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February 1, 2010

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA- 2009-D-0573, Addendum to ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1)

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the draft guidance *Addendum to ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1).*

BIO represents more than 1,200 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.

BIO has provided specific comments on sections of the draft guidance in the chart below. In the left column of the table, we identify the paragraph in the draft guidance; the middle column contains BIO's comments and rationale to support our position; and the right column carries our suggested changes, where applicable (single strikeout for deleted text and underlined type for added text). We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Katie McCarthy
Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

BIO SPECIFIC COMMENTS

Page # Paragraph #	Comment and Rationale	Proposed change (if applicable)
2. SPECIES SELECTION		
Major Objections		
Page 6, Section 2.2, Paragraph 1	"*Based on recent scientific data, the text in ICH S6…….should not be used for selection of relevant species for safety evaluation*."	If the wording stays as is, we suggest including references for the "recent scientific data."
Page 6, Section 2.2	The current language appears to eliminate any role for TCR in the battery of studies used to support species selection for monoclonal antibodies and related proteins. Although TCR should not generally be used as the sole rationale for species selection, it should be included because it has been important for interpretation of results from some nonclinical studies.	We recommend replacing the current text with the following language, "Tissue cross-reactivity (TCR) studies are ex vivo assays conducted for antibodies and related antibody-like products that contain a CDR (collectively referred to as mAbs), to characterize binding to antigenic determinants. TCR studies currently use immunohistochemical (IHC) techniques, although other technologies may be employed to determine binding sites/receptor distribution (e.g., TCR reference: Hall et al, 2008 and BioSafe (BIO's Preclinical Safety Committee) White Paper, draft manuscript). When technically feasible, TCR studies can identify potential target, off-target or unexpected interactions in human and animal tissues. A TCR study with a panel of human tissues is currently considered a standard component of the preclinical safety assessment package supporting initial clinical dosing for mAbs. Findings of interest should be further evaluated and interpreted in the context of the overall pharmacology and safety assessment data package. While selection of relevant species for toxicity studies is

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		primarily based on comparison of pharmacology (*i.e.*, binding and activity data) (Section 2.1), TCR studies may provide supplemental and some cases fundamental information (especially in cases where pharmacology cannot be demonstrated in normal animals) for the selection of toxicology species. TCR studies are not recommended for assessing comparability of the test article as a result of manufacturing changes over the course of a development program, or for determining tissue binding of surrogate mAbs. Evaluating each binding site of a bi-specific antibody is not generally recommended. Overall, the requirement for TCR studies and their design and implementation should follow a case-by-case approach recognizing that there is no single way to approach the TCR assay. As with any assay, the relevance and value of the TCR study should continue to be assessed as experience in animals and humans accumulate."
Page 7, Section 2.4, Title:	Knock outs (KO) are transgenic models; therefore listing KOs separately is inaccurate. Further, the title does not provide a complete listing of alternative models that might be considered, only those that are perhaps most common today; for example, a knock-in transgenic may provide a useful tool.	We suggest replace the current title with, "Alternative Approaches and Models."
Points for Clarification		
Page 7, Paragraph 2	It is unclear if "*exposure-based*" is meant by the strict	We recommend the additional text for clarification,

