Reviewer Comments and Suggestions

Title: WHO Guideline on the nonclinical and clinical evaluation of monoclonal antibodies and related biological products intended for the prevention or treatment of human infectious diseases (WHO/MAB/DRAFT/19 August 2022)

Written comments proposing modifications to this Guideline MUST be received no later than **28 October 2022.**

Reviewer(s) (Name, Organization, and contact details):	**Biotechnology Innovation Organization (BIO)** Rachel Coe, Manager of Science & Regulatory Affairs 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's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

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General / Overall Comments				
BIO greatly appreciates the opportunity to provide input on the World Health Organization's (WHO) current draft guideline regarding the nonclinical and clinical evaluation of monoclonal antibodies (mAbs) and related biological products intended for the prevention/treatment of human infectious diseases. BIO strongly supports WHO's mission to ensure the equitable and widespread availability of safe, effective, and quality health products. With this objective in mind, BIO has several overarching recommendations that we believe will increase the guideline's value. • First, BIO encourages further incorporation of the 3Rs principles (replacement, reduction, and refinement of animal use) throughout the guideline. While nonclinical *in vivo* (i.e., animal) studies continue to provide critical information to sponsors and regulators on the safety and efficacy of products, BIO urges WHO to reconsider when such studies are truly necessary in the context of this guideline. Where possible, *in vitro* technologies and computational/mathematical modeling techniques (e.g., physiological based pharmacokinetic (PBPK) models) should be leveraged to inform the nonclinical assessment of products. Likewise, it would be beneficial if the guideline acknowledged that there is no scientific merit presented by toxicology studies conducted in species that do not express the target. In these cases, an in vitro package accompanied by a limited in vivo study of short duration should be sufficient. • Secondly, BIO suggests that all recommendations on the design and conduct of nonclinical safety studies should be consistent with those in the current ICH S6 Guideline on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. • Lastly, though it may not be possible (or necessary) to ensure *complete* consistency with existing regional guidances, BIO suggests that the guideline acknowledges and incorporates the recommendations contained within current regional guidances where possible, especially those that have been issued since the COVID-19 pandemic. This additional consistency in regulatory expectations will make it more practical for sponsors to implement.				
1. Introduction				
Page 3, Lines 9-12	Because of their established history of safe use, the rapid onset of their clinical effect, and the relatively short time required to bring them to production, mAbs are considered a high priority for their potential impact in the control and treatment of infectious diseases, especially those	In reference to the safety of infectious agent targets, it is suggested to cross refer to the ICH S6 Addendum that mentions limited testing needed in relation to bacterial and viral targets, which is the topic of this guidance. To improve clarity, suggest adding "intrinsic and relative" in relation to safety of other	Because of their ~~established history of safe use~~ intrinsic, relative safety, (see ICH S6 Addendum on bacterial and viral targets), the rapid onset of their clinical effect, and the relatively short time required to bring them to production, mAbs are considered a high priority for their	

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	for public health emergencies, such as COVID-19 (4).	mAbs with different targets (e.g., CD28 targeting).	potential impact in the control and treatment of infectious diseases, especially those for public health emergencies, such as COVID-19 (4).	
Page 3, Lines 26-28	There was little advice on nonclinical or clinical evaluation specific to the pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), or to post infection treatment with mAbs.	These types of products are mentioned in the ICH S6 guideline regarding species selection. Cross referencing the guideline would be useful.	There was little advice on nonclinical or clinical evaluation specific to the pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), or to post infection treatment with mAbs (see to ICH S6).	
2. Scope				
Page 4, Lines 1-8	• Antibody fragments, such as single-chain variable fragments (scFvs) and antigen binding fragments (Fab),	Mention of antibody modifications (sequence substitutions) such as for half-life extension or reducing/enhancing effector function, would be useful.		
Page 4, Lines 6-7	• …mAbs or related antibody proteins which have been chemically modified, such as through conjugation…	It would be useful if further specification was provided regarding immunoconjugates or antibody drug conjugates in sub-bullets. For example, does this include conjugation to a small molecule toxin?		
Page 4, Lines 10-12	It should be noted that for the purposes of this guideline, the term “monoclonal antibody” or “mAb” is used to encompass the breadth of the substances and products represented above unless otherwise stated.	To improve readability, suggest including a comma before the text “unless otherwise stated”.	It should be noted that for the purposes of this guideline, the term “monoclonal antibody” or “mAb” is used to encompass the breadth of the substances and products represented above, unless otherwise stated.	

