EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10.03.2011

Submission of comments on

"Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use" (EMA/CHMP/BMWP/86289/2010)

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 draft "Guideline on Immunogenicity Assessment of Monoclonal Antibodies Intended for In Vivo Clinical Use." 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. In Section 2 below, BIO provides specific	

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	comments on sections of the draft guidance. In the left column of the table, we identify the line number in the draft Guideline; 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

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	Outcome ***(To be completed by the Agency)***
Lines 90-96		**Comment:** As mentioned on line 94, emerging constructs and framework variations may challenge the statement in line 91 regarding the immune response being predominantly anti-idiotypic. The statement in line 91 may be taken out of context. Revised wording would also support the statement on line 115, "Furthermore, previous exposure to similar or related monoclonal antibodies can also influence immunogenicity." **Proposed change:** "In such cases, especially with humanised or human sequence mAbs the immune response ~~is predominantly~~ **<u>may be</u>** anti-idiotypic ~~(as the CDRs are unique in sequence for mAbs), which clearly can compromise clinical responses to the mAb." In some cases, antibodies can be induced against the constant region of human or humanised mAbs and this can affect the immunobiological function of the mAb. There is	

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		~~less experience with clinical use of emerging constructs and these may add to the perception of risk~~**, however, with the increased clinical use of emerging constructs, exclusive specificity to the CDR region cannot be assumed.** Special consideration should be given to next generation products, for example, bivalent mAbs."	
Lines 125-126		**Comment:** If section 5 is retained, the title should clearly explain when to consider these approaches. **Proposed change:** "Approaches which may be helpful in predicting and reducing the **development of unwanted anti-drug antibodies**." The following should also be noted in the body of the text for this section: "**Predictions and de-immunization procedures are performed early in drug development and not usually during clinical trials**."	
Line 146-147		**Comment: "**It is important during the clinical development to measure antibody levels, [...] over a period of repeated treatments." This statement	

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		suggests that Anti-Drug Antibody (ADA) would not be measured after single dose. A statement regarding the measurement of ADA after single dose should be added. A consideration should be made for mAbs with long circulating half-lives and exposures ranging from weeks to months. **Proposed change:** "It is important during the clinical development to measure antibody levels, PK, PD markers, efficacy and safety simultaneously and over a period of **single and** repeated treatments."	
Lines 153-154		**Comment:** Anti-Drug Antibodies (ADA) can interfere with the PK assay, producing false-negative results that suggest that the drug is eliminated from the system. The drug may be present, but may not be detected due to ADA interference. **Proposed change:** We suggest revising the following sentence, "Antibodies can reduce the exposure, PD effect and efficacy, and can result in	

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		neutralisation of the mAb," to include the consideration for an "apparent reduction of exposure to the mAb" due to assay interference by ADA.	
Lines 158-162		**Comment:** We suggest leading into the IgE section with a statement regarding clinical consequences of IgE. We also suggest revising the IgE section with a statement similar to Line 163 for IgA: "IgA antibody testing may only be needed on a case-by-case basis." **Proposed change:** "In some instances, mAb **product may induce IgE-mediated allergic reactions. Route of administration and host cell structural modifications of the mAb product are among the factors considered for potential induction of IgE. IgE antibody testing may only be needed on a case-by-case basis**."	
Lines 158-162		**Comment:** "In some instances, IgE testing needs to be considered for patients if the mAb contains non-human carbohydrate structures." The "non-	

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		human carbohydrate structures" seem to refer to a reported correlation of IgE from humans treated with cetuximab cross-reacting with beef or tick carbohydrate structures. The patients had pre-existing IgE, prior to treatment with cetuximab. Therefore, the testing would only be useful as a pre-treatment screen when one knew what to screen for. The issue is that "non-human carbohydrate structures" can also originate from CHO and NS0 cell lines, and we do not believe that IgE screening should be required for all products derived from non-human cell lines. **Proposed change:** We suggest deleting the following sentence: "~~In some instances, IgE testing needs to be considered for patients if the mAb contains non-human carbohydrate structures~~." The fact that host cell alterations may be a factor can be included in the sentence suggested in the above comment on Lines 158-162 ("Route of administration and host cell structural modifications of the mAb product are among the	

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		factors considered for potential induction of IgE.")	
Lines 169-181		**Comment:** The intent to recommend post-marketing surveillance of clinical signs suggestive of ADA-mediated reactions should be clarified. **Proposed change:** We suggest combining Lines 169-172 with Lines 179 -181: "In many cases, the incidence of immune response is too low to be fully identified during Phase III clinical studies **and antibodies against mAbs are rarely monitored in clinical practice. In these situations, it is** ~~T~~therefore **important to have an adequately organised** ~~systematic~~ post-authorisation monitoring **process** ~~may be necessary and should be adequately organised~~ to capture clinical signs that could be related to immunogenicity. ~~The involvement of antibodies in this should be established by conducting appropriate assays.~~ **If an anti-drug antibody-related issue is identified, appropriate assay to characterise the immune response should be performed**. [...]	

