Biotechnology Industry Organization

October 14, 2014

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2014-N-1108: Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products—Considerations, 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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the *Draft Guidance for Industry on Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products—Considerations, Content, and Format*. BIO welcomes this Draft Guidance to ensure appropriate consistency in the format and content of product labeling for all prescription drug products approved by the Agency.

BIO represents nearly 1,000 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:

BIO applauds FDA for the release of this Draft Guidance, which addresses many of the comments raised during the comment period for the 2009 draft it replaces, most notably avoiding duplication of information in different sections of the label and providing better clarity on the level of study detail in the clinical pharmacology section of the label. The Draft Guidance now allows flexibility depending on the existing data and has added more structure and details around data presentation. There are, however, several aspects of the guidance for which BIO requests additional information or clarification.

A. Improving Consistency in Labeling

There is a great need for better consistency in labeling. A recent survey of drugs approved for rheumatologic conditions reveals large disparities in the content and amount of information contained in their respective *Mechanism of Action* and *Pharmacodynamics* labeling sections (Table 1).

1201 Maryland Avenue SW
Suite 900
Washington DC 20024
202.962.9200 P
202.488.6306 F
bio.org

Table 1. Comparison of Label Content for Drugs Approved for Rheumatologic Conditions

Drug	Mechanism of Action (Section 12.1)	Pharmacodynamics (Section 12.2)	Word count
Brand A	• Target, role in signaling • Relation to clinical effects unknown	• None	45
Brand B	• Target, role in inflammation • In vitro cell effects	• Clinical biomarkers (skin)	120
Brand C	• Target, role in disease • In vitro cellular effects	• Animal models • Clinical biomarkers (serum)	241
Brand D	• Target, role in disease • In vitro cellular IC50s • Clinical biomarkers (skin) • Relation to clinical effects unknown	• Clinical biomarkers (serum)	245
Brand E	• Target, role in signaling • In vitro IC50s • Relation to clinical effects unknown	• Clinical biomarkers (blood and serum) • PD effect timing onset and duration • PD relation to PK • Relation to clinical effects unknown	274
Brand F	• Target, role in inflammation • Animal models • Relation to clinical effects unknown	• Target, role in disease • Clinical biomarkers (serum, joint, skin, cells ex vivo) • Relation to clinical effects unknown	459

In some labels, Section 12.1 *Mechanism of Action* contains only a statement about the drug's binding target, while in others, the role of that target in the disease condition is generally stated. Sometimes, *in vitro* and *in vivo* pharmacology data are included. The statement, "The relationship between these effects and clinical efficacy is unknown" is usually, though not always, used. BIO recommends that the Agency provide criteria for determining whether this statement is always true and hence always must be included, or if not, the level of evidence required to obviate its inclusion.

The data in Section 12.2 *Pharmacodynamics* are similarly inconsistent, with some drug labels providing no information, others providing preclinical animal data and general information about the target's role in disease (which is perhaps better suited for section

12.1), and still others providing clinical pharmacodynamic data from various fluids and tissues, including blood, serum, joint, and skin. BIO believes the criteria for inclusion of pharmacodynamic data in this section are still unclear and would appreciate further clarification.

Further, BIO believes that Section 12.3 *Pharmacokinetics* would benefit from additional guidance regarding use of the Agency's preferred units of drug concentrations and pharmacokinetics values. The Draft Guidance indicates that results of studies or analyses conducted in specific populations should be described under the appropriate subheading, yet it is not explicit in the types of analyses that would be acceptable (*i.e.*, race, age, and gender are often examined as covariates in population PK analyses). BIO suggests that FDA include guidance on the use of population PK approaches to support label statements for specific populations, as well as how population analyses may also be useful for determining the potential drug-drug interactions (DDIs) when experimental drug is victim.

While BIO has compared these existing labels for illustrative purposes, we recommend that FDA's implementation of this guidance be restricted to labeling submitted for new NDA and BLA submissions (*i.e.*, the guidance should not be applied retroactively to the labels of drugs already approved).

