BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

1225 Eye Street NW, Ste. 400
Washington, DC 20005

July 13, 2005

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Draft FDA Guidance for Industry, Investigators, and Reviewers "Exploratory IND Studies," Docket No. 2005D-0122, Federal Register: April 14th, 2005

Dear Sir/Madam:

The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. We appreciate the opportunity to comment on the Food and Drug Administration's (FDA's, the Agency's) Draft Guidance on Exploratory Investigational New Drug (IND) Studies.

General Comments

BIO applauds FDA for preparing this draft guidance, which will provide BIO member companies with valuable assistance for planning exploratory IND studies in humans. We request that FDA offer additional clarity in certain areas of the draft guidance.

First, while therapeutic biological products are included in this draft guidance, the majority of the recommended toxicology studies (i.e., genotoxicity studies, studies using

primates as the primary species, studies involving use of a second species) are focused on chemical drugs. We request that FDA indicate in the guidance that biological drugs should be developed according to the International Conference on Harmonisation's (ICH's) Guideline *S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (available at http://www.ich.org/cache/compo/502-272-1.html#S6), and clarify that not all the toxicology studies recommended in the draft guidance are needed for biological drugs. In our Detailed Comments below we also suggest modifying several specific sections of the draft guidance to clarify these sections' relevance, or lack thereof, to biologic drugs.

Second, there does not appear to be much difference in the chemistry, manufacturing, and controls (CMC) data FDA recommends for exploratory vs. traditional phase 1 INDs. We request that FDA clarify (possibly by example) how much and what kind of data is required for exploratory INDs, and identify specific reductions in the amount of CMC data required in comparison to established guidance for traditional INDs (i.e., *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products*).

Third, in multiple areas the document refers to scaling based on body surface area. We note that scaling based on mg/kg or pharmacokinetic/pharmacodynamic modeling may also be appropriate, depending on the nature of the development program and data available for modeling. This is especially relevant to biological drugs and is consistent with FDA Draft Guidance entitled *Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers*. BIO requests that FDA revise the draft guidance to permit scaling based on criteria other than body surface area, when appropriate.

Finally, under the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments), drug sponsors' patents may be restored by a period equal to half of the interval between the filing of an IND and the submission of an NDA (the "development period"), plus a period equal to the interval between the submission of the NDA and FDA's approval (the "review period"). BIO recommends that the start of the development period – for the purpose of calculating the duration of patent restoration – should be dated from the filing of the exploratory IND, and we ask that FDA clarify this in the guidance.

BIO's detailed comments appear in the following table.

Detailed Comments

Section	Guidance Line(s)	Comment
I	37	Please clarify whether "7 days" refers to consecutive calendar days or dosing days. For example, can several "every-2-weeks" or "once-monthly" doses be

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		administered under an exploratory IND if the same number of doses and dosing interval were included in the pre-clinical tests?
IIB	97-8	Please clarify whether the phrase "have no therapeutic intent" implies that exploratory IND studies are limited to healthy volunteers.
IIB	125-6, and Footnote 6	The footnote states that "Generally, these types of studies would not be carried out in pediatric patients or in pregnant or lactating women," where the phrase "these types of studies" seems to refer to "traditional phase 1 studies that look for dose-limiting toxicities." Please clarify if women of child-bearing potential should also generally be excluded from exploratory IND studies.
IIA1	174-7	Please clarify the timing of expanding an exploratory IND to a traditional IND. If a sponsor chooses to amend an exploratory IND with data to support a traditional Phase 1 plan, at what point can the clinical studies proceed? For example, is there a 30-day wait similar to an initial IND? Alternatively, should sponsors submit an entirely separate traditional IND for a selected compound that was subject to an exploratory IND? With regard to the general investigational plan, we believe that the implication of the statement at line 175 regarding the "outlined study or studies" is that FDA expects an exploratory IND application to contain, in the initial submission, the complete list of related compounds the sponsor intends to study under the IND. Furthermore, upon completion of such studies, the IND must either be withdrawn or converted to a traditional IND. We request the addition of language clarifying whether the sponsor may amend the exploratory IND, either with additional exploratory studies of a compound included in the initial application, or with additional related compounds. An additional implication of the statement at line 175 may be that before amending an exploratory

