Guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010)

Comments from:

Name of organisation or individual
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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 Industry Organization (BIO) thanks the European Medicines Agency (EMA) for the opportunity to submit comments on the "Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies." BIO represents more than 1,100 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, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment. The Guideline in general is useful and contributes guidance to those planning to develop biosimilar versions of existing originator monoclonal antibodies. The Guideline attempts to cover a very wide and diverse group of products, including some novel types of monoclonals not yet envisaged as potential biosimilars. For this reason it has to allow for a range of circumstance and be potentially very flexible. However, this partly limits the Guideline's usefulness and may leave sponsors requiring further specific scientific advice in many circumstances. It may be more appropriate to revisit the concept of having sub-class specific sections/appendices or providing additional details rather than referring to a case-by-case approach in so many places. We request that the EMA be clear with regard to informing applicants whether or not this is an overarching Guideline, to be followed by more detailed guidelines for specific mAbs, similarly to what has been done for less complex biosimilars. If more specific guidelines are not envisioned, then this one may require additional detail and boundaries in order to effect efficient development. The Guideline offers a pathway for approval of a biosimilar monoclonal antibody. However, the benefits of this	

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	approach, where scientifically justified, will not be realised for sponsors unless they are universally/globally accepted. For example, if a sponsor meets the EMA expectation (described here) for a product that no *in vivo* data need be generated and extrapolation is possible to a number of indications, but this is not agreed with the United States Food and Drug Administration (FDA), then these additional studies will still be required. The acceptability of the risk based approach for non-clinical testing will also be critical for the review of proposed Clinical Trial Applications (CTAs) by national regulatory authorities. The omission of quality expectations and case-by-case inclusion of structural alterations for improved or different clinical performance leaves applicants unclear on the basis for abbreviation of study (same CDR, same epitope, or highly similar structure across all Critical Quality Attributes (CQAs)). The Guideline does not address the 'aggregate' minimal standard across non-clinical/clinical sections. Since flexibility is offered in a number of areas, the Guideline does not address whether a minimal approach in all areas would meet the agency's tolerance to allow abbreviated study. This may be ambiguous to companies without EMA expertise and minimum vs. expected standards should be clarified. It should be clear that the reference product for a biosimilar application must be CHMP approved. It is also not clear if the reference product for a biosimilar application must be CHMP approved. This should be clarified, as national approvals and approvals in other regions can be for mAbs manufactured under slightly different processes that could impact biosimilarity considerations. The Guideline would be more useful if it contained fewer generalities throughout the clinical section. It would also be helpful to know how this Guideline relates to previous guidelines or if this supersedes the earlier documents (*e.g.*, cross-reference with Immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use). Also, we find the Guideline as phrased could create the misimpression that not all non-clinical	

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	stages are necessary; it would be helpful to have clarification that a stage is considered unnecessary only if it is scientifically inappropriate.	
	General Recommendations: We suggest that the Guideline articulate core principles in order to define the boundaries of 'biosimilarity' for monoclonals. Language like "comparable safety with respect to pharmacologically mediated adverse events *could* also be considered as a measure of biosimilarity" (emphasis added) is unclear and leads an applicant to wonder if improved safety profile or increased purity without impact to efficacy would disqualify biosimilarity. Declarative statements on boundaries of 'biosimilarity' will assist all manufacturers in developing strategies and reducing waste. We also strongly suggest that the Guideline clarify that an abbreviated pathway is only available for monoclonal antibodies that meet the standards of similarity outlined in the EMA existing Guideline for quality aspects of biosimilars, including but not limited to the same primary structure. Also, even though the pathway is validated by the innovator, humans may have not been exposed to the specific biosimilar molecule and unique manufacturing process. An adequate (although abbreviated), non-clinical evaluation is needed before human testing. We ask that the guideline define an overall minimum data standard or acknowledge that the minimum across all aspects of nonclinical and clinical evaluation is not acceptable.	