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Page 4, Lines 14-27	…or their toxins, and used specifically in the pre- and post-exposure prevention or treatment of human infectious diseases. It does not address the evaluation of mAbs or related biologicals that target endogenous human proteins, such as cytokine responses to an infection, nor does it apply to mAbs or related biologicals used for the diagnosis of infections. Immunomodulatory antibodies are not within the scope of this guideline as they…	Suggest removing this text and continue directly with Line 20 in relation to what is considered out of scope. Also, suggest placing this paragraph prior to the list of mAb formats that are included in scope.	…or their toxins, and used specifically in the pre- and post-exposure prevention or treatment of human infectious diseases~~. It does not address the evaluation of mAbs or related biologicals that target endogenous human proteins, such as cytokine responses to an infection, nor does it apply to mAbs or related biologicals used for the diagnosis of infections.~~ Immunomodulatory antibodies are not within the scope of this guideline as they…	
Page 4, Lines 23-27	It should be noted that the general principles within this guideline would apply to mAbs which target endogenous human proteins with the intention of preventing or treating infections (e.g., mAbs to a cell surface receptor which prevents viral entry to the cell); however, such products may require additional nonclinical and clinical studies depending on the protein target(s).	The scope is clear in terms of the 'type of product' technology wise but other than the title, is not entirely clear that its target is an infectious agent. e.g., The ICH S6 Addendum clearly states "monoclonal antibodies and other related antibody products directed at foreign targets (i.e., bacterial, viral targets etc.)" although this could be implicit here from the guidance title.	Suggest removing for consistency/clarity: ~~It should be noted that the general principles within this guideline would apply to mAbs which target endogenous human proteins with the intention of preventing or treating infections (e.g., mAbs to a cell surface receptor which prevents viral entry to the cell); however, such products may require additional nonclinical and clinical studies depending on the protein target(s).~~	
3. Terminology				
Page 5, Lines 1-2	"…or antibody-dependent cellular cytotoxicity.	Repeat of initial name for this terminology	Suggest removing repetitive text.	

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Page 5, Line 23	N/A	Include chimeric antibodies, to align with description of humanized antibodies further down	Suggest: "Recombinant DNA-derived antibodies from non-human species whose genetic sequences still retain non-native amino acid sequences."	
Page 5, Line 49	"They are often known as antibody-drug conjugates"	This term is *only* used to describe antibodies when conjugated to a toxin or label. This is not used for antibody fragments (Fabs) when conjugated to non-active molecules such as PEG	Suggest moving end of first sentence to be stand-alone sentence at the end: "Antibody fragments can also be conjugated to non-bioactive compounds, such as polyethylene glycol (PEG) to extend the systemic half-life."	
Page 6, Line 1	"Neutralizing antibodies (NAbs) : ……	This is confusing, as NAbs have a different meaning when applied to all other antibody-based therapeutics – this term describes ADA that bind to and prevent the activity of the **mAb** itself	Suggest using a different terminology for this e.g., "Inactivating antibodies"?	
Page 6 Line 10	Whole paragraph and throughout document	Manufacturer is not the most accurate term here, as this could be assumed to mean a contract manufacturing organization	Suggest replacing "manufacturer" with "developer" throughout.	
4. General and Regulatory Considerations				
Page 6	N/A	Add "opsonophagocytosis"	Suggest: "The engulfment, by macrophages and other phagocytic cells like neutrophils, of bacteria coated (opsonized) with antibodies and/or complement proteins."	
Page 8, Lines 12-14	All of these biochemical properties can significantly impact the mAb half-lives, tissue distribution, stability,	Suggest adding the term pharmacologic.	All of these biochemical properties can significantly impact the mAb half-lives, tissue distribution,	