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	pharmacokinetic interpretation of "*AUC*", or if it is meant to cover all components of drug administration, including dose levels. If no other animal model exists for safety evaluation, how would first-in-human doses be determined? If the intent of this statement is that the differences between homologous proteins and the clinical candidate must be understood, then we recommend additional clarification.	"Homologous proteins can be used for hazard detection and understanding the progression of dose/exposure based pharmacology and the potential for adverse effects. Translation of these effects to human safety should consider differences in binding affinity, potency, functional activity and PK/PD relationships."
Editorial comments		
Page 6, Section 2.1, Paragraph 3	It would be helpful to be more precise when referencing ICH S6.	We suggest the additional language, "(see ICH S6, Section 4.4)."
Page 6, Section 2.1, Paragraph 4	A reference to later section (2.4) should be included in this text that speaks to alternative approaches.	We suggest the additional language, "(see Section 2.4)."
Page 7, Section 2.4, Paragraph 1	It would be helpful to be more precise when referencing ICH S6.	We suggest the additional language, "ICH S6 section 3.3, paragraphs 3 and 4 can be…"
3 STUDY DESIGN		
Points for Clarification		
Page 7, Section 3.1, Paragraph 2	Examples should be included of instances which would justify the use of a high dose that is lower than that eliciting maximum PD or a 10x exposure multiple.	We suggest the additional language, "The highest of these two doses should be chosen as the high dose group in pre-clinical toxicity studies unless scientific data supports a lower dose (e.g., maximum feasible dose or a dose beyond tolerable PD, or if the

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		patient population is at high risk (e.g. in oncology))."
Page 7, Section 3.1, Paragraph 3	Examples should be given of instances when "*PD endpoints are not available*". Utilize the phrase "10-fold multiple" rather than "*up to 10-fold*," which can be interpreted as anything less than 10.	We suggest the additional language, "When PD endpoints are not available (e.g., the target is not constitutively expressed, or assay development is not feasible), then a 10-fold multiple …"
Page 8, Section 3.1, Paragraph 3	In some cases, differences in absolute binding are meaningless because assay variability cannot adequately resolve the mean numerical differences, and in addition, dose/exposure response in pharmacology models indicates that the biologic response isn't different over a range of doses/exposures. Thus, binding differences don't translate to biologic differences.	We suggest adding a statement that considers these data, "For example, a large relative difference in binding affinity and/or in vitro potency … Assay variability and available dose-response data in pharmacology models should be taken into consideration."
4 IMMUNOGENICITY		
Points for Clarification		
Page 9, Section 4, Paragraph 2	This sentence does not clearly differentiate characterization of neutralizing potential through functional assays (*e.g.*, cell-based) from characterization of neutralizing potential through assessment of PK, PD, and adverse events.	We suggest the revised language, "Characterization, specifically of functional neutralizing potential, is generally not warranted, particularly if adequate exposure…" Or "~~Characterization, specifically of neutralizing potential~~ Functional characterization of ADA neutralizing potential is generally not warranted, particularly if adequate exposure…"
Editorial comments		
Page 8, Section 4,	"*…, and/or no evidence of immune mediated reactions…"* The	We suggest the revised language, "… and~~/or~~ no evidence of

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Paragraph 2	"*and/or*" is an inappropriate option for decision making within this sentence. Measurement of ADA in nonclinical studies is not routinely warranted if there is evidence of sustained PD, expected PK, and no evidence of immune-mediated reactions.	immune-mediated reactions…."
Page 9, Section 4, Paragraph 2	There is a possible typo in the sentence: "*When study results suggest there is a need to understand immunogenicity to interpret study data, potential for immunogenicity antibody detection assays should be conducted to evaluate the presence of ADAs."*	We suggest deleting, "potential for immunogenicity."
5 REPRODUCTION AND DEVELOPMENTAL TOXICITY		
Major Objections		
Page 10, Section 5.3	The guidance document should include the following points: 1. If the clinical candidate is active in rats/rabbits then these species can be used for reprotox, as for LMW products. The use of just one of the above species should be acceptable for EFD evaluation and a scientific justification is needed for species selection. 2. If the clinical candidate is NOT active in rats/rabbits but only in NHPs then the regulatory preference is to test the clinical candidate accepting the limitations of NHP studies. However it is up to the sponsor to provide a justification for the use of	