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	The Guideline appears to introduce many refined concepts, and some entirely new concepts, of a general nature (we identify these concepts in the section "Specific Comments on Text", below). This may not be the optimal or most transparent mechanism to revise the basic emphasis or logic of existing nonclinical and clinical guidelines, especially when many of the issues concerned are neither specific to, nor even specifically relevant to mAbs. We recommend these discussions (absent those not within the appropriate scope for biosimilars) be addressed in upcoming revisions of the overarching guidelines. Where the Guideline is general in nature (*e.g.* concerning matters not specific to mAbs) it is proposed that the EMA should provide clarifying statements, either in the Guideline itself or in a separate document. Such statements should cross-reference the existing non-clinical and clinical guideline and clarify either that: 1) The new Guideline is intended to be consistent with the existing Guideline, with elaborations on certain points, or 2) Where something significant has changed, the Guideline should be very specific as to the justification for departure from the current guideline (either it is specific to mAbs or the EMA intends to revise the non-clinical and clinical Guideline for a given reason). Without these additions, it appears that there are two "general" Guidelines on nonclinical or clinical requirements, with no justification as to why a different set of principles should apply to mAbs.	
	Overall, the Guideline does not adequately communicate that a biosimilar will differ to varying extents from the innovator product in chemical and manufacturing-derived attributes and/or formulation which could influence tolerability, immunogenicity and other aspects of product behaviour not evident in "simple" PK and PD assessments. As a result of this omission, the Guideline could be interpreted to convey that because a manufacturer calls something biosimilar based on the most obvious characteristics, it will be so when examined in depth. Unfortunately, the Guideline also leaves open the possibility of a somewhat superficial non-clinical	

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	and clinical evaluation in some circumstances. Our comments below emphasize that stringency in the evaluation of a biosimilar product is appropriate given the exigencies of the production and formulation of a biologic product and the opportunities for differences from the innovator product when only the protein's structure is considered as a primary determinant of biosimilarity.	
	The Guideline could be interpreted as saying that *in vivo* non clinical testing should not be routinely applied to biosimilar products prior to dosing in man. We agree that large scale comparative studies are unlikely to be valuable. However, due to the lack of ability to fully characterize the physico-chemical properties of the biosimilar and incomplete understanding of the mechanisms of off-target toxicity of biological therapeutics, we recommend that all biosimilars undertake a limited repeat dose *in vivo* study in a pharmacologically relevant species prior to human dosing. The purpose of this study is to detect any significant unpredicted off target toxicity and does not need to be comparative in nature. This approach is consistent with recently published guidance on testing of other biosimilar classes. The anticancer target is identified as a special class of mAb that needs special considerations (section 5.1.4). However, the scenario could potentially apply to any indication/therapeutic area where drug effect and PK are inter-related, *i.e.*, PK is affected by PD. As such, the section dedicated for the anticancer treatments could apply to other biologics from non-oncology indications. Therefore, additional language to cover a wider array of indications, *e.g.* beyond oncology, will be beneficial. In the EMA biosimilar guidances that have been issued for other classes of proteins, no non-clinical PK studies are recommended. PK information in animals is of limited value; however, drug exposure (concentration) data should be collected from the toxicology study only for the purposes of assisting the interpretation of the toxicology data. We suggest that a similar approach be taken for this biosimilar guidance.	

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	Issues Missing from the Guideline We feel the Guideline is missing clarity on expected implications for summary of product characteristics (SmPCs) for monoclonal antibodies – clarity of the status of data extrapolated or not is especially important. The Guideline does not address the clinical picture in which the biosimilar will be approved: should a higher standard of physiochemical and biological similarity be imposed for therapies where the innovator demonstrates a complete cure vs. therapies with only mitigating effects? BIO appreciates this opportunity to comment on "Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies." BIO provided specific comments on sections of the draft guidance in Section 2. In the left column of the table, we identify the line number in the draft guidance; the middle column contains BIO's comments and rationale to support our position and carries our suggested changes, where applicable (single strikeout for deleted text and bold, underlined type for added text). We would be pleased to provide further input or clarification of our comments, as needed.	