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	susceptibility to degrading enzymes, secretion, and their immunogenic potential.		stability, susceptibility to degrading enzymes, secretion, and their pharmacologic or immunogenic potential.	
Page 8, Lines 4-6	Therefore, ADE is an important aspect to assess as part of the nonclinical program for any mAb to infectious diseases, particularly if the functions of the epitope are not clearly understood.	Guidance on what to include for ADE assessment would be helpful, especially how to translate findings to the clinic.	Provide further guidance.	
Page 8, Lines 25-26	The ability of the mAb to reach site(s) of pathogen activity is another important consideration during its development.	Suggest use of PBPK modelling to address this.		
5. Nonclinical Evaluation				
Page 10, Lines 41-43	Scientific justification should also be provided for the selection of the animal species used for PK and toxicokinetic (TK) evaluation, taking into account that the PK profile in the chosen animal species should ideally reflect the PK profile in humans.	Unfortunately, this implies use of NHPs. Strong justification should be provided for the selection of NHP as a preclinical species. Deselection of other lower species for toxicology studies should occur prior to choosing NHP. Given the global shortage of NHPs this is going against the 3Rs. The value of PK/TK for the target should be considered as well. Need to take into consideration how the PK of a mAb against an infectious agent contribute to the clinical dose selection. See additional comments for further consideration on this topic.	Evaluation of pharmacokinetics may be considered to determine exposure. However, consideration in the translation of this data, if using rodents, would need to be taken into consideration, as would the general application in general of PK data.	

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Page 9, Lines 43-44	Internal SOPs should be maintained for any non-GLP compliant studies that have been conducted.	This is too restrictive. If novel assays are developed, there won't be SOPs for them or they are run in a lab where SOPs are not normally in use. This is particularly true for early pharmacology studies.	Suggest: ~~Internal SOPs should be maintained for any non-GLP compliant studies that have been conducted.~~	
Page 9, Lines 44-45	All relevant studies, whether GLP or non-GLP compliant, should be included in submissions for marketing authorization.	Suggest removing this statement and deferring to health authorities.	Suggest removing.	
Page 9, Lines 48-49	Consideration should be given to the use of appropriate *in vitro* alternative methods for safety evaluation.	Rather a vague statement - for ICH or FDA guidances these alternatives need to be validated. Would these in vitro alternatives need to be validated and the in vitro reprotox assays in ICH S5(R3).	Suggest providing further clarification.	
Page 10, Lines 13-14	Identification of possible toxicities and likelihood of potential adverse events or undesirable effects	What about reversibility? Evaluation of potential for reversibility may suffice without inclusion of recovery animals.	Identification of possible toxicities their potential for reversibility and likelihood of potential adverse events or undesirable effects.	
Page 10, Lines 26-28	This potential for resistance should be monitored by the manufacturer (e.g., with in vitro tests using antigens derived from circulating and emerging strains).	Sponsor would be better as manufacturer may be interpreted as the CMO that produced the mAb	This potential for resistance should be monitored by the ~~manufacturer~~ sponsors (e.g., with in vitro tests using antigens derived from circulating and emerging strains).	
Page 10, Line 34	"…PD, PT and toxicology studies."	What is PT? Is this meant to be PK?	Suggest editing text to either explain or correct.	
Page 10, Line 34	The selection of a suitable animal species for use in evaluating mAbs against an infectious disease could prove challenging and may not necessarily be the same for proof of	The tox assessment in healthy animals for mAbs against pathogens involves evaluating potential toxicity due to off-target binding but does not address the potential safety concerns due to		