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	alternative approaches including the use of surrogate molecules in rodent studies - so the flexibility exists for the sponsor to take this approach recognizing the general preference for testing the clinical candidate. 3. If the sponsor chooses to use NHPs as the only relevant species, then an ePPND study is acceptable. However alternative approaches such as separate EFD and PPND studies are also acceptable. Therefore again, there is flexibility in the study design of NHP studies. 4. To address aspects of fertility the sponsor may wish to develop a surrogate molecule and conduct rodent fertility studies and this is acceptable. However, the sponsor may also wish to address aspects of fertility in chronic toxicity studies in sexually mature animals and this is also acceptable. 5. Regulators also accept that if sponsors wish to assess aspects of fertility in sexually mature NHPs then there would not be a default requirement to produce a surrogate molecule just to fill the gap of mating studies which are very problematic in NHPs. However, an unacceptable position for clinical candidates active only in NHPs would be a requirement for a surrogate molecule produced only to conduct rodent fertility studies.	
Page 11, Section 5.3, Paragraph 4	Paragraph 4 regarding numbers of monkeys required for power to detect a 3-fold increase in pregnancy loss should be deleted. Caution should be exercised in stating specific details of study design to avoid conflict with ICH S5. We recommend	We suggest the revised language, "~~Because the~~ Developmental toxicity ~~study~~ studies ~~in NHP as outlined above is a~~ can only provide hazard identification ~~study, it might be possible to conduct these studies using a control group and one dose group,~~

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	defaulting to ICHS5 for rodent studies.	~~provided there is scientific justification for the dose level selected~~. Thus, the numbers of animals per group should not be based on statistical power from historical teratology data. Sufficient data are available for the number animals required to successfully evaluate pregnancy and live births in NHP (Stewart reference).
Page 11, Section 5.4, First Paragraph	*"Where there is embryo-fetal exposure during organogenesis and the product is pharmacologically active only in NHPs…"* This sentence should be revised to account for those biologics that have placental transfer and a cause for concern based on the target.	We suggest the additional text for inclusion, "For monoclonal antibodies for which embryo-fetal exposure during organogenesis is understood to be low in humans based on current scientific knowledge, the embryo-fetal development toxicity study can be conducted during Phase III (see ICH M3 (R2)). For other biological products where embryo-fetal exposure is demonstrated to be low during organogenesis, the same timing for testing can be applicable. For biological products active only in NHP and whose targets are known to or expected to cause malformations, no studies are needed and the appropriate precautions should be taken for clinical enrolment and labeling. For biological products with exposure during pregnancy but of uncertain pharmacology or uncertain effects on embryogenesis, embryo-fetal studies should be conducted to support enrolling women of child bearing potential (WCBP) in clinical trials. If the NHP enhanced pre- and postnatal developmental (ePPND) toxicity study design is utilized, an interim report (see note 2) that includes data to day 7 post-partum can be used in place of a more traditional embryo-fetal study, and should be submitted to

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		support WCBP in clinical trials consistent with ICH M3(R2). Oncology biologic products should follow ICHS9." ~~Where there is embryo-fetal exposure during organogenesis and the product is pharmacologically active only in NHPs and a sponsor elects to use the cPPND study design, an interim report (see note 2) for data to day 7 post-partum for all animals is called for to support Phase III.~~
Page 11, Section 5.3, Final Paragraph	We recommend deleting paragraph 4. This paragraph is unnecessary. In certain circumstances the principles outlined above can also be less appropriate than separate ICH S5a C and D to E studies.	
Points For Clarification		
	When the NHP is the only species in which the clinical candidate is pharmacologically active, BIO fully supports the ICH general preference for using the monkey while leaving open the option of using alternate approaches such as a homologous molecule in an alternate species. BIO also fully supports using the weight of evidence to avoid unnecessary nonclinical reproductive toxicity testing when the weight of evidence demonstrates clear reproductive hazard.	
	BIO agrees with ICH that mating studies in NHP are generally not warranted due to limits of this animal model and that standard histopathology with menstrual cycling monitoring is	

