of rodents. In addition FIH trials are generally designed as multiple rather than single dose in patient populations.	
Lines 1-6	**Executive Summary**	
Title	This guideline should be re-focussed so that it is a points-to-consider document that covers all IMPs (see general comments above), while allowing for the diversity of molecules taken into FIH clinical trials. Special emphasis may be given to novel molecules which have not previously been tested in the clinic.	The title should read "Points to consider document on risk management strategies and dose-setting for FIH clinical trials". The text of the guideline will need revision to be in line with the major comments above
Line 3-6		We suggest the alternate wording: "It provides criteria to classify some new investigational medicinal products (IMPs) as highly novel molecules which show a high degree of species specificity and for which there is little or no prior knowledge of the risk/benefit ratio in humans. These molecules will warrant special attention. It also gives guidance on quality aspects, non-clinical testing strategies and designs for first-in-human (FIH) clinical trials, including the calculation of the initial dose to be used in humans, the subsequent dose escalation and the management of risk.

[1] Where available

Section 1	**lines 7-52**	
Line 9-10	While subjects in FIH studies would not normally derive therapeutic benefit, this may not be true if the FIH studies were in patients, especially if the investigational product has a long duration of effect.	We suggest the alternate wording "Such subjects would not normally be expected to derive any therapeutic benefit, although this may not be the case if patients are included in the trial and/or the anticipated duration of effect is sufficient to observe a therapeutic benefit. An assessment of risk and benefit is an important part of the decision to test an IMP in humans."
Line 16-19		We suggest the alternate wording "The non-clinical testing and experimental approaches for first-in-human studies with novel IMPs that are species restricted (ie they show a high degree of species specificity) and/or for which there is little prior knowledge of the use of this class of molecules in humans, raise particular difficulties."
Line 24		We suggest the alternate wording "In defining an appropriate early development programme, information needs to be …"
Section 2	**lines 53-57**	
Line 54-56		"This guideline refers to all chemical and biological medicinal products and pays particular attention to those IMPs for which it may be difficult to assess the risk profile. It specifically covers …."
Section 4.1	**lines 65-105**	
Line 65-105	Change section title in line with major comments above. The concept of "potential" high-risk products is vague. Who decides whether a product fits this designation and when? What data are necessary to facilitate this decision? Definitions could be different among sponsors, Phase I units and regulatory agencies. This section provides a very general definition of "high-risk" and almost any compound would fit under this definition. We suggest that the definition of high risk be eliminated or that it be simplified (e.g. an investigational medical product is "high risk" if there are concerns that serious adverse reactions could occur and there is	The Section Title should read "Points to consider in defining appropriate risk mitigation strategies for a FIH clinical trial" **This section would need to be rewritten if the major comments from BIO are accepted.**

	significant uncertainty in predicting human effects from preclinical studies).	
Line 100	Relevance of animal models: The terms “animal species” and “animal models” must be carefully distinguished. The former should be used when speaking of the species selected for safety testing, including discussions of relevant species. The latter term, animal models, should be reserved for those instances in which a spontaneous or induced animal model of human disease is used in safety testing. This document mixes the two concepts and thereby creates confusion.	Line 100: The title should read “Relevance of animal species and models”
Line 101-103	Need to specify that *in vitro* bioactivity is important for defining species relevance.	
Line 104-105	Lack of data from a relevant animal species does not increase intrinsic IMP risk but rather the uncertainty in the dose calculation. Therefore caution must be increased. What should be said is that, if no data are available one must proceed with caution. This document effectively creates two classes of products: those that are of potential high risk and those that are not. However, many of the recommendations in this document could be applied to almost any product being tested for the first time in humans, including both biologics and small molecules. They are sound practices for avoiding and or mitigating adverse events (AEs) or severe adverse events (SAEs). Therefore we reiterate here our comments from above that the guideline would be more useful if it were refocussed to be a “points to consider” document that provides guidance on when and how to develop appropriate risk mitigation strategies through the integrated analysis of all pre-clinical data and the appropriate design of clinical trials. We also note that animal studies should never be relied on as “predictive”. Rather, these studies are informative. Nonclinical programs that reveal safety concerns are not the studies one has to worry about. Rather it is those that do not reveal safety concerns; that is, those for which the target and/or MOA suggests possible	