B. Incorporating Modeling Data

BIO notes that there is a lack of information on the inclusion of modeling data, specifically physiologically based pharmacokinetic (PBPK) modeling, for drug-drug interactions (DDIs) or other types of PK/PD modeling. FDA has published on the use of these approaches, and BIO therefore suggests FDA include a statement in the guidance on the use of PBPK modeling approaches to support labeling statements, as well as a section on where drug-drug modeling information and PK/PD modeling information, in general, should be placed in labels. Additionally, there appear to be inconsistencies between this guidance and the draft DDI guidance on where to place dosage adjustment recommendations, which BIO recommends harmonizing in the final guidance.

C. Additional Requests for Clarification

BIO requests that FDA clarify the specific types of clinical pharmacology information that should be included in the *Highlights* section of the label. Additionally, BIO recommends that the Draft Guidance provide advice on labels for fixed-dose combination products. Finally, BIO recommends providing greater detail across sections on clinical pharmacology for biologics.

CONCLUSION:

BIO appreciates this opportunity to comment on the *Draft Guidance for Industry on Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products—Considerations, Content, and Format.* Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew W. Womack, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE/COMMENT	PROPOSED CHANGE
II. BACKGROUND		
Lines 57-58:	BIO believes that the parenthetical, as currently written, is unclear and should be modified to make it clear that pharmacodynamic (PD) effects referred to in this sentence should include both on- and off-target pathways.	BIO requests that FDA revise to read: "…drug mechanism of action, pharmacodynamic (PD) effects (e.g., including both on-target~~/pathway,~~ and off-target~~/~~ pathways), and PK properties in a variety of settings and specific populations."
Lines 63-65:	BIO believes that "dose adjustment," rather than "dose selection," better describes what prescribers do when determining the appropriate dose for a patient.	BIO suggests that FDA revise to read: "Examples of specific recommendations include strategies for dose ~~selection~~ adjustment, therapeutic individualization, and adverse reaction risk minimization."
Lines 64-65:	BIO believes it is unclear whether "adverse risk minimization" is separate and distinct from listing "adverse reactions," and if so, what the expectations are for inclusion in the *Clinical Pharmacology* section on adverse reactions.	BIO requests that FDA clarify whether "adverse risk minimization" is separate from adverse reactions, and if so, elaborate on what should be included in the *Clinical Pharmacology* section on adverse reactions.
III. GENERAL PRINCIPLES FOR THE CLINICAL PHARMACOLOGY SECTION		
A. CONTENT AND ORGANIZATION		
Lines 90-95:	Regarding "pharmacologic information based on *in vitro* data using human biomaterials or pharmacologic animal models, or relevant details about *in vivo* study designs or results," BIO believes that the use of the term "may be included" suggests less stringent inclusion criteria, depending upon a subjective evaluation.	BIO recommends that FDA include more specific guidance on the relative importance of *in vitro* data, animal studies, and clinical pharmacodynamics data, including a potential framework for determining appropriate data to include.
B. CROSS-REFERENCING OF CLINICAL PHARMACOLOGY INFORMATION		

SECTION	ISSUE/COMMENT	PROPOSED CHANGE
Lines 143-147:	Because the ADVERSE REACTIONS section is often referenced when there are dose/concentration dependent adverse events, BIO believes that it should be added to the parenthetical list of sections that may be cross-referenced.	BIO requests that FDA revise to read: "Instead, a cross-reference should be made to the appropriate sections/subsections that include this information (e.g., INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE EVENTS, DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS, and OVERDOSAGE)."
Lines 147-153:	The terms "clinical relevance" and "clinical significance" are used interchangeably, but BIO believes that it is possible for some studies to demonstrate statistically significant differences that are not deemed to be clinically relevant.	BIO recommends that FDA revise these last two sentences of the paragraph for clarity and suggests a common terminology be used with respect to clinical relevance to aid clarity. Moreover, BIO believes that these sentences could be simplified to indicate that clinically relevant results should be appropriately cross-referenced with other sections of the label (e.g., Dosing Recommendations, Warnings and Precautions, Contraindications, Drug Interactions); otherwise, the label should indicate that "There is no clinical significance or the clinical relevance of the findings are unknown."
IV. INFORMATION TO BE INCLUDED IN EACH SUBSECTION		
A. SUBSECTION 12.1 MECHANISM OF ACTION		
Line 163-165:	"Unintended effects due to additives" may also imply toxicological effects of the additives or contributions to the clinical efficacy of the drug, which must be reported in the other sections of the label, assume the additive is (*e.g.*, Warnings and Precautions, Adverse Reactions, *etc.*).	BIO requests that FDA clarify whether a cross-reference to these sections should be included in subsections of *Clinical Pharmacology.*

