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June 1, 2009

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

Re: Docket No. FDA- 2009-D-0095. Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format

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Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the draft guidance *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products*.

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 general, we found the guidance well written and easy to follow. The level of detail in the section on Microbiology was especially helpful. However, we found there to be duplication of information in many sections, and information misplaced, making it confusing for healthcare providers to locate information from labeling. Examples of this re-occurring and/or misplaced information are found in Lines:

- 75-77 - Lists *Drug Interactions* as subheader in *Pharmacokinetics* when there is a primary section for this topic and it is also included in *Highlights*.

- 108-110 - Lists pharmacogenomic factors in *Mechanism of Action* when much of this information could be in *Dosing*.
- 149-152 - Discusses receptor selectivity under *Pharmacodynamics*, when it belongs in *Mechanism of Action*.
- 424-429 - Repeats pharmacogenomic information found in other sections.

The pharmacokinetics content appears to be oriented towards synthetic molecules after oral administration. We suggest acknowledging different characteristics between synthetic and biotech-derived molecules and among different routes of administration.

Intrinsic and extrinsic factors could impact all the processes of drug disposition (absorption, distribution, metabolism, and excretion), but they are mentioned only for the excretion/metabolism processes (line 350). Instead of repeating these factors in different subheadings, we suggest inserting a separate section to describe these impacts (e.g., special population subheading) which could be a more effective way to present the information.

We agree that the *Pharmacokinetics* (PK) subsection should begin with a summary of the information that can influence treatment by the prescribers; however, the guidance mentions scientific points that could be useful for compound development but may be too technical to be generally useful for prescribers or patients (e.g., absorption and distribution half-lives, Line 303).

Comments on Specific Line Items

Line 50, *Clinical Pharmacology Section* – We suggest “Special Populations” be added to the list of labeling sections since it is also one of the sections that potentially could have PK information.

Line 83, *Pharmacology Section* - We agree with the importance of discussing the parent drugs or metabolites that contribute significantly to the overall efficacy or toxicity. However, we suggest the quantitative cut off be science- and case-based and should not generally be pre-specified in the guidance.

Line 108, *Mechanism of Action (How Therapeutic and Adverse Effects Occur)* - While the mention of pharmacogenomic factors is relevant, other endogenous or environmental factors equally affect drug action and should be included.

Lines 120-121 and 132-134, *Pharmacodynamics* - Please clarify the level of detail regarding the dose-response relationship to be presented here and how it varies from that presented in the *Clinical Studies* section of labeling.

Line 130 *Pharmacodynamics* - The term “autoantibodies” is confusing. We suggest the term “autoantibodies” be replaced with “biological product-induced antibodies”, and that the term “biological product-induced antibodies” be further subdivided into “binding” antibodies and “neutralizing” antibodies with reference to the testing steps involved.

Line 149 *Pharmacodynamics* - A drug elicits its pharmacological effects through its binding to a target, which may not be a receptor. Therefore, we suggest ‘receptor’ be replaced with the word ‘target’.

Line 176, *Pharmacodynamics* - Refers to *racial/ethnic factors*. We prefer to delete *racial/ethnic factors* because *racial/ethnic factors* are substantially environmental as well as endogenous. However, if *racial/ethnic factors* are to be included, the text should clearly distinguish these from genetic factors.

Line 200 *Pharmacodynamics* - Antibody formation is considered a pharmacodynamic (PD) effect in this draft guidance; therefore, this sentence is confusing. We suggest rewording this sentence to read, “Antibody formation and any resultant impact on pharmacologic effects pertinent to effectiveness and safety.”

Line 239, *Pharmacokinetics* – States, *If important PK information is not available, this should be noted.* Please provide examples of the types of information that when unavailable, should be described here.

Lines 250-251, *Pharmacokinetics* – We disagree that, *The Pharmacokinetics subsection should begin with a summary of the information that can influence treatment by the prescriber. . .* This information belongs in the *Drug Interactions, Dosing, or Warnings and Precautions* sections of labeling and should be cross-referenced to the *Pharmacokinetics* section. Prescribers are likely to look to these other sections before consulting the *Pharmacokinetics* section of a label. Consideration should be given for drug-drug interactions for medications that are co-administered for the purpose of increasing efficacy or for the purpose of avoiding toxicity where there is no basis for metabolic or transporter related interaction. This information might include pertinent negatives [e.g. no interaction observed for combination drug products].

Lines 279-281, *Absorption and Distribution* - This section appears mainly focused on absorption, but then diverges to address polymorphic drug metabolizing enzymes (CYPs). We would prefer that CYP 450 enzymes be included in the *Metabolism* section, where the text should be expanded beyond CYPs.

Lines 295-297, *Absorption and Distribution* – It appears that the parenthesis is inadvertently closed after "... secretion into breast milk" and we suggest moving it to the end of the sentence to convey the appropriate meaning.

Line 300, *Metabolism and Excretion* – We suggest the use of separate subheaders to distinguish between small molecules vs. biologicals, as their properties differ.

Line 335, *Metabolism and Excretion* – Refers to *racial/ethnic factors*. We prefer to delete *racial/ethnic factors* because *racial/ethnic factors* are substantially environmental as well as endogenous. However, if *racial/ethnic factors* are to be included, the text should clearly distinguish these from genetic factors. Rather than focusing only on *polymorphic metabolism*, suggest the term, *polymorphic ADME*, to reflect growing knowledge of absorption, distribution and excretion mediated by polymorphic transporter proteins.

Lines 395-429, *Pharmacogenomics* – A *Pharmacogenomics* header is warranted when such information assists in understanding the dosing regimen or risk-benefit profile for select patient groups. However, it may be more appropriate to place this header in *Special Populations* rather than *Clinical Pharmacology*. The information provided and how it is used should closely mirror information currently provided in labels for other special populations, such as the elderly, children, hepatically-impaired, and renally-impaired.

Lines 397, *Pharmacogenomics* - Although *Pharmacogenomics* by definition includes analysis of both genetic (DNA) and expression (RNA) variations, all the examples provided are genetic (DNA) in nature. Therefore, using the term ‘genetic’ in this sentence seems at odds with the section title. We suggest deleting “genetic” from this sentence.

Line 421, *Pharmacogenomics* - Biomarkers that are associated with safety and/or efficacy could include those that arise through somatic events. We suggest that a parenthetical statement such as “(inherited polymorphisms or somatic mutations)” be inserted after the word ‘genetic’.

Lines 424-425, *Pharmacogenomics* - Pharmacogenomic changes that impact safe and effective use of the drug may not be limited to genetic variation only as currently stated. We suggest the revised language, “When pharmacogenomic information has important implications for safe and effective use of the drug and the consequences of ~~the genetic differences~~ this information result in recommendations for restricted use...”

CONCLUSION:

BIO appreciates this opportunity to comment on the draft guidance *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products*. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Katie McCarthy, MPH
Director, Science and Regulatory Affairs