2. Specific Comments on Text

Sections 1-3

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)*
64-66		**Comment:** Disease-specific guidelines should, in principle, be followed to assure similarity and provide an adequate test of comparative safety. In deviating from guidelines, the safety in relation to duration of treatment/clinical observation time cannot be adequately assessed unless it is clear that the duration of observation is adequate for nearly all critical safety findings, including immunogenicity, to be observed. We suggest that study designs include endpoints which allow for sufficient durations of treatment to permit evaluation of safety/immunogenicity and its relationship to efficacy. **Proposed Change**: "To establish biosimilarity, deviations from disease-specific guidelines issued by the CHMP (for example, choice of endpoint, timepoint of analysis of endpoint, nature or dose of concomitant therapy, etc.) may be warranted. The focus of the biosimilarity exercise is to demonstrate similar efficacy and safety compared to the reference product.~~, not patient benefit per se, which has already been shown for the reference product.~~ **However, the study designs should include endpoints which allow for sufficient durations of treatment to permit evaluation of safety/immunogenicity and its relationship to efficacy.**	
76-77		**Comment:** The Guideline states, "Comparable safety with respect to pharmacologically mediated adverse reactions could also be considered as a measure of biosimilarity." **Proposed Change:** If this sentence describes the intent of a study endpoint, then we ask that further clarity be provided on expectations.	

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80-82		**Comment:** The Guideline states, "As regards post-authorisation follow-up, the concept to be proposed by Applicants may have to exceed routine pharmacovigilance, and may have to involve more standardized environments." We suggest that until sufficient experience is achieved with the biosimilar, active methods of pharmacovigilance should be required to provide the best chance for observation of unexpected safety signals, including evidence of neutralizing antibodies, allowing for the possibility that unique attributes of the biosimilar and/or its formulation may predispose to the formation of antibodies in patients, including patients previously exposed to innovator product. **Proposed Change:** We suggest strengthening the requirement for active pharmacovigilance measures. Additional text could include, "**Active pharmacovigilance measures covered in the risk management plan could include labeling notifications to ensure traceability of adverse events to the manufacturer, tracking of adverse events that were not fully evaluated in the pre-licensing period, and, if necessary, active surveillance for the incidence and impact of anti-drug antibodies.**"	
93-96		**Comment:** The Guidance states "However, it may at the current stage of knowledge be difficult to conclude on the relevance of minor quality differences in the physicochemical and biological characterization." We suggest that the statement should provide a clear consequence of these limitations. **Proposed Change:** "However, it may at the current stage of knowledge be difficult to	

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		conclude on the relevance of minor quality differences in the physicochemical and biological characterization. **Until such time as this knowledge exists, clinical studies of comparable safety and efficacy are required.**"	
115-119		**Comment:** It is unclear why this mAb guideline should mention the topic of structurally-altered biologics. This is a general topic and was not addressed in existing CHMP guidelines. It is out of place to mention it in a non-clinical and clinical guideline specific to mAbs. Indeed, the premise appears incorrect that any concepts contained in this Guideline could apply to such a situation since there would be no premise that the products should have the same pharmacology or pharmacokinetics. Such structurally altered products should only be approved on the basis of full data sets showing safety and efficacy in each condition of use. **Proposed Change:** We suggest the mention of structurally-altered biologics (lines 115-119) be removed or that the text stop at line 117, concluding that such biologics are out of scope.	

4.0 NON-CLINICAL

125		**Comment:** The Guideline states, "A risk-based approach to evaluate mAb on a case-by-case basis is recommended." This section of the Guideline does not follow other EMA biosimilar guideline principles. Indeed some principles if valid may be relevant beyond biosiomilar monoclonal antibodies and we suggest consideration be given to these remarks in alternative guidelines in Europe.	
130		**Comment:** *In vitro* studies are typically appropriate to evaluate the pharmacology of a medicinal product, but it would be difficult to construe these as studies of pharmacodynamics. **Proposed Change:** We suggest changing the section title to "In vitro **pharmacology** studies = step 1"	
139-142		**Comment:** The Guideline states, "These concentration/activity studies should be comparative in nature and should be designed to exclude all differences of importance in the concentration – activity relationship between the similar biological medicinal product and the reference medicinal product and should not just assess the response per se." Acceptable levels of comparability could be clarified, including a suggestion that a high degree of similarity is expected.	
150-161		**Comment:** We suggest that this section be extended to clarify that *in vivo* mechanisms of action are not fully elucidated for some mAbs. This has been recognized in lines 146-147 ("It is acknowledged, however, that some mAbs may mediate effects in vivo in ways that are not yet fully elucidated.") and merits inclusion in the list of critical factors to evaluate. One risk factor that is notable for its absence is the potential for the mAb to induce a severe immunological response (*i.e.* acute reactions, separate from the formation of ADAs). If such was observed for the reference product, it would seem prudent to evaluate the comparative	