SECTION	ISSUE/COMMENT	PROPOSED CHANGE
Lines 175-187:	BIO believes it is unclear whether the term "*untested*" is equivalent to "*unproven in clinical studies*," which, if true, would be problematic as it is not usually possible to directly measure target engagement in the context of a pivotal phase 3 study to prove cause and effect, hence determination of the mechanism of action (MOA) of a drug in any human disease requires a collection of multiple nonclinical and clinical studies, which essentially constitute the whole of the New Drug Application (NDA) submission.	BIO requests that FDA provide a definition for "*untested MOA*" that clarifies it is not simply "*unproven in clinical studies*."
B. SUBSECTION 12.2 PHARMACODYNAMICS		
Lines 197-202:	The statement "*The relevance of the PD biomarker is a function of how mechanistically related the biomarker is to the drug's clinical effect or toxicity*" is offered without citation to, or discussion of, criteria for determining whether a PD marker is mechanistically related to a drug's clinical effect. Also, it is unclear whether PD biomarkers data from the pivotal studies should be reported in *Section 12.2 Pharmacodynamics* or in the *Clinical Pharmacology* section.	BIO requests that FDA either reference or include a discussion of criteria for determining whether a PD marker is mechanistically related to a drug's clinical effect. Also, BIO requests that FDA clarify whether PD biomarkers data from the pivotal studies should be reported in *Section 12.2 Pharmacodynamics* or in the *Clinical Pharmacology* section
Lines 197-215:	BIO believes it would be helpful for Sponsors if FDA provided a definition of the level of rigor required for PD biomarker data to establish a relationship to the drug's beneficial effect or adverse effects/toxicity, such as whether: • The importance of data derived from phase 1, 2, or 3 studies are viewed differently	BIO requests that FDA provide a definition of, or guiding principles for determining, the level of rigor required for PD biomarker data to establish a relationship to the drug's beneficial effect or adverse effects/toxicity.

SECTION	ISSUE/COMMENT	PROPOSED CHANGE
	• Data from double-blinded placebo controlled studies are required, or if mechanistic data from open–label studies are acceptable • The PD biomarker data must come from clinical studies conducted by the Sponsor, or if they may be derived from investigator-initiated trials • The PD biomarker analysis must be conducted according to a pre-specified statistical analysis plan	
Lines 226-227:	While Sponsors often assesses the impact of antibody formation on efficacy and safety, they rarely assess their impact on pharmacodynamic markers.	BIO recommends that FDA revise to read: "~~• Impact of anti-product antibody formation on pharmacodynamics of a biologic product.~~"
Lines 229-230:	BIO notes that QT interval is not assessed for therapeutic proteins.	BIO recommends that FDA reference the QT/QTc Guidance[1] and revise to read: "Because the evaluation of drug effects on the QT interval is common for drugs other than therapeutic proteins[REF] the *Pharmacodynamics*…"
Line 229-237:	BIO believes that it may be confusing to prescribers to include description of drug effects on QT interval (or other safety biomarkers) among PD biomarkers, as electrocardiograms (ECGs) and routine laboratory tests have established	BIO suggests that FDA include drug effects on QT prolongation under a separate subsection of the label entitled "*Cardiac Electrophysiology*" rather than under the "*Pharmacodynamics*" subsection.

[1] FDA Guidance for Industry on *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (2005), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf

SECTION	ISSUE/COMMENT	PROPOSED CHANGE
	relationships with clinical safety, whereas some PD biomarkers may not have an established relationship with clinical efficacy. Additionally, some prescribers typically think of PD biomarkers as those related to drug target or disease pathway modulation, rather than safety biomarkers.	
C. SUBSECTION 12.3 PHARMACOKINETICS		
Line 241:	As the Draft Guidance emphasizes that repetition in multiple sections should be avoided, BIO believes that information included in the brief introduction should not be repeated under subsequent subsections.	BIO requests that FDA clarify that information included in the brief introduction should not be repeated under the subsections *Absorption*, *Distribution*, *Elimination*, *Specific Populations*, and *Drug Interaction Studies*.
Lines 247-249:	BIO believes that introductory pharmacokinetics (PK) paragraph is not the best place to describe the effect of anti-product antibody formation on PK. Rather, BIO believes that subheading in the *Specific Populations* section should be added, because: A. Such placement would make it more notable, and not hidden; B. The effect of anti-product antibody formation on PK is often based on population PK analysis like other covariates such as age, weight, and race; and C. Such information is specific for biologics.	BIO requests that FDA (i) add a separate subheading under Specific Populations for a discussion of the impact(s) of anti-product antibody formation; and (ii) revise to read: "…in pharmacokinetics over time. ~~Information regarding the impact of anti-product antibody formation on the pharmacokinetics of a biologic product also should be included in this introduction.~~"
Lines 251-254:	While the Draft Guidance states that "Available PK measures and parameters (e.g., maximum plasma concentration (C_{max}), area under the plasma drug	BIO requests that FDA revise to read:

SECTION	ISSUE/COMMENT	PROPOSED CHANGE
	concentration time curve (AUC), clearance, volume of distribution, half-life) should be included in this subsection and can be used to provide context for the optimization of drug administration," there is a discrepancy between this statement and another statement on lines 275-278 (Section IV.A.1 *Absorption*) regarding the inclusion of C_{max} values.	"Available PK measures and parameters (e.g., ~~maximum plasma concentration (C_{max}),~~ area under the plasma drug concentration time curve (AUC), clearance, volume of distribution, half-life) should be included in this subsection and can be used to provide context for the optimization of drug administration."
1. ABSORPTION		
Lines 281-282:	BIO believes that the description of the absorption kinetics should be expanded to the range of doses studied as this may be higher than the range of clinical doses and more relevant (*i.e.*, if absorption is affected by drug-drug interactions (DDIs) resulting in higher exposures (C_{max}) than associated with a "clinical dose," but the higher C_{max} is not deemed to be of clinical relevance, then it would be important to know that absorption was linear or nonlinear at a level higher than the clinical dose).	BIO recommends that FDA revise to read: "• A description of the absorption kinetics (i.e., linear or nonlinear) over the range of ~~clinical~~ doses studied."
Line 283:	In addition to differential absorption, BIO suggests describing differential distribution, metabolism, and excretion of isomers in a racemate (in the respective subsections) to better reflect on the absorption, distribution, metabolism, and excretion of a racemate.	BIO recommends that FDA add to the distribution and elimination subsections a bullet that reads: "• Differential [distribution/metabolism/excretion] of isomers in a racemate, if both enantiomers are active"
Lines 286-287:	As written, BIO believes it is unclear whether or not the bullet on lines 286-7 is applicable to all drugs/drug products.	BIO recommends that FDA revise to read: "• Clinical relevance of disease-related changes, if any, in absorption (e.g., due to fast or slow gastrointestinal transit time, short bowel syndrome)."

SECTION	ISSUE/COMMENT	PROPOSED CHANGE
Line 288:	BIO believes that the difference in absorption for different injection sites for injectable drugs should be noted.	BIO suggests that FDA revise to read: "• Clinical relevance of disease-related changes in absorption (e.g., due to fast or slow gastrointestinal transit time, short bowel syndrome) • Differences in absorption for different injection sites for injectable drugs"
Lines 289-291:	BIO believes that the description of food(s) and meal(s) with respect to total calories and composition should as brief and non-technical as possible.	BIO suggests that FDA revise to read: "A brief, non-technical description of the food(s) or meal(s) used with respect to total calories and composition (fat, carbohydrate, and protein content) should be stated (*e.g.*, "a high-fast, high-caloric (928 kcal) and normal caloric (533 kcal) breakfast")."
Lines 295-298:	BIO believes that it would not be useful (or intuitive) to prescribers to place the effects of food substances that influence transporters/metabolic enzymes under the *Absorption* heading, while placing the impact of drugs that affect absorption (e.g., acid reducing drugs) under the *Drug Interaction Studies* section. BIO believes that the *Drug Interaction Studies* section should include typical metabolic- and transporter-related drug-drug interactions, whereas interactions between food substances and acid reducing drugs should be mentioned under the *Absorption* header.	BIO recommends that FDA revise to read: "The effect of food substances that influence transporters and/or intestinal metabolic enzymes that ultimately affect absorption (e.g., grapefruit juice) should be included under the *Absorption* heading~~.~~ ~~However~~, as well as the impact of drugs that affect absorption (e.g., acid reducing agents) ~~should 297 be included under the *Drug Interaction Studies* heading~~."
2. DISTRIBUTION		
Lines 308-312:	While the Draft Guidance states that volume should be compared to physiologic volumes, BIO	BIO suggests that FDA either remove this comparison or allow Sponsors to describe the volume in more