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	concept, PD, PT and toxicology studies.	exaggerated pharmacology because of the absence of relevant targets in these animals. BIO recommends highlighting this in the guideline as a unique aspect for mAbs targeting infectious diseases.		
Page 10, Lines 37-39	Where possible, preference should be given to studying mAb functionality in an animal model where the mechanism of the infection and pathology is similar to that in humans.	Relies on using the same biology and tox species. ICH S6 (R1) requires one study in healthy animals. Where there is no endogenous target i.e., off target binding, is this statement indicating this study be replaced with safety assessment endpoints in studies in infected animals?		
Page 10, Lines 41-46	Scientific justification should also be provided for the selection of the animal species used for PK and toxicokinetic (TK) evaluation, taking into account that the PK profile in the chosen animal species should ideally reflect the PK profile in humans. The nature of the mAb product itself, whether murine, humanized or human, or a mimetic based on a non-immunoglobulin scaffold, should be kept in mind since it may influence study results, as should the stability of a mAb or immunoconjugate.	Unfortunately, this implies use of NHPs. Strong justification should be provided for the selection of NHP as a preclinical species. Deselection of other lower species for toxicology studies should occur prior to choosing NHP. With advances in modelling and humanized mice (e.g., human FcgR), could these not be sufficient? Given the global shortage of NHPs this is going against the 3Rs. The absence of infectious target in the healthy animal will influence the PK profile compared to patients with disease. In the case of standard or widely used mAb formats it may be possible to extrapolate the PK profile from other mAbs including marketed products.		
Page 10, Lines 30-46	These two paragraphs discuss the selection of the animal species for PK, PD and safety.	ICH S6(R1) advises “For monoclonal antibodies and other related antibody products directed at foreign targets (i.e., bacterial, viral targets etc.), a short-term	Consider including the ICH S6 text or similar, advising that there is no need for a standard toxicology package if the species does not	

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		safety study in one species (choice of species to be justified by the sponsor) can be considered; no additional toxicity studies, including reproductive toxicity studies, are appropriate." In line with 3Rs considerations, there is no scientific merit in conducting a toxicology study in a species that does not express the target.	express the target. The same may also be true for PK/TK.	
Page 10, Lines 48-50	The induction of anti-mAb antibodies in animals is generally not relevant in terms of predicting the potential immunogenicity of mAb products in humans, although it may provide some insight as to potential complications for the mAb-related products.	Along with previous comments, this could be stated in the context of using alternative models. Strong justification should be provided for the selection of NHP as a preclinical species. Deselection of other lower species for toxicology studies should occur prior to choosing NHP.		
Page 11, Lines 2-3	Nevertheless, immunogenicity studies if undertaken may assist in the interpretation of in vivo animal studies	It is considered that ADA or its sequelae in healthy animals is of no relevance to humans with the infection. In addition, use of NHP for safety testing of mAbs against infectious targets is considered unnecessary and unacceptable based on the 3R principles. Use of healthy rodents only where necessary should suffice.		
Page 11, Lines 13-15	Monoclonal antibodies with ADCC activity (with an Fc region that is recognised by the animal species or mAb preparations with pseudo-allergens) require more extensive non-clinical testing in more than one animal species over a range of doses.	Suggest clarifying pseudo-allergens.		

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Page 11, Lines 29-30	The unintended reactivity of an anti-infectious agent mAb with human tissue should be determined using frozen panel of adult tissues, or representative cell cultures	Does this refer to off-target screening platforms? ICH S6(R1) Note 1 should be referenced. Suggest inclusion of embryofetal and pregnancy proteins in arrays as well.		
Page 11, Line 32-33	When cross reactions are encountered, studies should be expanded to more tissues.	GLP TCR includes FDA list of tissues, unclear what additional tissues would need to be evaluated?		
Page 11, Line 36-38	Therefore, cross-reactivity studies should usually be conducted prior to Phase I human studies to search for non-target tissue binding or any cross-reactions.	ICH S6(R1) TCR GLP Studies are required prior to Phase I and potential impact of any nonspecific staining is usually addressed in the GLP tox study. If the target is cross reactivity with another infectious target other in vitro studies should be considered.		
Page 11, Lines 45-47	For co-formulated mAbs, the neutralising activity of each of the constituent mAbs should be tested and any potential synergistic effect of the combination reported.	Depending on information available on the single entities within the co-formulation e.g., marketed products are such co-formulated in vitro studies really necessary?		
Page 11, Lines 48-50	In vitro activity studies using tissues or cells from different species is also important in order to determine the most relevant animal model to use for toxicology work and in aiding the selection of appropriate animal model(s).	For a mAb against a foreign target it is unclear how this would be helpful.		
Page 12, Lines 3-4	Animal models might also be used, but only if they closely resemble human responses (e.g., in NHPs).	Strong justification should be provided for the selection of NHP as a preclinical species. Deselection of other lower species for toxicology studies should occur prior to choosing NHP.		