		toxicity of the biosimilar *in vivo* regardless of the presence or absence of the other risk factors. **Proposed Change:** We suggested the additional bullets: • **"Reference to an acute toxicity or off-target reactions.** • **If known toxicity exists for the reference product, then a comparative toxicity study should be conducted."**	
165-168		**Comment:** We suggest that the Guideline clarify and add that *in vivo*, non-clinical evaluation should be a default expectation unless the sponsor can justify the absence. We suggest the Guideline clarify that the intention to omit *in vivo* studies prior to human exposure requires scientific advice to confirm the acceptability of such an approach. **Proposed Change:** We suggest the alternative text in lines 165-168 to indicate a presumptive requirement for *in vivo* toxicology studies unless otherwise justified, and where "**If the outcome of steps 1 and 2 ~~raises concerns, the need for comparative in vivo studies should be decided case-by-case~~ suggests that in vivo studies may not be necessary, the decision to waive in vivo studies should nevertheless be decided on a case-by-case basis in consultation with regulatory authorities**."	
169-172		**Comment:** This section appears to emphasize that animal PK data would be considered the necessary component of any *in vivo* program, with the inclusion of safety and PD endpoints as optional elements. This emphasis on comparative PK is not fully described or justified as specifically relevant to MAbs. Existing guidelines emphasize a comparison of pharmacology (PD) and toxicity (safety) with PK included in the context of toxicokinetics. Comparative PK in animals is not emphasized as a requirement for non-clinical biosimilarity evaluations. We recommend placing the emphasis on toxicology and PD. **Proposed Change:** We suggest the alternative text, "the focus of the study (**safety, PD and/or PK**)…" Animal studies should be designed to maximize the information obtained **and PK or PD endpoints may be included in a safety study, such as to evaluate toxicokinetics, if considered appropriate and feasible.**"	

177		**Comment:** Due to likely differences in exposure across species (from animals to humans) at a particular dose, the use of "dose" as a reference to relate the "exposure" from animals to humans is less appropriate than using "concentration" or "exposure" as a reference. **Proposed Change:** We suggest that the phrase "dose-response" should be expanded to be "**dose-concentration-response**" and "covering therapeutic dose in humans" should be expanded to "**covering therapeutic dose and/or exposure in humans**."	
185-186		**Comment:** This message by itself could be interpreted differently, particularly when no relevant species exists or when there is no relevant PD marker. **Proposed Change:** We suggest the alternative text, "In the absence of appropriate cross-reactivity in a nonhuman species, the biosimilar candidate should be assessed by other means that will ensure the product can be safely administered to humans."	
192-194		**Comment:** These data may be necessary if the biosimilar product is at risk for the list of toxicity due to non-active substance, such as formulation components, product or process related impurities that are unknown. It should be acknowledged that such factors would not justify use of higher species such as non-human primates. **Proposed Change:** We suggest that the text should be more explicit about the potential risk factors that may drive requirements for additional toxicology studies.	

5.0 PHARMACOKINETICS

199-201		**Comment:** The guidance recognizes that the pharmacokinetics of mAbs are different than therapeutic proteins and small molecule drugs; it specifically states that parallel group designs are acceptable due to the longer half-lives of mAbs. However, as cross-over pharmacokinetic studies are internationally recognized as the preferred norm due to reducing subject PK variability ("each subject is his/her own control") more guidance should be given as to which situations truly warrant a parallel pharmacokinetic study. Care should be taken that this parallel approach is only taken after careful exploration of a cross-over PK design.	

5.0 CLINICAL

214-227		**Comment:** The text is lacking clarity on acceptable/expected PK endpoints (or PK parameters) to be monitored in single dose PK studies. Please address in similar fashion to section 5.1.3. **Proposed Change:** We suggest this clarity could be provided related to expected PK endpoints (*e.g.*, Cmax and AUC).	
214-227		**Comment:** There is no discussion of the potential risks associated with studying PK only in healthy volunteers (where similarity/differences can be most sensitively studied without confounders) prior to performing larger confirmatory studies in a disease population. **Proposed Change:** We suggest this section further clarify what expectations would be if healthy volunteer studies were undertaken, providing remarks on whether this would cause an increased risk in the disease population.	