	AEs/SAEs but for which the nonclinical program does not reveal safety issues.	
Line 81	All dose-responses are inherently nonlinear and highly dependent on the dosing design, i.e., range, placement and amount. In the context of safety/tolerability, the steepness of the dose-response should be considered as well as the shape.	We suggest that "and steepness" be added so that the text reads: '….and the type and steepness of dose response….'
Line 90	Novel fusion proteins could include pegylation or Fc modifications of marketed or well known proteins. We believe the guideline is referring to fusions of two proteins each with its own pharmacology.	Provide more clarity on what's considered 'novel', to exclude protein modifications directed toward altering the biodistribution of existing therapies.
Section 4.2	**lines 106-142**	
Line 107-142	We agree with the statement "*The requirements for high-risk medicinal products regarding the physico-chemical characterization and, additionally biological characterization of biological products, are not different from any medicinal products.*" Therefore the quality section that follows should not imply that a higher standard of characterization and method development should be applied to qualify a high risk drug for an FIH study than that applied to "non-high risk" drugs. There may be some confusion about whether the guideline is suggesting that the exact clinical formulation, and not just the active pharmaceutical ingredient (API), be required for the "pivotal" animal studies to support FIH. It should be made clear that use of a comparable API is still acceptable.	
Section 4.2, page 5, paragraph 2, lines 116-117	It is very difficult to characterise all major product-related variants, including heterogeneity and degradation products that "may have an impact on the pharmacological profile of the molecule", especially at this early stage of development. It would not be practical and there would be limited value to manufacture these variants for pharmacodynamic (PD) and toxicity characterization.	We suggest the alternate wording "A characterisation of product-related variants, including heterogeneity and degradation products of the molecule, should be performed."

Section 4.2, line 118	Clarification is requested regarding the statement "Special consideration should be given to the suitability and qualification of methods to sufficiently characterize the active substance and drug product."	We suggest the alternate wording "It is expected that analytical methods are demonstrated to be suitable for their intended purpose."
Section 4.2, page 5, paragraph 3, lines 122-127	Potency of the molecule is typically assessed in a cell-based potency assay. The wording here implies that the potency assay should be an *in vivo* assay, which is not always practical or relevant, reliable or qualified. A potency range based on pharmacological and statistical fundamentals should be justified for each bioassay.	We suggest the additional text "A potency range based on pharmacological and statistical fundamentals should be justified for each bioassay." We also suggest the alternate wording "For a biological medicinal product, the lack of a cell-based potency assay should be fully justified."
Section 4.3.1	**lines 144-158**	
Lines 149-150	There should clear guidance that *in vivo* data should only be generated in species that display relevant cross-reactivity. For example, misleading data will be generated in non-primate animal models when the only cross-reacting species is the non-human primate. For some products relevant pharmacodynamic parameters may only be available if a surrogate molecule is manufactured or from *in vitro* studies with human cells/tissues. The sponsor should justify the approach taken.	We suggest that "chosen" be replaced with "relevant" (to read: "…in one or more relevant animal models…").
Line 150	Receptor occupancy and binding should ideally be linked to a functional response.	We suggest an expanded sentence to read: 'These studies should include receptor binding and occupancy (preferably linked to a functional response), duration of action of effect and dose response.'
Line 150, 151	The statement 'should include receptor binding and occupancy' applies only to compounds that bind to cell receptors. Many investigational compounds that fit into the proposed 'high risk' category are likely to be monoclonal antibodies or other biologics that bind to soluble ligands and therefore this statement is not relevant for all compounds. Add a statement to address evaluation of the quantitative interaction of investigational compounds with soluble ligands.	We suggest the alternate wording: 'These studies should include binding and occupancy (whether soluble ligand or receptor) duration of effect and dose-response'.