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Page 12, Lines 12-13	Pharmacodynamics should be studied where possible, but classic PD/PK assessment may be of limited relevance in animal models in most situations.	Suggest starting sentence with phrase "Classic PK/PD…" to add clarty.	Classic PD/PK assessment may be of limited relevance in animal models in most situations.	
Page 12, Lines 19-26	Whole paragraph	There is considerable reliance on animal models of infection to understand PD. However, if the pathogen is well studied and the removal/killing of the pathogen can be demonstrated in vitro, there seems to be little benefit in using more animals just to demonstrate what was already known. Could an in vitro only package be sufficient in these cases as well?	Suggest clarifying the text. Consider adding in possible scenarios in which an in vitro only package would be sufficient.	
Page 12, Lines 24-26	The development and use of animal models based on transgenic and humanized mice could be considered when an animal model is not available for a particular infection.	On first read, this appears to indicate that the Tg model will be a model expressing the infection, rather than expressing the human cells relevant to an infection response.	Suggest clarifying the text.	
Page 12, Lines 37-39	When two or more mAbs are co-formulated in the final product the PD of each mAb should be evaluated separately as well as in the intended combination.	Purpose of this statement is unclear. Is it to determine the fixed dose combination levels?	Suggest clarifying the text.	
Page 13, Lines 15-16	However, in accordance with ICH guidelines S6(R1) and S7A (31, 35), no standalone safety pharmacology studies might be necessary. .	The ICH S6 wording for safety pharmacology was written for mAb targeted against a human target. This guideline and type of mAb are targeted against infectious agents. There are different considerations for each. Unless there is some concern of the mAb by its engineered state, that targets a	The purpose of a safety pharmacology study is to investigate the effects of the candidate on vital functions. Although not usually required, safety pharmacology studies may be recommended by a Health Authority in some cases. For example, if data from nonclinical	

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		specific organ or potential excretion route concerns etc. The human TCR data would help understanding. Suggest recommending only to conduct these studies if there is a considered risk (as determined in a stepwise manner and incorporating data from TCR and /or a finding in a tox study).	and/or human clinical studies suggest a candidate may affect physiological functions other than the immune system (e.g., the central nervous system, or respiratory or cardiovascular system, renal function, or body temperature) then safety pharmacology studies should be incorporated into the safety assessment program.	
Page 13, Lines 17-18	Instead, functional indices of potential toxicity could be incorporated in the design of toxicity studies. Differences in tissue distribution between mAbs and low molecular weight mAb mimetics due to significant differences in their molecular weights should always be borne in mind and could be an important factor in this respect.	Inclusion of endpoints should be justified. What functional effects related to the central nervous system, respiratory or cardiovascular system do we expect to see for a mAb against these targets? Also, to note, including these endpoints in studies does not always work well, and has to be case-by-case. Suggestion to include similar wording to WHO 2013 vaccine guideline. Is there evidence that tissue distribution will impact on function of respiratory, CV or CNS system if target is against an infectious agent?	Instead, functional indices of potential toxicity determined by the potential for exaggerated pharmacology could be incorporated in the design of toxicity studies.	
Page 13, Line 25	cross-species comparisons	To improve clarity, suggestion for alternative text.	animal to human extrapolation	
Page 13, Lines 25-28	PK and TK studies are undertaken in order to understand exposure in safety studies, to allow cross-species comparisons and to predict margins of safety for clinical trials based on exposure. Additional guidance can	See Ovacik and Lin 2018 for understanding PK and mAb's – then consider the target. In general, preclinical PK studies answer two categorical questions: whether the lead candidate mAb exhibit optimal efficacy and safety	PK and TK evaluations may be considered in the pharmacology and/or toxicology studies.	

