BIOTECHNOLOGY INDUSTRY ORGANIZATION
1201 Maryland Avenue SW, Suite 900, Washington, DC 20024
202-962-9200, www.bio.org

March 23, 2009

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

Re: Docket No. FDA- 2009-D-2007. Animal Models - Essential Elements to Address Efficacy Under the Animal Rule

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Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the draft guidance *Animal Models-Essential Elements to Address Efficacy Under the Animal Rule.*

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

Biotechnology scientists and executives are eager to use the technologies that have transformed mainstream health care to develop an arsenal of products for biodefense: diagnostics, therapeutics and vaccines that could be used to detect, thwart or respond to attacks with biological, chemical or radioactive weapons. Although desperately needed, such products present development challenges. For example, they generally cannot ethically be tested for efficacy in human clinical trials, because to do so would necessitate exposure to anthrax, smallpox, and other infectious agents. For these reasons they present unique ethical and liability issues.

BIO supports implementation of the Food and Drug Administration's (FDA) Animal Efficacy Rule that allows appropriate studies in animals to provide substantial evidence

of the effectiveness of new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances. Additionally, BIO supports the issuance of guidance on the identification of critical characteristics of an animal model that need to be addressed when developing drug or biological products for approval or licensure pursuant to the Animal Rule. BIO recognizes that effective implementation of the Animal Rule is an urgent priority for biodefense.

BIO suggests that the guidance would benefit from input from experts within the Center for Biologics Evaluation and Research (CBER) and the Center for Veterinary Medicine (CVM). For example, CVM has published a number of guidances that could be useful in clarifying issues related to animal welfare and statistical power. We also encourage the Agency to modify the Guidance to differentiate chemical, biological, radiological and nuclear agents to ensure clear interpretation and rational nomenclature. Additionally, we believe the Guidance should state directly whether studies under the Animal Rule are only to be considered in the context of counterterrorism or military situations or if there are other instances where the Animal Rule applies.

We offer the following specific comments.

SPECIFIC COMMENTS:

Lines: 26-34

Comment: The introduction states "…details of study design and conduct for … animal efficacy studies…" are not addressed." This appears to directly contradict the title of the Guidance. Further, the document clearly states in the introduction that preclinical pharmacology/toxicology studies are not addressed. Therefore it is confusing why the title page of the document identifies the draft guidance as a "Pharm/Tox" Guidance. We request that the title, description, and content of the document be aligned.

The guidance would be improved by providing references for information on the second bullet and fourth bullet referring to study design issues and the threshold for determining that human efficacy studies are not ethical or feasible.

Lines: 57-64

Comment: This and other sections of the guidance recommend early and frequent discussions with the Agency. Please describe the mechanism(s) that a sponsor should use to hold these discussions. Would these be formal discussions at meetings with the Agency?

Lines: 76-77

Comment: The term "toxicity" often does not apply to biological agents. If the Guidance is to include discussion of all agents that can be evaluated under the Animal Rule, we suggest using the term "pathologic effects" rather than "toxicity".

Lines: 79-82

Comment: The definition provided for a well characterized animal model is circular and non-informative. Please provide some clear examples of a well characterized animal model.

Lines: 86- 87

Comment: We suggest the sentence be revised to include the word "safe", i.e., "…allows selection of *a safe* and effective dose."

Lines: 99-103

Comment: Please clarify what type of clinical data from other approved indications of a product may be required.

Lines: 121-122

Comment: "All studies … must … be carried out under…good laboratory practice (GLP)…" Does this mean that an otherwise scientifically sound study not carried out under GLP would not be acceptable? Many of the types of studies that could be useful to demonstrate efficacy under the Animal Rule are unlikely to be conducted under GLP. Where feasible, GLP studies should be conducted. Use of the term "must", however, is not only inconsistent with accepted nomenclature (e.g. ICH guidance documents use the term "should"), but would result in otherwise valuable information being considered inappropriate for regulatory decisions.

Lines: 126–128

Comment: Please provide guidance on reconciling Animal Welfare in the context of exposure to chemical warfare agents. Reference to relevant Center for Veterinary Medicine Guidance, for example, could be useful.

Lines: 154–155

Comment: "Purity" in this context needs clarification, i.e., does this specifically apply to microbial challenge agents?

Lines: 172–175

Comment: "Mechanism of toxicity" is an odd phrase to apply to anthrax. We suggest caution in mixing discussion of microbial and chemical agents, because it may result (as it did here) in the use of inapplicable terminology.

Line: 203

Comment: Sections A.2 and B are redundant.

Lines: 205-213

Comment: This paragraph uses the example of radiation exposure to illustrate that the animal model chosen should be susceptible to the threat agent. It states that if the threshold for insult in the animal model differs significantly from that of humans then the suitability of the animal model may be called into question (a logical conclusion). Please clarify what difference in threshold would be considered significant.