225-227		**Comment:** For nonlinear drugs the statement "a comparison with the highest dosage regimen would be advisable" can be contradictory to the aim for the study design to be the most sensitive for differences because the highest dosage regimen may not be the regimen most sensitive to differences between reference and biosimilar products. It is more appropriate to have a qualifier such as "provided that the sensitivity to detect differences is similar across the range of dosage regimen." **Proposed Change:** We ask that EMA consider the alternative text that appears in line 291-292, "**Subject to reasonable justification, there is no need to test all therapeutic dosage regimens**."	
239		**Comment:** Determination of the listed other PK parameters (*i.e.,* CL and t1/2) is often not feasible for multi-dose studies because the chosen dosing interval may not allow adequate PK sampling. Additionally target-mediated drug disposition is commonly observed for mAbs. In those situations, it is not relevant to estimate CL and t1/2. **Proposed Change:** It is recommended that the sentence starting with "Other PK parameters like clearance and half-life…" should be deleted from the text..	
244		**Comment:** The phrase "long loading dose interval" is not a conventional term. **Proposed Change:** We ask EMA to please clarify what is meant by "long loading dose interval."	
234-242		**Comment:** We ask that EMA clarify the conditional requirements for multidose PK and indicate that class-by-class discussions could be available to sponsors.	
257-259		**Comment:** The sentence "A significant difference, yet fulfilling equivalence criteria…" should be clarified to explain what types of statistical evaluation could result in a conclusion of significant difference within the context of an equivalence evaluation. A separate test for significance is not typically performed within an equivalence evaluation, and could undermine the integrity of the pre-defined equivalence acceptance criteria. **Proposed change:** The wording is unclear and needs to be revised.	
260-279		**Comment:** The section on non-determinative PK studies (where variable response is	

		expected) is general in nature and should be in the general guideline.	
260-279		**Comment:** We suggest EMA include consideration of an exploratory PK study as part of an investigation of tolerability and initial trend for evidence of PK equivalence. Formal PK can be assessed as part of efficacy assessment in a larger study. **Proposed change:** We suggest line 260 be revised as follows: "Usually, proof of similar PK profiles should precede **confirmatory** clinical trials."	
280-281		**Comment:** While the title of 5.1.4 refers to "cytotoxic mAbs in anti-cancer indication," the essence of the described situation actually applies to all mAbs that have PD mediated drug disposition. **Proposed change:** We suggest EMA broaden the scope by either changing the title or including a statement in this section to state that the described cases for anticancer cytotoxic mAbs can apply to other indications where PK induces PD change, which in turn affects the PK disposition.	
283		**Comment:** It is not clear what "in case of response increase of half-life" means. **Proposed change:** We ask EMA to please clarify what is meant by "in case of response increase of half-life."	
302-303		**Comment:** The text suggests that *in vitro* testing could somehow compensate for the lack of PD endpoints that could be studied clinically. Further, it refers to *in vitro* pharmacology tests as non-clinical PD evaluations. *In vitro* pharmacology tests can certainly provide some insight into the comparative functionality of a biosimilar, but cannot be expected to reconstitute or predict *in vivo* pharmacodynamics. Thus, the emphasis of this text should be that the relevance of *in vitro* pharmacology studies to predict *in vivo* pharmacodynamics will be limited, and that comparative efficacy studies will be required in these situations. **Proposed change:** We suggest the alternative text, "**In these situations in vitro non-clinical pharmacology studies cannot be expected to predict the similarity of the pharmacodynamics in vivo, and comparative efficacy studies will be required.**"	