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	be found in Section of the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (29).	profiles to justify further development and whether the antibody has the desired PK behavior that will enable dosing regimen selection that is compatible with predefined target candidate profile. Fully integrated PK/PD evaluations in both efficacy and safety studies and/or stand-alone studies help address these two questions. For both purposes, PK studies in pharmacologically relevant species provide the best information and optimal support for safety and efficacy evaluations. Is there a relevant species? Is the guideline relating to recombinant DNA technology depending again on target relevant? Also again, consider the target: Doses may best be selected, and PK done in the pharmacology studies – then toxicology studies support with a simplified at worse 2 doses : human dose and x 10 human dose. This needs to tie up with the toxicology /safety strategy and the comments made in the guideline relating to PD.	There are limitations in the interpretation of the PK and TK in consideration of the limitations of PD and selection of relevant model for an mAb target against an infectious agent.	
Page 13, Lines 38-40	The assay method should, preferably, be the same for animal and human studies, one validated method usually being sufficient.	This sentence does not allow for cross-validation in human vs nonclinical species matrices (blood, serum, CSF etc.)	Suggest removing: ~~The assay method should, preferably, be the same for animal and human studies, one validated method usually being sufficient.~~	
Page 13, Line 50	Product-specific assays should: • ….Represent all modes of action of the product	Recommend including some examples for product specific assays to clarify		

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		representation of all modes of action of the product.		
Page 14, Lines 8-11	Due to their molecular weight, mAbs do not usually distribute well and, following intravenous application, are initially confined to the vascular system.	Biodistribution of mAbs is generally well understood. Consider adjusting text in line with ICH S6(R1).		
Page 14, Line 21	Elimination: Apart from absorption and disposition, information on clearance/elimination in relevant animal models should be available prior to clinical studies in order to predict margins of safety based on exposure and dose.	The word disposition should be replaced with distribution because disposition includes all aspects of ADME.	Elimination: Apart from absorption and ~~disposition~~ distribution, information on clearance/ elimination in relevant animal models should be available prior to clinical studies in order to predict margins of safety based on exposure and dose.	
Page 14, Lines 21-23	Apart from absorption and disposition, information on clearance/elimination in relevant animal models should be available prior to clinical studies in order to predict margins of safety based on exposure and dose.	This would only be required for ADCs for the small molecule. Is this in scope, if so this should be made clear.		
Page 14, Lines 43-44	Generally, a short-term study that investigates 2 or more doses with a minimum of 2- week dosing period should be considered.	In the absence of target in healthy animals extending the duration beyond 2 weeks would not provide additional useful information suggest limiting dosing to 2 weeks.		
Page 14, Lines 46-47	The study recovery period should reflect the exposure to mAb (e.g., 5 half-lives).	Not practical for half-life extended mAbs. Should be on case-by-case basis - e.g., if tox yes, if no tox no recovery; should consider nature of findings and understood recovery mechanisms (expert		

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		assessment) prior to have animals on studies for recovery (3Rs).		
Page 14, Lines 49-50	Toxicity testing should be carried out in healthy animals to allow for a clearer interpretation of toxicity and to represent prophylactic conditions.	Toxicity in healthy animals is of limited value unless there is off-target cross reactivity and/or if the target is expressed endogenously. Testing for prophylactic use may be best established in humans.		
Page 14, Lines 49-50	Toxicity testing should be carried out in healthy animals to allow for a clearer interpretation of toxicity and to represent prophylactic conditions.	This section does not appear to provide guidance on species selection. Suggest cross-referencing to cross refer to ICH S6 and its Addendum in the text.	Toxicity testing should be carried out in healthy animals to allow for clearer interpretation of toxicity and to represent prophylactic conditions (See ICH S6 and its Addendum).	
Page 15, Lines 4-5	When two or more mAbs are developed to be used in combination, the combined mAbs should be tested individually and in combination.	Suggest referring to toxicity guidance on combinations where different approaches for combination or co-administration of marketed products are provided. Using 'should' implies a requirement – this needs to be flexible and only required case-by-case if concerns – again 3Rs.		
Page 15, Lines 6-8	For mAb conjugates, nonclinical safety studies should be conducted on the unconjugated mAb, the toxic agent (antibiotic, radionuclide), as well as on the combined antibody-drug conjugate.	This calls for much greater testing required than under ICH. Recommend a case-by-case approach using prior knowledge for each component of a conjugate.		
Page 15, Lines 10-11	The development of anti-immunoglobulin antibodies greatly complicates the study and interpretation of the effects of repeated dose studies in animals.	Suggest ADA to be consistent with other guidances. Suggest referring to ICH S6(R1) as this paragraph is somewhat confusing.		