Line 151, 152	The concentration effect relationship should be established, not just dose/effect. These lines should refer to concentration effect (and then section 4.3.2 could be deleted).	We suggest that 'dose' be replaced with 'concentration'.
Line 151	Receptor occupancy and pharmacodynamic effect are both markers of downstream effect. It should also be recognized that receptor occupancy is not necessarily relevant for all targets (e.g. some enzymes and kinase inhibitors). Species specificity may entirely preclude *in vivo* PD information from preclinical models. Where preclinical models do provide information with conserved target sequences, the effects of immunogenicity must be considered when evaluating experimental results.	We suggest the alternate wording: "These studies should include the duration of the effect and dose-response, with receptor occupancy or cell signalling as markers of downstream effect." "In cases where species specificity precludes assessments of *in vivo* pharmacodynamics, use of a homologous protein (species specific surrogates of the product) may provide additional information." "In some cases, immunogenicity to the medicinal product can impact the maximal effect and duration of effect observed in animals. The immunogenic response to the product in definitive pharmacodynamic studies may add value to the interpretation of the experimental results, particularly if repeated dose administration is employed in these studies."
Line 158	It is important that pharmacokinetic (PK) and PD studies in these early stages of drug development are designed, conducted and analysed consistent with principles of Good Laboratory Practice (GLP). The term "high quality" is vague and impractical to define in these early stages of development and may be prone to misinterpretation, leading to impractical resource intensive studies that may not be informative or useful for the design of FIH studies.	We suggest deletion of "of high quality and" because compliance with principles of GLP will sufficiently assure appropriate 'quality control' of the study.
Section 4.3.2	**Line 159-162**	
Line 160-162	With species specific biologics, you may not be able to get exposure in the animal model of disease with the clinical candidate and thus the exposure information comes from a surrogate molecule. The wording should be changed to 'relevant animal species'. In addition, the assay sensitivity for biologics (ELISA vs. HPLC for small molecules) may not be sufficient to detect drug at the low end of the dose-response curve.	We suggest the alternate wording "… exposures at pharmacological doses in the relevant animal species should be determined. Consideration should be given to the sensitivity of the assay for biologics, where a pharmacologic effect may be seen even in the absence of detectable drug. In these cases, exposure in the nonclinical studies may not be accurately assessed at the lowest end of the dose-response curve."

Lines 160-162	It should to be clarified that a complete absorption, distribution, metabolism and elimination (ADME) package, as implied by the use of the descriptive phrase in the draft guideline, is not required at this stage of development, but rather PK or toxicokinetic (TK) data.	We suggest the alternate wording "standard absorption, distribution, metabolism and elimination (ADME)" to "pharmacokinetic or toxicokinetic".
Line 160-162	ADME does not generally add value and is not generally required for large proteins with limited distribution volumes.	We suggest the addition of this sentence to the end of the paragraph: "Traditional ADME evaluations do not generally add value for large proteins with limited distribution volumes".
Section 4.3.3	**Line 163-194**	
Lines 164-194	The list of potential tests for relevance is extensive and many are not practical or feasible for all molecules. There must continue to be flexibility in the requirements for testing species relevance. It needs to be clarified and stated that this is not an inclusive "check-list" requirement for all molecules, but a set of points to consider case by case based on scientific rationale and feasibility. Cross-reactivity studies using human and animal tissues must be interpreted in the context of the available pharmacodynamic and toxicity data. Until human *in vivo* data are generated, there is a potentially high level of uncertainty in the value of the nonhuman data.	
Line 170-172	In most cases, the only comparative data across humans and test species is *in vitro*. Thus, the sentence indicating that similar *in vitro* data may not predict *in vivo* data could be applied to almost all development programs. The key statement that questions the translation of the nonclinical to the clinic is contained in the previous sentence (lines 168-170) and this statement adequately frames the remainder of this section.	We suggest eliminating the sentence 'It should be noted … response will be similar'.
Line 178	Low and infrequent doses are likely to be immunogenic, but experience has shown that higher and frequent doses minimise immunogenic response.	We suggest the alternate wording: "It should be noted that human specific proteins can be immunogenic in animal species".

Section 4.3, page 6, paragraph 9, lines 178-182	This section is unclear as to whether the endpoint being discussed is pharmacodynamic or toxicity. Further, immunogenicity in animal species does not mean that useful information will not be collected. Binding anti-drug antibodies alone do not *a priori* interfere with pharmacodynamics or toxicity.	We suggest that lines 178-182 be deleted.
Lines 183-194	This section should indicate that the extent to which the relevant species is relevant should be discussed, i.e. a discussion of the limitations of the available species and models to predict human safety.	
Section 4.3, page 7, sub-bullets 1 and 2, lines 185-189	It may not be possible to understand the 'functional consequences' in the relevant animal model. Again, in a justified circumstance a surrogate molecule may be required. There needs to be some recognition that you can't always get this information in the relevant species as these assays may be extremely difficult (or impossible) to adapt to the animal species being used. In addition, Fc regions are very different in nonhuman primates and rodents compared to humans, so data on functionality of the Fc regions in animals has dubious value.	We suggest the alternate wording "Receptor structure, binding, occupancy and functional consequences, including cell signalling if relevant. In cases where it is not possible to get these data from the relevant animal species, data from a homologous protein may be used to understand these PD effects." and "Data on the functionality of additional functional domains in an *in vitro* assay with human cells, if applicable e.g. Fc receptor system for monoclonal antibodies."
Line 192-193	There may be some reservations about the use of transgenic animals and the data generated in these models, e.g.: • There may insufficient data to confirm that the pharmacological response between human and animals is comparable particularly with novel targets. • There may be limited historical data for use as reference when evaluating study results in these genetically modified animals. • The stability of the transgene needs to be continually confirmed. The use of homologues may not be the ideal solution either as a different molecule to the IMP is being tested.	We suggest revising this paragraph to read: "Where no relevant species exists, the use of transgenic animals or the use of homologous proteins may be the only way to conduct a preclinical assessment. However, the relevance and limitations of such models should be carefully considered and discussed fully in the supporting documentation."