308		**Comment:** The Guidance states, "Thus, PD data from lower dose(s) may, in principle, provide already pivotal information for the biosimilarity exercise." It is suggested that the most relevant assessment relates to the steepest part of the dose-response curve (most sensitive part of the curve) instead of a "lower dose," which may not be sensitive. Further, we suggest clarifying the word "pivotal." Is it being recommended that PD based on a lower dose is adequate to support registration of a biosimilar? This might be relevant with regards to a prediction of similar efficacy profiles in some situations, but would not appear to be sufficient for a comparative evaluation of safety or immunogenicity under the most sensitive conditions. **Proposed change:** We suggest the alternative language, "**Thus, PD data from the steepest part of the dose-response curve may provide the most relevant information for the biosimilarity exercise**."	
320		**Comment:** We suggest that this section emphasise that superiority (so called "biobetters") is not an acceptable outcome upon which to conclude biosimilarity.	
321 - 324		**Comment:** We ask that further clarity be provided on the phrases "highly sensitive" and "clinical relevant." The Guideline should specify equivalence or non-inferiority, and indicate how much room there is to use surrogate PD markers of activity and for what duration. The equivalence trial design must be strongly favored. Should applicants believe that there are special circumstances that justify the use of an non-inferiority design, they should be required to provide robust justification to support this. Such circumstances will be rare.	
328-329		**Comment:** The Guidance states, "deviations from these guidelines (choice of endpoint, timepoint of analysis of endpoint, nature or dose of concomitant therapy, etc.) may be warranted." This text suggests flexibility on these points without providing the criteria for such flexibility. **Proposed change:** We ask that further clarity be provided on circumstances where deviation may be tolerated and what cumulative limits exist for such deviations.	
337-339		**Comment:** This section contradicts the EMA Guideline on Similar Biological Medicinal Products (CHMP/437/04), which notes that, "The chosen reference medicinal product, defined on the basis of its marketing authorisation in the Community, should be used throughout the comparability program for quality, safety and efficacy studies during the	

		development of a similar biological medicinal product in order to allow the generation of coherent data and conclusions." This reference also seems to conflict with the recognition that patients should be treated "as medically indicated." (Lines 347-348) **Proposed change:** We suggest ommiting reference to unlicensed conditions, "**Biosimilarity should be demonstrated in scientifically appropriately sensitive human models and study conditions ~~(whether licensed or not)~~...**"	
349-352		**Comment:** The Guidance states, "Clinical studies in special populations like the paediatric population or the elderly are normally not required since the overall objective of the development programme is to establish biosimilarity, and therefore the selection of the primary patient population is driven by the need for homogeneity and sensitivity." The text appears to contradict other biosimilars Guidelines, as well as the EMA's draft immunogenicity guideline (EMA/CHMP/BMWP/86289/2010), which recommend evaluation of safety and/or immunogenicity in the most sensitive populations. **Proposed Change:** We ask that this guidance be aligned with the EMA's draft immunogenicity guidance (lines 318-321) which recognizes that, "**Children may have higher protein metabolism and a different immune status than adults, and cases are known where data suggest a considerably higher immunogenicity of mAbs. In this patient group immunogenicity should be evaluated separately as for adults.**"	
353		**Comment:** "The inclusion of patients from non-European countries is generally possible." We suggest that it should be clarified if this sentence refers to the biosimilar clinical studies to be conducted or those from the reference product. If the reference product is not licensed by EMA, then how will the EMA leverage any safety or efficacy understanding of the reference product? Is the EC willing to have medicinal products distributed in the Community based on the extrapolation and/or adopt the confirmation without verification of safety and efficacy from a foreign agency? **Proposed Change:** We suggest that the EMA clarify the sentence with regards to the sourcing of the comparator product used in studies conducted in non-European countries.	
386		**Comment:** Extrapolation of safety described here in different disease settings requires	