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Page 15, Lines 15-17	Repeated dose studies in rodents may therefore be of little predictive value as to what might happen in humans, although they might be useful in establishing safety margins.	This statement is unclear. Suggest better explaining how ADA affects TI if ADA in animals is not predictive of humans.		
Page 15, Lines 19-20	"….(e.g., evaluation of erythema/eschar and oedema according to dermal Draize score)	Draize scoring is rarely used in local tolerance evaluations, which are usually incorporated into the repeat dose toxicology study and recorded as clinical observations.	Suggest removing as this is too prescriptive.	
Page 15, Lines 20-22	If feasible, the potential adverse effects of the product can be evaluated in the toxicity studies, thus obviating the need for separate local tolerance studies.	This guidance should be putting evaluation of local tolerance on tox study by first intent - could suggest Draize alternative if non-terminal studies are planned.		
Page 15, Lines 26-33	Genotoxicity studies are generally not applicable to mAbs nor to related biologicals (29). Any product specific issues, such as a toxic molecule conjugated to a mAb, should be addressed on a case-by-case basis. Carcinogenicity is less of an issue when the mAb target is exogenous. Standard carcinogenic studies are therefore generally inappropriate for these products. However, careful consideration should be given to bi-specific mAbs which may include an endogenous host antigen.	Suggestion to edit first sentence and remove entire paragraph (Lines 26-33) relating to carcinogenicity.	Suggest: Genotoxicity and carcinogenicity studies are generally not applicable to mAbs ~~nor to related biologicals~~ (29). ~~Any product specific issues, such as a toxic molecule conjugated to a mAb, should be addressed on a case-by-case basis. Carcinogenicity is less of an issue when the mAb target is exogenous. Standard carcinogenic studies are therefore generally inappropriate for these products. However, careful consideration should be given to bi-specific mAbs which may include an endogenous host antigen.~~	

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Page 15, Lines 31-33	However, careful consideration should be given to bi-specific mAbs which may include an endogenous host antigen.	Please provide examples and refer to ICH S6(R1).		
Pages 15-16, Lines 35-50	Section 5.4.3 Developmental and Reproductive Toxicity Entire section	This section should be better aligned with ICH S6(R1) and S5(R3); as written, it implies more testing than is necessary under current regulatory guidances. There is no consideration of molecules where the target is not present in healthy animals. In line with 3Rs considerations, there is no scientific merit in conducting DART studies in these cases. For products that are directed at a foreign target such as bacteria and viruses, in general no reproductive toxicity studies would be expected (See Section 2.1). Consider adding additional text to indicate DART is not relevant if there is no human or nonclinical species cross-reactivity, as per ICH S6 (R1).		
Page 16, Lines 7-50	**"Other Toxicity Studies"** Assessment of antibody formation / immunogenicity should be conducted only to assist in the interpretation of study results and to improve the design of subsequent studies. Such analyses in animal studies are usually not relevant in terms of predicting potential immunogenicity of mAbs in humans. See Section C.7 of the WHO Guidelines on the	Since some points include aspects of pharmacology, suggestion to include this content in an entirely separate section.	Addition of new section (Section 5.5) titled "Other Considerations"	