	A definition of relevant species might be needed. Is it only pharmacologically responsive animal models carrying the target which are considered relevant or should a model without the target but with similar non-specific staining in cross reactivity be considered relevant? In that case studies in a species not carrying the target could be considered relevant. It would be preferable to have a combination of a relevant non-specific toxicity study and a study in a transgenic or homologous model then to just have the transgenic or homologous study alone. Transgenic or homologous models are supplements for assessing pharmacological effects but require a number of compromises that disqualify them from being stand-alone safety models.	
Section 4.3.4	**Line 195-200**	
Lines 195-200	It needs to be stated that safety pharmacology endpoints can be incorporated into the toxicity studies and that separate safety pharmacology studies are not required when the only relevant species is the non-human primate. Stand alone safety pharmacology studies should only be conducted in non-human primates if there is scientific rationale to do so.	
Lines 198-200	The sentence "In particular, for medicinal products targeting the immune system, potential unintended effects should be investigated, e.g. using *in vitro* studies, including human material" is confusing and we are not sure what is being requested. If what is being requested is information about the potential for cytokine release using human peripheral blood mononuclear cell (PBMC) *in vitro*, then it is worth being more specific. However, it should be recognised that while an *in vitro* assay for cytokine release using human PBMCs may be relevant for certain products with agonistic activity or antibodies directed against certain cell surface targets on immune cells, such a test may not be relevant for all medicinal products targeting the immune system.	We suggest that this sentence be deleted: "In particular, for medicinal products targeting the immune system, potential unintended effects should be investigated, e.g. using *in vitro* studies, including human material."

Section 4.3.5	**Line 201-213**	
Line 204	The sentence 'Toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged' should be reconsidered. 'Discouraged' may be too strong a word if the guideline applies to new chemical entities (NCEs) as well as biologicals. For NCEs, in the absence of pharmacologically responsive species, the sponsor is usually required to conduct toxicology studies in non-responsive species to detect off-target effects or chemically-mediated toxicity.	We suggest revising the sentence to read: "For biological products, toxicity studies in non-relevant species may give rise to misinterpretation …"
Line 209	Animal models of disease often exhibit different pharmacokinetic characteristics than normal animals (e.g. absorption, distribution, protein binding, metabolism and elimination), introducing complexity in the prediction of human pharmacokinetics (typically performed using normal/non-diseased animals). Normal animals should be used to predict human PK. However, a comparison of exposure differences between normal and disease animals may be helpful in the interpretation of data.	We suggest deletion of the word "pharmacokinetics". Perhaps additional clarification can be added in a separate statement that pharmacokinetics in diseased animals may be different from normal animals.
Lines 208-213	The guideline should state that if toxicology studies are conducted in animal disease models rather than in normal animals then these studies may be conducted non-GLP if GLP is not feasible.	
Section 4.3.6	**Line 214-241**	
Section 4.3, page 7, Calculation of the first dose in man.	It should be acknowledged that the MABEL is only one method to determine the starting dose for FIH studies.	
Line 222-223	Regarding the sentence "safety factors are usually applied for the calculation of the first dose in man from MABEL," we note that depending on the risk profile of the IMP and clinical population, the starting dose may be set above the MABEL, at the MABEL or at some fraction of the MABEL. Also, the wish to provide flexibility and to cover all applications in a	Recommendations should take account of the frequent circumstance with biologicals where a PK assay may not be adequately sensitive to return reliable data at exposure levels which provoke a biological effect. Often there is not a true PD assay other than estimates of *ex-vivo* occupancy at the cellular level. Thus if the MABEL approach is taken (ie the minimal anticipated dose predicted to give a reliable estimate of biological effect) and a fraction of this MABEL is used for the FIH dose, the resulting