SECTION	ISSUE/COMMENT	PROPOSED CHANGE
	believes it is unclear the specific volumes being suggested for comparison (*i.e.*, plasma, blood, lymph, and/or body water). Also, BIO believes that the Agency should provide additional guidance with regard to which volume of distribution [e.g., Terminal Phase Volume (Vz), Steady State Volume (Vss)] should be described in the label, as Vss from non-compartmental analysis (NCA) for biologics can be inaccurate or misleading.	general terms (*e.g.*, volume of distribution is 1000L indicating extensive distribution into tissues). Also, BIO recommends that the Agency provide additional guidance with regard to which volume of distribution [e.g., Terminal Phase Volume (Vz), Steady State Volume (Vss)] should be described in the label, particularly for biologics.
3. ELIMINATION		
Line 320:	BIO believes that parsing out "Metabolism" and "Excretion" as separate subsections, rather than grouping them under "Elimination," would provide greater clarity to Sponsors.	BIO recommends that FDA parse out "*Metabolism*" and "*Excretion*" as separate subsections and delete the header "*Elimination.*"
Line 326-327 JNJ	BIO notes that it is not always possible to determine time to reach steady state (*e.g.*, for a monoclonal antibody given every 8 or 12 weeks, or very infrequently). Also, BIO believes that the associated therapeutic dose level should be reported, in addition to effective half-life, for drugs that exhibit non-linear PK for their elimination.	BIO recommends that FDA revise to read: "~~The drug's half-life should be stated here. The half-life value reported should usually be the half-life based on the time to reach steady state (i.e., the effective half-life)~~ The effective half-life, which can often be determined based on the time to reach steady state, should be reported here. When a drug product exhibits non-linear PK for its elimination, both the effective half-life value and the associated therapeutic dose level should be reported."
Lines 332-334:	As written, BIO believes it is unclear what constitutes a major metabolite and whether circulating metabolites or excreted metabolites should be considered.	BIO recommends that FDA revise to read: "The Metabolism subheading should include a description of the in vitro and in vivo

SECTION	ISSUE/COMMENT	PROPOSED CHANGE
		biotransformation pathways, including the contribution of specific enzymes and identification of ~~major~~ metabolites of regulatory concern per regulatory guidance definition (i.e., those constituting >10% of total drug related material in systemic circulation).”[2]
Line 335:	BIO believes that metabolic pathways that have been ruled out should not be included under the Metabolism subheading.	BIO requests that FDA modify to read: “~~Metabolic pathways that have been ruled out should also be stated.~~ A description of…”
Lines 339-340:	BIO believes that this sentence, as written, may lead the reader to believe that human radiolabel mass balance studies (hADME) are not routinely performed or used to inform clinical pharmacology labeling. BIO notes that chemical measures tend to be the rare exception rather than an equally informative alternative to radiolabel studies.	BIO recommends revising to read: “…excretion from the body, as defined primarily by ~~chemical measures or~~ radiolabel (mass balance) studies. Conclusions on the basis of chemical measures are acceptable when clinical studies are not feasible.”
4. SPECIFIC POPULATIONS		
Lines 366-419:	BIO recommends presenting the information in the same order provided by the labeling regulations for Section 8 *Use in specific populations* [CFR 201.57(c)(9)].	BIO suggests moving the “Pregnancy” subheading (Line 413-419) to begin at Line 366 as the first heading under “Specific Populations.” We would also recommend switching the ordering of “Age: Geriatric Population” (Lines 366-383) and “Age: Pediatric Population” (Lines 374-383). With these changes, the subheading “Pregnancy” will appear first, followed by “Age: Pediatric Population,” then by “Age: Geriatric Population,” followed by the remaining headings.
Line 384:	Since weight is often an important determinant of PK and is important for dose adjustment, BIO	BIO recommends that FDA add “Weight” as a subheading.