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	generally sufficient to assess fertility or reproductive organ function; <u>further data should be evaluated from chronic repeat does studies for variability in menstrual cycling to confirm the usefulness and practicality of this endpoint.</u> BIO also agrees with ICH that additional reproductive endpoints such as semen evaluation and hormone levels can be evaluated for cause, if appropriate and thought to provide additional useful information.	
Page 10, Section 5.1, Final Paragraph	On occasion, NHPs are a relevant species for DART studies; however affinity for the NHP target is less than that for the human target. If a mouse transgenic for the human target exists, this should still be an option even in the face of a "relevant" NHP model.	We recommend the revise language, "~~When no relevant animal species exists for the clinical candidate, the use of transgenic mice expressing the human target or homologous protein in a species expressing the human ortholog should be considered~~. <u>The use of genetically modified mice might be used for hazard identification in DART studies and their use is covered in ICHS6 (ref section).</u>"
Editorial Comments		
Page 9, Section 5.1, First Paragraph	The word "with" is unnecessary.	We suggest the revised language, "…principles outlined in ~~with~~ ICH S5(R2)…"
Page 10, Section 5.2, Third Paragraph	"Should" is a strong statement suggesting a requirement. The selection of endpoints should be based on the specific concern. Hormones evaluations are resource intensive and may not provide useful information in all cases where additional endpoints are warranted. In addition, these endpoints may be too	We suggest the revised language, "…hormone levels ~~should~~ <u>could</u> be evaluated in the repeat dose toxicity study <u>or a stand-alone fertility study.</u>"

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	difficult to add a repeat dose toxicity study and could be evaluated in a stand-alone fertility study.	
Page 10, Section 5.2, Paragraph 3, Sentences 2 and 3	Sentences 2 and 3 should be combined for simplicity.	We suggest the revised language, "If there is a specific concern from the pharmacological activity about potential effects on conception/implantation and the NHP is the only relevant species, the concern should be addressed ~~experimentally. A~~ using a homologous product or transgenic model ~~could be the only practical means to assess potential effects on conception or implantation when those are of specific concern~~. However, it would not…."
Page 10, Section 5.3, Paragraph 3		We suggest the additional language, "Ultrasound is useful to track maintenance of pregnancy but not for routine monitoring of embryo-fetal development or detecting malformations."
6 Carcinogenicity		
Major Objections: None. BIO strongly supports the balanced approach to carcinogenicity assessments provided in this addendum. This draft guidance further clarifies the importance of a product-specific assessment that incorporates hypothesis-driven experimentation on an as needed basis.		
Points for Clarification		
Page 11, Section 6, paragraph 1	In this and other introductory sections, it might be useful to provide cross-reference to the appropriate section of ICH S6. In addition, we believe stating the overall goal (providing data to communicate risk), currently contained in paragraph 3, would	We suggest the revised language, "As indicated in ICH S6, Section 4.8, a product-specific assessment of carcinogenic potential ~~for~~ may be required for a biopharmaceutical ~~should be determined with regard to the intended clinical population and~~

Page # Paragraph #	Comment and Rationale	Proposed change (if applicable)
	be more impactful if moved to this introductory paragraph.	~~treatment duration (see ICH S1a)~~. The need for such an assessment should be determined with regard to the intended clinical population and treatment duration (see ICH S1a). When an assessment is warranted, the sponsor should design a strategy to address ~~the issue~~ carcinogenic risk. This strategy should focus on providing an assessment that will be used to communicate risk and allow the appropriate design of risk management elements such as labelling proposals, clinical monitoring, post-marketing surveillance.
Page 12, Section 6, Paragraph 2	In this paragraph, which discusses the initial review of data to determine potential carcinogenic concerns, it is important to consider the mode of action of the biopharmaceutical in gauging the degree of theoretical risk. This concept is referred to briefly in paragraph 5.	We suggest the revised language for paragraph 2, "This strategy should be based on a weight of evidence and should include a review of data relevant to the carcinogenic potential of the molecule and could come from a variety of sources. The data sources can include published data (*e.g.*, information from transgenic, knock-out or animal disease models, human genetic diseases), information on class effects, detailed information on target biology, in vitro data, data from chronic toxicity studies and clinical data. The mode of action should be carefully considered in the context of carcinogenicity concerns. Some biopharmaceuticals might raise concern regarding potential for promoting the growth of existing tumors, whereas other modes of action might raise concern regarding changes in tumor surveillance mechanisms. Certain mechanisms of action may not raise substantial concern related to carcinogenic potential (*e.g.*, anakinra, enfuvirtide)."