	guideline often renders it more or less useless due to vague or broad statements that can be understood and interpreted freely and differently. In that respect some guiding safety factors to apply when calculating FIH dose would be a useful addition to this guideline. Statements on recommended minimum safety factors to be used in e.g. life-threatening diseases vs. non-life threatening diseases, with "high-risk compounds" would be helpful, perhaps with an example of how different levels of risks and uncertainties can be visualized. It should be noted that a different safety factor may be used if it is justified.	exposure for the subject will effectively be a placebo and not a test of safety and tolerability. This may be appropriate when a steep dose-response is anticipated and unacceptable toxicity is predicted to be coincident with maximal pharmacologic activity.
Line 233-234	PK/PD modelling per se is not essential. No mention is made of target density and target turnover.	We suggest that this sentence be replaced with: "All available preclinical concentration-response (PK/PD) data should be extrapolated to humans with relevant adjustments for potency, pharmacokinetics, target density and target turnover, where known."
Section 4.4	**Clinical Requirements**	
Lines 248 to 255	Although this section omitted that FIH studies are typically **single-dose**, dose-escalation studies, in some diseases individual patients only receive multiple 'single doses' separated by a suitable washout period. The 'number of doses' is omitted from the list. This is relevant as monitoring requirements may be different between a design that administers only a single dose to each subject and one in which multiple 'single doses' are administered.	We suggest addition of "number of doses".
Lines 259-260	The statement seems to imply an independent safety monitoring board is always required. This is not always the case, as is been stated in the latter sections of this guideline.	We suggest the alternate wording: "The protocol should describe the strategy for managing risk including a plan for monitoring safety and managing ~~of~~ any adverse reactions and the use of an independent safety monitoring board, if deemed necessary by the sponsor."
Line 276	Rephrase for clarification.	We suggest the alternate wording: "The disease state and concurrent medication in patients may give rise to

		greater variability in response and the potential for interaction…"
Section 4.4, page 8, paragraph 7, lines 275, 280-281	This paragraph discusses in several places the potential for long-term toxicity, potential long-term consequences on physiological systems and potential long-term safety problems. Very little information on long term toxicity is likely to be available at this stage of development. We request addition of examples of what information is available on potential long-term toxicity.	We suggest the deletion of the last sentence "Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety problems." We suggest the alternate wording "Several factors should be considered, such as…c) immediate and potential long term toxicity (e.g., information from transgenic or knock-out mice, data from other molecules with similar pharmacological mechanism, etc.), d)…"
Line 281	Text should be added to focus on agents likely to require a long-term monitoring plan.	We suggest that the following text be added to the end of the sentence: "for agents anticipated to produce a demonstrable PD effect beyond the period required to fully assess PK."
Line 281		We suggest addition of information on half life (or mean residence time). Drugs with long duration of action may be more appropriate to dose in patients since toxicity may be prolonged.
Section 4.4, page 9, paragraphs 4 and 5, lines 306-314	Not all PK and PD data would have to be analyzed before escalating to the next dose level.	We suggest addition of the word "available" so that the text reads "In addition, any available PK and PD data from the previous cohorts should be compared to known non-clinical PK, PD and safety information. … Administration in the next cohort should not occur before all the participants in the previous cohort have been treated and available data/results from these participants reviewed."
Line 319		We suggest the addition of typical dose escalation decisions including geometric rather than arithmetic schemes (typically half log increments) because of the biologic basis of receptor occupancy issues, except at higher doses where smaller increments may be needed because of incipient toxicity.
Section 4.4, page 10, paragraph 3, lines 348-354	The sentence from 280-281 is repeated here. Additional clarification is needed.	We suggest the alternate wording "Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety problems (e.g., mechanisms that deplete cell populations). … In these circumstances, it may be necessary to implement follow-up for an appropriate period of time for the participants after the end of the study

		(i.e., until there is no longer measurable drug in the serum or until recovery of a PD effect)."
Lines 347-354	This section on long-term monitoring is very vague. How will this monitoring be carried out? How will an infection or malignancy be evaluated to determine it was a consequence of drug exposure? Any findings will be difficult to interpret at time points too far removed from the treatment period.	We request specification of the type of study design and special circumstances that would absolutely require long term monitoring.
Line 351	Adding an example here would be valuable. As currently written, any immune modulator could be construed to require a long-term monitoring plan despite the fact that a single dose is being studied.	We suggest addition of "(e.g. therapeutics effecting a demonstrable PD effect persisting beyond the duration of the study)".
Line 320	Typographical error	The dose/toxicity or dose/effect relationship