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April 20, 2009

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

Re: Docket No. FDA-2009-D-0006 S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

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Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Draft Guidance for Industry on S9 Nonclinical Evaluation for Anticancer Pharmaceuticals.

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.

GENERAL COMMENTS

In some cases throughout the draft guidance, sections are quite declarative and in some cases very general. In the case of the latter, we recommend providing examples of instances where the general proposal for oncology drugs does not apply (i.e. to clarify statements such as "generally not warranted" or "might not be warranted", "might be exceeded"). This comment applies specifically to Sections B5, Reproduction Toxicology, B8 Immunotoxicology, D3 Evaluation of Drug Metabolites, and D5 Evaluation of Impurities.

At places within the draft guidance the terms "anticancer pharmaceuticals", "biopharmaceuticals," and "chemotherapeutics" are used. It would be helpful to confirm that the term "anticancer pharmaceuticals" refers to all modalities unless otherwise specified.

Please see the attached chart with BIO's specific comments.

We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Katie McCarthy
Director, Science and Regulatory Affairs

cc: James Green, PhD (Biogen Idec), Biotechnology Industry representative to ICH S9 Expert Working Group.

Section, Paragraph, and Line	Key Concerns with Explanation of Position	Proposed change
Section A. 3-Scope **Line 69**	We recommend providing a more detailed description of what is intended by "late stage or advanced cancer".	
Section A. 3-Scope **Line 74**	Please clarify what is considered 'long life expectancy".	
Section B. 1-Pharmacology **Line 107**	Please clarify that although the information from the Pharmacology studies is used to design nonclinical and clinical programs, these supportive studies do not need to be conducted in accordance to Good Laboratory Practices.	We recommend the addition of this text for clarification, "While necessary to appropriately design the nonclinical safety assessment of a candidate therapeutic, these descriptive and investigational pharmacology studies are not expected to be conducted under the auspices of GLPs."
Section B. 2 – Safety Pharmacology **Lines 118-120**	Please clarify whether specifically hERG and purkinje evaluations are included in the recommended study list "in case of concern".	
Section B. 2 – Safety Pharmacology **Lines 114-120**	The current wording suggests that an assessment of vital organ function, including cardiovascular, respiratory and central nervous systems, should be available before initiation of clinical studies; such parameters could be included in general toxicology studies. However, the available technology does not allow accurate measurement of hemodynamic or respiratory parameters in toxicology studies. ECGs are the only parameter that can be accurately measured as part of a toxicology study.	We recommend the insertion of the following language, "An assessment of vital organ function, including cardiovascular, respiratory and central nervous systems, should be available before initiation of clinical studies; such parameters could be included in secondary pharmacology or general toxicology studies. Stand-alone safety

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		pharmacology studies need not be conducted to support studies in patients with late stage cancer or advanced disease. In case of concern, appropriate safety pharmacology studies, core battery described in ICH S7A and /or follow up or supplemental studies should be considered."
Section B. 4 – General Toxicology **Lines 132-143**	To the extent that these studies may simultaneously inform other safety endpoints, please consider some design recommendations such when to include sexually mature animals (especially non-rodent), and appropriate inclusion of safety pharmacology and/or immunotoxicology endpoints.	Specific changes are suggested in our comments on sections B. 5 and B. 8 below.
Section B. 4 – General Toxicology **Lines 138-140**	The current wording states that "Evaluation of reversibility and delayed toxicity should be addressed". The current practice for small molecules regarding recovery groups is to only assess reversibility of target tissues identified at the end of the treatment period. Does the comment to evaluate delayed toxicity suggest that all tissues need to be evaluated at the end of the recovery period for a biologic? Please clarify if the Agency seeks evaluation of reversibility for small molecules and delayed toxicity for biologics.	
Section B. 4 – General Toxicology **Lines 140-143**	*"To support Phase I clinical trials* ***at least one nonclinical study*** *should incorporate a recovery period at the end of the study to assess for reversibility of toxicity findings or the potential that toxicity continues to progress after cessation of drug treatment."*	We recommend requiring recovery data pre FIH only in the case of toxicities which are predicted to be non-premonitory and have the potential to be life threatening in humans at therapeutic doses, and where there is no