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		~~Because detection of antibodies against mAbs is rarely monitored in clinical practice, it is unclearother than in instances of obvious clinical evidence of one of the presentations listed above whether~~ the development of antibodies to mAbs has additional unrecognised consequences.	
Lines 175-178		**Comment:** The Industry current practice is to determine the extent of characterization of antibody induction based upon the risk assessment. Lines 175-178 seem to suggest that there would be no need to perform a risk assessment, and that any observation that suggests induction of immunogenicity, adverse events or loss of efficacy would require full characterization regardless of the perceived risk to patients. **Proposed change:** Please clarify the seriousness of the development of unwanted immunogenicity as it pertains to mAbs.	
Lines 182-184		**Comment:** The intentions of this statement are unclear.	

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		Proposed change: We suggest removing or expanding upon to clarify the point to be made.	
Lines 185-186		**Comment:** Title should be revised to be consistent with verbiage across the document. **Proposed change**: "~~Problems experienced with screening and confirmatory assays used in assessing immunogenicity of mAbs~~" "**Considerations for detection and confirmation of antibodies to mAbs**"	
Line 215		**Comment:** The discussion of the presence of mAb product in samples begins with the observation that mAb products "are usually administered in relatively high doses." The nature of the comparison (i.e., relative to what) is not apparent. Moreover, when a mAb is administered at low doses, the presence of the product in samples collected for antibody assessment can interfere with accurate assessments. **Proposed change**: "~~MAb products are usually~~	

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		~~administered in relatively high doses.~~ **MAbs** have […]".	
Lines 236-238		**Comment:** We suggest using the term "competitive inhibition" to improve the overall clarity of this section. **Proposed change:** The most common approach for this is ~~to include an incubation step with the mAb product in the assay to show that this results in a significantly diminished signal when assaying real antibody positive samples~~ **the addition of a competitive inhibition step in the screening assay. Significantly diminished signal resulting from an incubation step with the mAb product confirms that the assay is measuring drug-specific antibody**."	
Line 243-245		**Comment: "**Non-human primates produce primarily anti-CDR responses [...]". Our experience is that non-human primates produce both anti-CDR and anti-framework antibodies. However, whether the non-human primate	

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		response most closely mimics the potential human response is a topic that is frequently challenged. **Proposed change: "**Non-human primates produce ~~primarily~~ **both** anti-CDR ~~responses against human or humanized mAbs~~ **and anti-Ig framework antibodies**, ~~which~~ **and** may ~~most closely mimic~~ **be an appropriate control.** ~~human responses~~".	
Lines 248-249		**Comment:** The statement, "For confirmatory assays, spiking samples with an irrelevant mAb or (better) with a mAb with the same Fc but different CDRs as the product can be used to confirm specificity," would be more appropriately placed in the Section 7.2 "Confirmatory assays" and modified for clarity. **Proposed change:** We suggest moving to Section 7.2 and re-wording as follows: "For confirmatory assays, spiking samples with an irrelevant mAb, or ~~(better)~~ with a mAb with the same Fc but different CDRs as the product, can be used to ~~confirm~~	

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		additionally characterize the specificity **of the immunogenicity response**."	
Lines 253-254		**Comment:** "It is normally expected that the neutralizing capacity of any antibodies induced is measured." The term "measured" suggests that a neutralizing antibody assay must be performed. However, there may be situations where a neutralizing assay is not feasible, and an alternative method for assessing neutralization of the drug is considered. **Proposed change:** "It is normally expected that the neutralizing capacity of any antibodies induced is measured. **However, in the event of a demonstrated inability to develop a neutralizing antibody assay, consideration of alternative methods for assessment of neutralizing activity (e.g. pharmacodynamic marker measurement) should be discussed with regulatory authorities."**	
Lines 268-273		**Comment:** "[...] care must be taken not to	

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		assume [...] Fc [...] not involved [...] In such cases [...] thorough [...] characterization [...] appropriate neutralizing assay strategy." These statements do not connect properly. **Proposed change:** We suggest replacing lines 268-273 with: "**It is important to understand the biologic function of the molecule and to assess neutralizing antibodies appropriately.**"	
Line 275		**Comment:** "[...]every therapeutic mAb needs to be evaluated for immunogenicity." We agree, but note that diagnostic mAbs to be administered to patients should be similarly evaluated. **Proposed change:** "Every therapeutic **and in vivo diagnostic** mAb needs to be evaluated for immunogenicity […]."	
Line 277-283		**Comment:** It may be helpful here to define "Risk-based Approach." This term is sometimes misunderstood to simply mean the risk of developing an immune response.	