Lines: 230–233

Comment: We suggest discussing the role of *in vitro* methods (e.g. minimum anticipated biological effect level, or MABEL) in this section.

Lines: 259–262

Comment: Although the point regarding similarity of disease progression is well-taken, it appears to discount the utility of proof-of-concept studies. Activity in a model such as anthrax/hamster might yield useful information.

Lines: 272-290

Comment: Because histopathology and gross examinations are indicated specifically in this paragraph, it should be clarified that these examinations are not conducted in a blinded fashion as this is not clear as it is stated in beginning and end of the paragraph. There is no value in conducting these examinations in a blinded fashion in most situations. In special circumstances blinded review may be appropriate to discern effects but this is not done prospectively.

Lines: 278-280

Comment: Please indicate that evaluation of certain disease manifestations could be accomplished in subgroups of animals or special studies if the disease model is sufficiently reproducible and consistent, as telemetry or other technically sophisticated monitoring techniques may not be feasible in large numbers of study animals. Additionally, sophisticated monitoring techniques may interfere with study outcomes in large groups of animals.

Lines: 281 – 283

Comment: We suggest this statement regarding frequency of observation should be qualified, as more frequent observation may not be necessary unless there are particular endpoints that warrant more frequent monitoring or test substance interventions dependent on certain clinical or biomarker endpoints.

Lines: 294-295

Comment: The sentence may not be accurate, especially if studies are considered for prophylactic administration.

Lines: 391–392

Comment: Absorption, distribution, metabolism, and excretion (ADME) studies would not typically be conducted for biotherapeutics (i.e., antibodies, vaccines etc). We would suggest that this wording be altered to better reflect a case-by-case discussion between the sponsor and the FDA to conduct ADME studies only when scientifically justified.

Lines: 392–399

Comment: The example involving P450 system modifiers and effects on metabolism is an oversimplification of the real world scenario. Additionally, responses in the test animal (rat, guinea pig, hamster, etc.) may not be relevant to human P450s. There are numerous drugs/agents metabolized by the P450 system which could impact on PK/PD of a molecule. It is unlikely that these could be sufficiently explored in preclinical studies or that appropriate doses relevant to human exposures could be mimicked in animal studies. Such drug/drug interactions should only be investigated if there is some reasonable possibility that an adverse outcome would be likely.

Drug/drug interaction studies on both the perpetrator and victim are justifiable and commonly conducted for small molecules. However, we would suggest that this section should be rewritten to better reflect case-by-case determination of needs between the sponsor and the FDA when large molecules are involved (either as perpetrator or victim).

Lines: 407–409

Comment: Please provide a reference (or references) for this, or related, example(s). The implication here is that the number of animals needed would be much greater than would be needed to demonstrate efficacy under the Animal Rule.

Lines: 420-422

Comment: Please explain why a placebo control would be needed in addition to an active comparator in the case where a drug is already approved for the indication being sought by the new drug. Is this to provide an internal control that the already approved drug is active in the study? Wouldn't there be ethical concerns in treating patients with placebo after exposure to a noxious agent?

Lines: 440-490

Comment: We note that much of the information in these paragraphs is redundant with information in previous sections.

Line: 477

Comment: In general, biologics such as cell therapies are not addressed here, though there are several cell therapies currently being considered for indications requiring the Animal Rule for treatments of such indications as radiation poisoning. In many cases, cell therapies require treatment either 1) into an immunocompromised host or 2) using

'surrogate' mouse cells. Will use of either of these approaches be acceptable for fulfilling the Animal Rule requirements?

Lines: 488–490

Comment: CDER/FDA has published a guidance on this topic entitled *Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*. Please include this guidance as a reference.

Line: 492

Comment: When addressing vaccine dosing, does this guidance suggest that a full human dose should be applied? It does mention making appropriate 'extrapolations' to the human scenario, and this can be confusing, especially at a time when vaccine guidances are being formulated that specifically address this topic.

Lines: 501-505

Comment: The guidance recommends seeking a Special Protocol Assessment (SPA) for the animal efficacy studies. Please expand this paragraph to provide guidance for seeking a SPA for such studies.

Lines: 512-519

Comment: The guidance speaks to using healthy volunteers to complete the safety profile of the product. Please specify the circumstances under which healthy volunteers could be used to obtain human safety information.

Line: 551

Comment: Please explain the significance of the shaded cells in the table provided in the guidance.

CONCLUSION:

BIO appreciates this opportunity to comment on the draft guidance *Animal Models-Essential Elements to Address Efficacy Under the Animal Rule.* We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Katie McCarthy
Director, Science & Regulatory Affairs
BIO