		careful pharmacovigilance. We suggest that there is a stronger link between these sections. Further, we suggest that the section should more strongly state that a different safety profile would indicate lack of similarity and would require specific justification to support continued biosimilarity conclusion.	
394-398		**Comment:** We suggest this section specifically state that sample size estimates for the program should take the demonstration of safety profile and immunogenicity into account. Ultimately, active surveillance post marketing could be required for sufficient exposures treated for a sufficient duration to be achieved, but pre-marketing, a certain level of confidence in the safety/immunogenicity profiles must be established by study of sufficient patients to avoid a "Type II error."	
402-404		**Comment:** The Guidance states, "Usually, similar pharmacovigilance activities as those of the reference product would be required, rather than a direct comparison with the reference product, since data will most likely be difficult to interpret due to their rarity of occurrence." We suggest that if rare events have been identified for a monoclonal antibody, that active monitoring be recommended for that event to confirm similar incidence to the originator. We also suggest EMA require more active methods since they are necessary to ascertain with reasonable confidence that incidence rates for such rare events are not more frequent when product attributes, including formulation, are considered. (Passive identification may not be feasible if product are multisourced without unique identification.) **Proposed Change:** We suggest the additional language, "**To ensure that the risks of rare events could be accurately evaluated post-approval, the risk management plan should require active monitoring for those events, and should also include unique naming and labelling measures to ensure that there is clear tracking of the rare events to the manufacturer.**"	
410		**Comment:** The causes of immunogenicity are not fully understood. There are multiple risk factors including aggregation, oxidation, reduction, adjuvant effects, and improper folding which could impact the immunogenicity of a protein therapeutic. Because not all of the risk factors are fully understood, and the degree to which these multiple risk factors contribute to overall immunogenicity are also not well understood, it cannot be assumed that different manufacturers of a therapeutic protein will produce products with identical immunogenicity.	

		Antibodies against a therapeutic protein can reduce the level of circulating drug to a degree that can limit the drug's efficacy. It is important for physicians to understand the immunogenicity of similar mAbs so they can make an informed decision on which version is best for their patient. Only through properly powered clinical trials lasting at least 12 months can the immunogenicity of a mAb be determined. **Proposed Change:** We recommend that the EMA maintain the requirement for a pre-authorisation evaluation of immunogenicity including at least 12 months follow-up data, unless otherwise justified by the limited duration of therapy.	
413-415		**Comment:** The Guidance states, "It is recommended to exclude patients previously treated with the reference mAb where possible as this could hamper interpretation of the safety data and thus also decrease sensitivity for detecting differences." We suggest that EMA not allow exclusion of such patients as "repeat" exposures from an innovator to biosimilar, or vice versa, could be the rule in practice and, if order of treatment affects tolerability/antigenicity to any degree, it is better that this be known up front rather than using exposures in an uncontrolled setting for such assessments. **Proposed Change:** We suggest deleting this sentence or modify to suggest that immunogenicity studies should include both patients naïve to reference mAb as well as those switched from reference mAb to reflect actual conditions of use once the biosimilar is approved.	
421-423		**Comment:** The Guidance states, "As regards safety across different indications licensed for the reference mAb and claimed by the biosimilar mAb, a post-authorisation concept for obtaining further indication-specific safety data may be needed." This requirement needs to be strengthened as the sensitivities of the different populations to immunogenic effects and other adverse consequences of treatment could easily differ as a consequence of the biosimilar product's attributes. Recent severe clinical adverse reactions (dramatic increase in rates of pure red cell aplasia due to erythropoietin source and container/closure leachate changes) should provide adequate cautionary evidence for extrapolating immunogenic properties. Another example is infliximab, well known to have a widely variable immunogenicity rate, ranging from less than 5% to 35%. Moreover, differences in indications for the reference product's patient populations differ between indications in	

		disease progression, immunocompetence, dose, age, and/or concomitant therapies. All of these factors are known to affect immunogenological prosperities. Small changes in biochemistry of the mAb could influence and change the mAb's immunogenicity in ways that should be studied in each clinical indication, as studying only one patient population may not represent the immune reactions in a more immunocompetent population, etc. **Proposed Change:** We propose to revise "~~may be needed~~" to "**<u>should be obtained</u>**".	
428-430 and 435-436		**Comment:** The section on extrapolation of indications applies the correct principle to ensure that data is generated for each separate mechanism of action for a product, however, the section is not precise. We suggest that additional clarity be provided regarding the expectations especially where the mechanism of action is unclear. It should be unambiguous that if comparative clinical data are required to establish biosimilar efficacy via a given mechanism of action, then this should be true for all mechanisms of action. However, the text is vague on whether clinical data (PD or outcome) or non-clinical PD data would suffice. In particular, the text on 435-436 implies that quality and non-clinical data can suffice for extrapolation between two radically different MOAs (cytotoxic vs. immune modulator). This appears to contradict previous guidance which requires clinical evidence of biosimilarity using either a relevant PD marker or a clinical outcome measure for a given mechanism of action. **Proposed Change:** (428-430) We suggest the additional language**, "**If pivotal evidence for biosimilarity is based on PD and for the claimed indications different mechanisms of action are relevant (or uncertainty exists), then Applicants should provide relevant **<u>clinical</u>** data to cover pharmacodynamics for all claimed clinical indications." **Proposed Change:** (435-436) We suggest the alternative text, **"**The basis for such extrapolation **<u>should, at a minimum, include evidence that the same mechanisms of action are relevant to both the clinically evaluated indications and the proposed extrapolated indications</u>**. **<u>Further, because some mechanisms of action, e.g ADCC, could be more relevant in certain indications, the rationale for extrapolation should be supported by</u>** an extensive quality and non-clinical database, including potency assay(s) and in-vitro assays that cover the functionality of the molecule."	
436-437		**Comment:** Guidelines on mAb and immunogenicity should be consistent. The recent	