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		IND with the additional preclinical information necessary to permit expanded testing, the studies proposed under the exploratory IND must be completed. However, we note that there may be situations in which information derived from other development activities may warrant either amending the exploratory IND or submitting a new traditional IND to permit expanded testing before the studies proposed in the original exploratory IND are completed. Therefore, we recommend revised language to remove any implication that the progression to a traditional IND is dependent on completing the exploratory human studies.
IIIA1	176	For increased clarity, we suggest changing "supplement" to "amend."
IIIB1	217-9, 257-8	Lines 257-8 require the sponsor to provide information showing the stability of the test article during the toxicology studies, but no specific duration of stability testing is mentioned. The statement at lines 217-9 refers applicants to earlier FDA guidance (named in footnote 10) that also does not mandate any set period of stability testing, but contains the following statement (Section IIIF, first paragraph): "For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly very limited." We assume, therefore, that it would be generally acceptable for investigational material that is used in toxicology studies to have no pre-existing stability data, if the batch used is found to be within specifications immediately before and immediately after the dosing period. If this is the case, it would be helpful for this to be explicitly indicated in the guidance. If this is not the case, and a longer duration of stability must be shown, then we ask that this be indicated in the guidance, together with an

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		explanation of the need for the longer duration.
IIIB2	264-289	BIO recommends that when the same batch is used for toxicology and clinical lots, regulatory requirements focus on ensuring safety. For biological drugs, the emphasis should be on sterility, pyrogens, and freedom from adventitious agents.
IIIC	299-300	We suggest that the last sentence be deleted. The paragraph discusses why the toxicology evaluation recommended for an exploratory IND is more limited than for a traditional IND; the final sentence does not seem relevant to this point.
IIIC1-2	308-87	The microdose and pharmacological effects examples are based on chemical drugs rather than biological drugs. For instance, a biological drug with a 2-week half-life could have a single 2-week study in cynomolgus monkeys supporting the first single-dose study in humans under a traditional IND. In addition, often the rodent is not an appropriate species for biological drugs based on a lack of pharmacology, but the rodent is the preferred species in the examples used in these sections. Lines 372-377 recommend genotoxicity testing, which usually is not appropriate for biological drugs. We request that FDA clarify which examples in lines 308-87 are focused on chemical drugs rather than biological drugs.
IIIC3	388-415	This section includes an antibody as an example of a biological drug. Thus, the single species use for toxicology studies (lines 402-03) is appropriate and appreciated. We request additional clarification regarding the minimal endpoints that would indicate a sufficient assessment of toxicity. For example, what safety pharmacology evaluations, and clinical and morphologic pathology parameters, are minimum requirements? It may be sufficient to indicate that novel approaches may be used and recommend that these approaches be discussed with the review

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		division in advance of executing the animal studies. Consideration should be given to how much testing is needed for biological drugs toward the same target, but with different potencies and/or structural changes that alter pharmacokinetics. For example, could different levels of pegylation of the same primary structure be tested without comprehensive toxicology studies of each variant? Would it be possible to demonstrate comparable in vitro potency and toxicology studies only of the variants with the shortest and longest half-lives? Clinical studies would then focus on finding the variant with optimal single dose pharmacokinetics and pharmacodynamics. Consideration should also be given to multiple antibodies that have structural differences that alter pharmacokinetics and/or potency but are directed toward a common target. Could the toxicology program for these variants include tissue binding for all variants, but toxicology studies for only the most potent and longest half-life variants? Please consider incorporating these or similar examples into the guidance.
IIIC3	417-425	FDA indicates flexibility with regard to the requirement for studies to have been conducted using Good Laboratory Practices (GLPs). We would suggest indicating more specifically those types of studies for which formal compliance with GLP will be essential. In addition, please clarify how sponsors should discuss potential GLP exemptions with FDA. Is a formal pre-IND meeting needed or can this be accomplished through a teleconference with a Pharmacology/Toxicology reviewer?
Attachment	445-9	The flowchart in the Attachment is specific for chemical drugs, and does not appear to be relevant for biological drugs. For example, the flowchart recommends studies in rodents but the rodent is often not an appropriate species for testing of biological drugs. BIO recommends revising the title of the flowchart to indicate clearly that it does not

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		apply to biological drugs.

BIO appreciates this opportunity to comment on the FDA's Draft Guidance on Exploratory Investigational New Drug (IND) Studies. We look forward to seeing the final guidance, and would be pleased to work with the Agency to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Sara Radcliffe
Managing Director, Scientific and Regulatory Affairs