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	Reversibility/Recovery/Delayed toxicity data should not be necessary for the first in human (FIH) filing. Waiting for this type of data for molecules with a long half life in particular (e.g. monoclonal antibodies) would greatly delay the start of clinical trials of new pharmaceuticals. Please clarify that this data can be sent to regulatory agencies when available, post FIH start.	NOAEL.
Section B. 5 – Reproduction toxicology Lines 148-155	The guidance specifically highlights late stage/advanced cancer. Please provide guidance on the timing of reproduction toxicology studies supporting treatment of advanced cancers in patients young and old. Also, please discuss categories of therapy other than those that target rapidly dividing cells where other mechanisms of action and/or class effects clearly indicate a likely reproductive toxicity. Also, for exclusion based on a class of molecule 'that has been well characterized…' please clarify what criteria and/or body of evidence might be considered sufficient to mitigate the need for reproductive toxicity studies (and/or examples, if possible).	We recommend the following language, "An embryofetal toxicology assessment is warranted to communicate potential risk for the developing embryo or fetus to patients who are or might become pregnant. Embryofetal toxicity studies of anticancer pharmaceuticals should be available when the marketing application is submitted. ~~, but~~ These studies are generally not considered essential to support clinical trials intended for the treatment of patients with late stage or advanced cancer or for pharmaceuticals which target rapidly dividing cells (e.g. crypt cells, bone marrow) in general toxicity studies or belong to a class which has been well characterized in causing developmental toxicity (e.g. corticosteroids). ~~These studies are also not considered essential for pharmaceuticals which target rapidly dividing cells in general toxicity studies or belong to a class which has been well characterized in causing developmental toxicity.~~ Evidence to

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		support a "class effect" maybe constituted by but is not limited to published literature, lethality in knockouts or other experimental evidence, and description of a plausible mechanism. For guidance on the timing of reproduction studies supporting treatment of patients with advanced cancers in women of childbearing age, ICH M3 guidance should be consulted.
Section B. 5 – Reproduction toxicology Lines 161-163	We recommend adding the reference to the ICH S6 document as appropriate.	
Section B. 5 – Reproduction toxicology Line 167	General toxicology study designs do not necessarily warrant the use of sexually mature animals. If fertility endpoints are to be assessed, designs should be modified accordingly to ensure these assessments are made on sexually mature animals.	We recommend including the additional language ", provided sexually mature animals were recruited".
Section B. 6 - Genotoxicity Lines 175-178	The current wording suggests that to support marketing, a full genetic toxicity battery should be conducted (bacterial mutation test, *in vitro* cytogenetics, *in vivo* rodent micronucleus test). In the cancer population, if either of the two *in vitro* tests for genotoxicity were positive, would there be any need to conduct an *in vivo* assessment for genotoxicity? Deeming the drug to be genotoxic on the basis of *in vitro* tests will save animals and potentially time and resources. Most anticancer drugs by their nature have some form of genotoxic mechanism; this is the	We recommend the paragraph be reworded as follows: "Genotoxicity studies are not considered essential to support clinical trials for therapeutics intended to treat patients with late stage or advanced cancer. ~~Genotoxicity studies should be performed to support marketing~~ *In vitro* genotoxicity studies performed should be enough to support marketing (see ICH S2) independently of the results. The principles outlined in ICH S6

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	reason these genetic toxicity tests are not considered essential for this patient population. The *in vivo* genetox result would have little benefit for an anticancer program strictly for marketing purposes when the *in vitro* findings suggest genotoxicity and the mechanism of action would be expected to produce genotoxicity. Removal of the requirement for an *in vivo* assessment in light of an *in vitro* positive result would also be in the spirit of the 3 Rs.	should be followed for biopharmaceuticals."
Section B. 8- Immunotoxicity Lines 187-190	For immunomodulatory drugs, the general toxicology studies design may not be adequate to evaluate immunotoxic potential.	We recommend the additional language for inclusion, "Additional endpoints, such as immunophenotyping by flow cytometry, may be included in the general toxicology study design for oncology products with potential for immunomodulatory effects."
Section C. 1- Start dose for first administration in human Lines 197-198	In order to safely escalate, the starting dose may not always be anticipated to have pharmacologic activity.	We recommend the additional language for inclusion, "The goal of selecting the start dose is to administer a pharmacologically active dose that is reasonably safe to use. In some cases, due to potential toxicity concerns from nonclinical studies, the starting dose may be lower than that anticipated to provide reasonable prospect of benefit. The start dose should be scientifically justified…"
Section C. 1- Start dose for first administration in human Line 206	We recommend including a reference to using AUC/exposure parameters as an example in addition to body weight. For biopharmaceuticals this can be especially useful in establishing appropriate starting dose and dose escalation schemes.	We recommend the additional language for inclusion, "…doses based on other parameters (e.g., body weight, AUC or other exposure parameters) might be more appropriate…"