[2] FDA Guidance for Industry on *Safety Testing of Drug Metabolites* (2008), available at http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0065-GDL.pdf

SECTION	ISSUE/COMMENT	PROPOSED CHANGE
	suggests adding "Weight" as a specific subheading under *Specific Populations*	
Line 420:	As discussed above (in reference to Lines 247-249), BIO suggests adding a subheading in *Specific Populations* for anti-product antibody formation. This subheading would be specific to biologics and providing this information under its own subheading will make it more readily accessible to prescribers. In addition, the effect of anti-product antibody formation on PK is often assessed based on population PK analysis or through the examination of the effect of anti-product antibodies on observed trough drug concentrations.	BIO recommends that FDA add "Anti-Product Antibody Formation" as a subheading.
5. DRUG INTERACTION STUDIES		
Lines 423-428:	BIO notes that the Draft Guidance provides additional clarification on the types of information to include in the *Drug Interaction Studies* section versus the types to include in the *Clinical Pharmacology* section; however, BIO believes that additional clarification would be helpful for Sponsors.	BIO requests that FDA provide additional examples in an Appendix to clarify the types of information to include in the *Drug Interaction Studies* section versus the types to include in the *Clinical Pharmacology* section.
Lines 426-428:	BIO recommends adding "DOSAGE AND ADMINISTRATION" to the list of examples, in the event that dosage modifications of the drug are required, based on the effects of concomitant drugs.	BIO recommends that FDA revise to read: "Other sections of labeling, e.g., CONTRAINDICATIONS, ~~or~~ WARNINGS AND PRECAUTIONS, or DOSAGE AND ADMINISTRATION, may include information regarding drug interactions."
Lines 430-431:	BIO notes that current understanding is that FDA prefers Forest plots and that these should include all drug-drug interaction studies whether positive	BIO requests that FDA clarify that a Forest plot or table is not needed in addition to or in lieu of a

SECTION	ISSUE/COMMENT	PROPOSED CHANGE
	or negative; however, this seems counter to what the Draft Guidance recommends.	"sentence that conveys the knowledge…without the need for extensive elaboration."
Lines 431-434:	BIO believes that the effect of concomitant medication on anti-product antibody formation should also be described under the *Drug Interaction* Studies section.	BIO recommends that FDA revise to read: "…results should be included there. When a concomitant medication has significant effect on anti-product antibody formation and consequently has an impact on efficacy and safety, such drug-drug interactions could also be described. The input on clinical efficacy and safety can be cross-referenced with the *Immunogenicity* section."
V. PRESENTATION OF INFORMATION		
A. CENTRAL TENDENCY AND VARIATION		
Lines 477-481:	BIO notes that the level of detail and potential inclusion of details, such as the type of distribution of observations and/or skewness, may become very technical and of very limited value for making clinical decisions.	BIO recommends that FDA (i) clarify that information about central tendency and variation should be included in the drug label only insofar as they are relevant to and inform a prescriber's dosing decision for the drug, and (ii) include examples of such drugs (*e.g.*, drugs with a narrow therapeutic range).
Lines 486-487:	BIO believes that a plot of the "cumulative distribution function" (CDF) conveys more detailed information than histograms, and BIO notes that CDFs allow quantification of the fraction of the population affected for any threshold value of interest.	BIO recommends that FDA consider adding a plot of the "CDF" as an example of a means for conveying information on a data distribution.
B. PRESENTATION FORMAT		
Lines 507-511:	BIO notes that current understanding is that FDA prefers Forest plots and that these should include all drug-drug interaction studies whether positive	As per the comment on lines 430-431, BIO requests FDA to clarify if Forest plots are preferred for presentation of drug-drug interactions (DDIs) or other intrinsic/extrinsic effects on PK.

SECTION	ISSUE/COMMENT	PROPOSED CHANGE
	or negative; however, this seems counter to what the Draft Guidance recommends on lines 430-431.	