Page # Paragraph #	Comment and Rationale	Proposed change (if applicable)
Page 12, Section 6, paragraph 4	We support the concept expressed in this paragraph that when existing data have clearly identified a potential hazard, additional experimentation is not warranted and the issue is best approached from a labelling and risk management perspective. Determining what constitutes sufficient data to inform clinical risk will remain a judgement-based, case-specific issue and therefore we agree with not providing specific guidance in this area. We note that as currently written the paragraph could imply that all immunomodulators and growth factors have clear, well-defined risk of tumor induction. While this may be true for some modes of action (*e.g.*, potent T-cell suppression), this may not be true for other modes of action (e.g. B-cell modulation). Finally, we believe it is appropriate in this paragraph to introduce the concept described in a later paragraph indicating that if animal data to date clearly demonstrate risk, that further animal work is not warranted. As such we suggest the edits in the column to the right.	We suggest the revised language, "In some cases, the available information can be considered sufficient to address carcinogenic potential and inform clinical risk without warranting additional nonclinical studies. For example, some types of immunomodulators~~,~~ and growth factors, or hormones may be known to pose a potential carcinogenic risk ~~which can best be evaluated by post-marketing clinical surveillance rather than further nonclinical studies~~. In addition, data from existing animal studies may have already demonstrated a potential clinical risk. In these cases, the risk can best be evaluated by post-marketing clinical surveillance rather than further nonclinical studies."
Page 12, Section 6, paragraph 5	This paragraph contains several different concepts which seem to be better addressed in other sections. We suggest deleting the paragraph so that the flow of the section is from those cases where the initial data review appears sufficient to define risk to those cases where the data is insufficient and the sponsor.	
Page 12, Section 6,	The intent of this paragraph should focus on factors to consider if the data review described above is not sufficient to inform	We suggest the additional language, "In other cases, there is insufficient knowledge about specific product characteristics and

Page # Paragraph #	Comment and Rationale	Proposed change (if applicable)
Paragraph 6	risk. In this paragraph two important concepts should be emphasized: 1) additional experimentation should be focused on the specific concern raised by the data review and 2) a variety of approaches, some of which are referred to in the current ICH S6 section, may be appropriate. Given the diverse range of modes of actions, we agree that it is not appropriate to provide a listing of potential approaches in this guidance. As with any other safety assessment issue, the sponsor should propose hypothesis-based experimentation to address the issue.	mode of action in relation to carcinogenic potential to inform clinical risk. In these cases, a more extensive assessment which may include additional experimentation might be appropriate. The sponsor should consider if additional in vitro or in vivo studies will further inform risk. ICH S6, Section 4.6 lists a few of the potential approaches; however, this list is not exhaustive and the sponsor should consider those experimental options most appropriate to the specific concerns raised by the mode of action. In some cases, it may be determined that additional studies will not be useful in informing risk. Rodent bioassays or ~~short-term~~ carcinogenicity studies with homologous products are generally of limited value to assess the carcinogenic potential of the clinical candidate. Following the completion of the product-specific assessment, the weight of evidence should be considered to determine the level of concern for carcinogenic potential. . If the weight of evidence suggests a concern about carcinogenic potential, then product labelling and risk management practices should reflect the specific concern."

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