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Section C. 4- Duration of toxicology studies to support continued clinical development and marketing **Lines 238-243**	We agree that for most anticancer pharmaceuticals, nonclinical studies of 3 months duration would also be considered sufficient to support marketing. We suggest the guidance clarify that it would be the rare exception where this would not apply, in which case ICH M3 guidance should be consulted. In addition, please indicate if the 3 month duration of toxicology studies supporting continued clinical development applies to both species (with respect to small molecules) and for the one relevant species in case of biologics. Finally, does this recommendation change with longer life expectancy in some special or younger patient populations?	
Section C. 5- Combination of Pharmaceuticals **Lines 245-253**	We recommend referring to drug combination guidance for more detailed information/considerations relative to determining if combination toxicology is needed.	
Section C. 6- Nonclinical studies to support trials in pediatric populations **Lines 257-260**	We recommend that dose escalation in pediatrics follow a similar paradigm as that in adults, and possibly exceed adult MTDs, if tolerated, to maximize potential benefit.	
Section D. 1- Conjugated Agents **Lines 272-277**	The guidance highlights conjugated agents of pharmaceuticals covalently bound to carrier molecules, and cites examples of proteins, lipids, and sugars, which could mislead readers that this section is limited to carriers that are naturally-occurring molecules. However, we presume that non-naturally occurring carrier molecules (e.g., polyethylene glycol [PEG]) are also intended to be included, and if so this should be clarified in the	We recommend the revised language, "Conjugated agents are pharmaceuticals covalently bound to carrier molecules, such as to proteins, lipids, or sugars. The safety assessment of the conjugated ~~material~~ pharmaceutical is the primary concern. The safety of the unconjugated ~~material~~

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	guidance. In addition, the guidance refers to conjugated and unconjugated compound or material. We assumed that "compound" and "material" refer to the pharmaceutical rather than the carrier molecule. To avoid ambiguity, we recommend replacing these words with "pharmaceutical".	pharmaceutical including the linker used can have a more limited evaluation. Stability of the conjugate in the test species and human plasma should be provided. A toxicokinetic evaluation should assess both the conjugated and the unconjugated ~~compound~~ pharmaceutical.
Section D. 1- Conjugated Agents **Lines 274-275**	Please clarify whether the intention is to require evaluation of free linker or linker associated with unconjugated material or carrier.	
Section D. 3- Evaluation of Drug Metabolites **Lines 289-296**	We recommend referring to the February 2008 FDA metabolite guidance for more detailed information/considerations.	
Section D. 3- Evaluation of Drug Metabolites **Lines 293-295**	The current final Metabolites in Safety Testing (MIST) guidelines are not applicable to oncology drugs.	We recommend deleting the sentence, "If the parent compound…might not been warranted".

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Table 1- **Line 307**	Under the Clinical schedule header, it indicates "Twice or three times weekly", but under the Nonclinical study schedule header, it indicates "two or three times a week for 4 weeks". The words "twice" and "two" should be harmonized to "two".	
Table 1 **Lines 309-311**	Indicating "should" seems to contradict the flexibility for including recovery or not.	We recommend the alternative language, "Schedules described in the table do not specify recovery periods, which ~~should~~ may be incorporated into the study design. Timing of recovery sacrifices should be scientifically justified (also see Note 1)."
Table 1 **Lines 313-316**	More clarification is needed on the rationale for supporting a FIH clinical schedule with a nonclinical program with two rodents instead of one rodent and one non-rodent. It implies that the non-rodent is not relevant to human safety just because a compound is genotoxic and hits rapidly dividing cells.	
Table 1 **Line 316**	For a toxin (targeting rapidly dividing cells) conjugated to an antibody, repeat dose toxicology in two rodent species may not be appropriate (e.g., species selection should be also based on pharmacological relevance per antibody binding, etc.).	We recommend the additional language, "…sufficient with the exception of cytotoxic drugs conjugated to antibodies, where the standard approach for species selection for monoclonal antibodies applies."
Table 1 **Lines 327-329**	Please provide an example of an instance where recovery groups would not be warranted.	
Table 1 **Lines 332-336**	This is small molecule focused. Additional guidance for biologics is needed, i.e. although a safe dose based on agonistic therapies might be best dealt with case by case, would one tenth	

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	the dose-limiting toxicity for antagonistic therapies be a reasonable suggestion?	