		immunogenicity guideline is stronger on this position and states, "Every therapeutic mAb needs to be evaluated for immunogenicity individually and all immunogenicity strategies should be adapted for each mAb development programme." The two guidelines should be aligned. **Proposed Change:** We suggest EMA add, "**Immunogenicity cannot be extrapolated to other indications where patient populations may exhibit differences in immune competency, co-morbidities, etc. For example, the immunogenicity observed when a biologic is administered to an immunosuppressed population (*e.g.*, when rituximab is given to cancer patients) cannot be extrapolated to the situation where the same biological product is administered to patients with rheumatoid arthritis. The patients in the latter category would be far more likely to mount a severe immune response to the biological product.**"	
425-432		**Comment:** The Guidance states, "If pivotal evidence for biosimilarity is based on PD and for the claimed indications different mechanisms of action are relevant (or uncertainty exists), then Applicants should provide relevant data to cover pharmacodynamics for all claimed clinical indications. Applicants should support such extrapolations with a comprehensive discussion of available literature on the involved antigen receptor(s), and mechanism(s) of action." "If a reference mAb is licensed both as an immunomodulatory and as an anticancer (cytotoxic) antibody, the scientific justification as regards extrapolation between the two (or more) indications is more challenging." If "uncertainty exists," as suggested by both of these excerpts, then extrapolation should not be allowed. We suggest that this could be clarified **Proposed Change:** We suggest the additional language, **"Comparative PD studies may be sufficient to extrapolate to the reference product's efficacy profile when the following are true:** **1. The mechanism of action of the biological product is shared in the intended**	

		condition(s) of use; **2. The proposed biosimilar has been shown to have equivalent PK and PD profiles to the reference product in the same route of admistration intended in all indiactions** 3. **Clinical studies in the most senstitive indication have been conducted and demonstrate equivalent safety and efficacy. If PD supports such a showing, PD markers must have a well-established relationship with the efficacy of the biologic and are validated and approved by regulatory authorities as an endpoint to support registration in the intended condition of use; and even when the relationship between dose-exposure and the surrogate marker is well known, is sufficiently characterized, and can be extrapolated to different populations, clinical safety and immunogenicity studies should not be waived."**	
447-465		**Comment:** Regulators have suggested that the known and unknown (but anticipated by mechanism of action) risks should be addressed in the PASS and RMP activities. **Proposed change:** We suggest this section be strengthened to take the regulators suggestions into account.	
458		**Comment:** We ask the following statement be further clarified**,** "Pharmacovigilance may have to exceed routine pharmacovigilance and may have to involve more standardised environments."	

463-465		**Comment:** Use of brand name and unique identification should be more than a recommendation. They are essential parts of effective pharmacovigilance and it is suggested this is further emphasised. It is important in the post-approval phase to distinguish easily between the biosimilar product and the reference product so that it is clear which product a patient has received. A record of the brand name, manufacturer name and lot number is essential to traceability and the conduct of effective pharmacovigilance. The draft guideline should be amended to take account of the recommendation in Dir 2010/84. *i.e.* that the product name and the batch number (lot number) should be recorded. **Proposed change:** We suggest the revised text:~~"Recommendations like recording the brand name of the drugs used by physicians, could be taken into account to reinforce traceability."~~ **"The product labelling should include a statement that the brand name of the medicinal product as well as the non-proprietary name, manufacturer's name, and lot number should be recorded when a medicine is administered or dispensed to a patient."**	