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	quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (29).			
Page 16, Lines 9-14	***Assessment of antibody formation / immunogenicity*** should be conducted only to assist in the interpretation of study results and to improve the design of subsequent studies. Such analyses in animal studies are usually not relevant in terms of predicting potential immunogenicity of mAbs in humans. See Section C.7 of the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (29).	This appears to be a repeat of text from previous sections.		
Page 16, Lines 29-32	Additional information can be found in Part A of the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (29) as well as the ICH Q3 guideline on impurities in new drug products (37).	Suggestion caution in referencing Q3b as biologics/mAbs are out of scope for this quality guideline.		
Page 16, Lines 44-46	However, the results of guinea pig anaphylaxis tests, which are generally positive for protein products, are usually not predictive of reactions in humans and are usually not conducted.	This would be very odd to be conducted for a mAb. Title might be better as 'Infusion Reactions' which can be quite common. Otherwise, suggest including stronger wording as these studies have no value.	However, the results of guinea pig anaphylaxis tests, which are generally positive for protein products, are usually not predictive of reactions in humans and ~~are usually not conducted~~ should not be conducted.	

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Page 16, Lines 48-50	Immunotoxicity studies should be conducted to determine the possible adverse effects of mAbs on the immune system resulting in decreased host resistance to infectious agents (29).	Suggest that this is not mandatory and should only be included when relevant.	Immunotoxicity studies should be ~~conducted~~ considered to determine the possible adverse effects of mAbs ~~on the immune system resulting~~ if results in decreased host resistance to infectious agents (29).	
Page 16, Lines 48-50	Immunotoxicity studies should be conducted to determine the possible adverse effects of mAbs on the immune system resulting in decreased host resistance to infectious agents (29).	Again, as written this implies a requirement and not a need to assess on a case-by-case basis. This is target related and not toxicity related in a healthy animal.		
6. Clinical Evaluation				
Page 19, Lines 45-49	If animal studies are judged to be impossible or of no relevance and initial in vivo studies are to be performed in humans, testing should begin at a low dose that is based on extrapolation from in vitro tissue culture studies or else from available information gathered in clinical trials of a similar mAb.	This statement is not very clear - what should be the basis for FTIH dose justification - pharmacology or toxicology studies? As most anti-infective mAbs are non-toxic with NOAELs of 100's mg/kg, should discuss that PD studies can inform on starting dose.		
Page 20, Lines 28-30	Similarly, participants with prior parenteral exposure to any components or proteins contained within the clinical trial material, to the comparator product, or with a history of relevant allergies, should be excluded from product development clinical studies.	This statement is too restrictive. While there's a higher risk of immunogenicity in subjects who had prior exposures to similar products, it's not 100%. Unless there's allergic reactions which is a safety concern, not sure if the guidance needs to be so restrictive to require exclusion of subjects with prior exposures.	~~Similarly, participants with prior parenteral exposure to any components or proteins contained within the clinical trial material, to the comparator product, or with a history of relevant allergies, should be excluded from product development clinical studies.~~	

Page/Line Number	Original Text	Comment	Recommended Text Changes	Internal Use Only
Page 21, Line 18	A potential limitation of mAbs for the treatment of infections is the unknown bioavailability of the passively infused mAb into tissues affected by the disease. The mAb isotype, its subclass, and glycosylation pattern may have a large impact on its bioavailability at the site of infection.	The lack of info on drug exposure at the site of action applies to all drugs, not just mAbs for infectious diseases.	A potential limitation of drugs, including mAbs, for the treatment of infections is the unknown bioavailability of the passively infused mAb into tissues affected by the disease.	
Page 27, Lines 36-38	Including pregnant subjects should be based on safety data gathered from nonclinical studies, from clinical trials in adults, as well as an assessment of the potential benefits and risks for the mother, foetus and the newborn.	General tox or reprotox? See prior comment in Nonclinical section and ICH S6(R1): For products that are directed at a foreign target such as bacteria and viruses, in general no reproductive toxicity studies would be expected (See Section 2.1). Inclusion of embryofetal and pregnancy protein targets in array can provide additional information that may facilitate administration to pregnant subjects.		
References				
	Reference 17	Hyperlink does not work.		
	Reference 19	Hyperlink does not work.		
	Reference 29	Hyperlink does not work.		
	Reference 39	Hyperlink does not work.		
Appendix				