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		Proposed change: We suggest adding: **"<u>The risk-based approach is an assessment of the potential for the patient to develop a drug-specific immune response combined with the potential for consequences of an induced immune response</u>.**"	
Line 315-317		**Comment:** The recommendation in these sentences could be interpreted to mean that an applicant should determine the effect of dosing interval on unwanted immune response. Given the rare nature of many immune responses and the dependence of the immune response on various patient and disease state related factors, this interval would be impossible to predetermine. **Proposed change:** In general, short-term treatment is usually associated with a lower risk of inducing an unwanted immune response than long-term treatment. ~~For the latter, the optimal time period between repeated administrations should be determined.~~	
Lines 352-358		**Comment:** Although important, the examples	

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		provided in this paragraph cannot be predicted and cannot be taken into consideration during risk-based approach. This statement is more appropriate in the "Clinical Consequences" section. **Proposed change:** We suggest moving this paragraph to the "Clinical Consequences" section 6, Lines 158-162.	
Lines 360-361		**Comment:** This sentence suggests that a neutralizing antibody assay is required for all mAbs that are confirmed positive, without exceptions or alternative approaches for assessing neutralizing antibodies. **Proposed change: "**For all mAbs a validated screening and confirmatory assay should be performed, ~~followed by a validated neutralizing assay in case of positive results in the confirmatory assay~~ **and the neutralizing potential of confirmed drug-specific antibodies should also be evaluated with a neutralizing antibody assay or acceptable alternative**."	

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Lines 361-		**Comment:** Non-neutralizing antibodies can also affect efficacy and safety. An increase in clearance (caused by non-neutralizing antibodies) can have as profound an impact on efficacy as neutralization. In addition, it is currently unclear whether neutralizing and non-neutralizing antibodies pose different risks relating to infusion or injection site reactions, a common adverse event associated with mAb therapies. **Proposed change: "**Distinguishing between neutralizing and non-neutralizing antibodies is essential for all mAbs, regardless of their risk level, ~~as lack of, or even reduced efficacy due to the neutralizing activity of the antibodies may result in a discontinuation of treatment with the mAb.~~ **to identify potential mechanisms of impact on safety and efficacy."**	
Editorial comments:			
Lines 55-58		**Comment:** The statement, "This guideline addresses the major quality and clinical aspects	

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		that are important to consider in order to adequately address the problems with detection of and risk related to the development of an immune response to the particular mAb in the particular clinical indication sought," is a very good description of the proposed scope of the document. **Proposed change:** We suggest moving this sentence into the "Scope" (Line 60).	
Lines 78-79		**Comment:** The title of this section is misleading. It does not explain or describe variability of immunogenicity as much as it instructs on the considerations for the potential causes of development of unwanted anti-drug antibodies. **Proposed change:** We suggest the following title: "**Considerations for development of unwanted immune responses,**" or "**Factors affecting the monoclonal antibody immunogenicity.**"	
Line 145		**Comment:** The term "present" may not be the appropriate word here.	

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		Proposed change: We suggest "[...] not all induced antibodies are ~~present~~ **detectable** in the serum."	
Line 280-293		**Comment:** The term "risk factors" is used throughout this section. We suggest removing the work "risk" as risk factors are patient and or product factors that are evaluated to identify risk. **Proposed change:** We suggest replacing "risk" factors with "patient" or "product" (as appropriate) factors that influence induction of anti-drug antibodies. It may be helpful to add these as sub-headings within section 9.1.	
Line 284		**Comment:** The term "Risk" may not be appropriate word here. **Proposed change:** ~~Risk of~~ **Potential for** mounting an unwanted immune response.	
Lines 291-293		**Comment:** Lines 291-293 make a good introductory statement for a risk-based approach.	

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		Proposed change: We suggest moving Lines 291-293 up to section 9.0 as an introduction.	
Line 295		**Comment:** "[...] to study immunogenic potential and measures implemented to potentially handle the clinical consequences [...]" **Proposed change:** "[...] to study immunogenic potential and ~~measures~~ **procedures** implemented to potentially handle the clinical consequences [...]"	
Lines 305-308		**Comment:** Lines 305-308 are good introductory topics for a risk-based approach. **Proposed change:** We suggest moving Lines 305-308 up to section 9.0 as an introduction and then using "product factors" and "patient factors" as sub-headings within the text of section 9.1 to organize the topics to the reader.	
Lines 326 -327		**Comment:** This statement appears out of place here and is not a clear summary statement.	

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		Proposed change: We suggest moving Lines 326-327 into introduction section 9.0.	
Line 328		**Comment:** We suggest rewording the title to provide a range of impact from "not severe" to "severe." **Proposed change:** "The ~~severity~~ **impact** of clinical consequences of an immune response"	
Line 359		**Comment:** The content within section 9.3 is not necessarily the "consequences with regard to risk classes" as much as it is the considerations for characterizing an induced immune response based upon the risk level determined in the risk assessment. **Proposed change:** "~~Consequences with regard to different risk classes~~" "**Risk level-dependent characterization of immune response.**"	
Line 372		**Comment:** "The approach outlined above [...]". It is not clear what approach this statement refers to.	

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		Proposed change: We suggest clarifying the statement above.	