Biotechnology Industry Organization

February 2, 2015

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

Re: Docket No. FDA-2014-D-1551: Draft Guidance for Industry on Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products

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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the *Draft Guidance for Industry on Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products*.

BIO is the world's largest trade association representing 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.

BIO thanks the Agency for their work on developing the final rule for *Content and Format of labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling* ("PLLR" or "final rule") and this Draft Guidance. BIO would like to note that the elimination of the pregnancy categories is a major paradigm shift for the healthcare community. FDA's final rule discusses the development of educational materials for FDA staff, health care providers, and patients. BIO wholeheartedly agrees that outreach efforts by FDA are essential in ensuring that providers are aware of the new requirements for labeling and are able to navigate the information without relying on the pregnancy categories. We also greatly appreciate FDA's efforts on this matter, as these materials will inform stakeholders on the changes in labeling regulations and how they will have a positive impact on labeling regarding the use of drugs and biologics during pregnancy and lactation.

There are several aspects of the Draft Guidance for which BIO requests additional information or clarification.

A. PLLR Labeling Examples

In the final rule, FDA concluded that development of fictitious labeling would not be useful to drug developers or the Agency reviewers responsible for developing, revising, and approving product labeling under the new rule. While we understand that there will be wide

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variation in the available amount of data for a given product and that each label will be unique to the specific available data, we still believe that it would be beneficial to industry for FDA to provide various examples of the extent and depth of information required by the new rule. In instances where there are no data are available, we recommend the Agency provides standardized statements for inclusion by the Sponsor.

We would also suggest that FDA emphasizes in the background section that the implementation guidance is about labeling content and is not guidance on strategies on conducting studies or trials that support each section of the new label.

B. Risk Summaries

While the Draft Guidance provides comprehensive and detailed information on the content of sections intended to provide information and data, information regarding risk summaries *derived* from this information/data is insufficiently detailed. As discussed above, BIO recommends that the Agency provides specific examples for these sections in the Guidance, perhaps in an appendix. These examples could include wording for the required statements and examples of what data should be included. For example, it is noted multiple times in the *Risk Summary* sections in the Draft Guidance (e.g., 189-191, 204-205, etc.) that risk summary data can include risk statements based on human, animal, and pharmacologic data. However, when referring to required subheadings, the sections entitled *Data* list only human and animal data, excluding pharmacologic data. BIO requests clarification on whether or not the *Data* sections require inclusion of pharmacologic data.

It would be useful for the Agency to clarify what "systemically absorbed" does and does not mean, and provide examples (*e.g.*, topically-applied drugs or intravitreally-administered drugs). There may always be a minimal amount of drug that becomes systemic depending on detection levels. Because systemic exposures are ultimately determined by overall bioavailability rather than just absorption, it is suggested to replace all references to absorption with availability or bioavailability. Likewise, in multiple sections, the Draft Guidance refers to dose or to the dose-response relationship. Because of variability in dose-exposure relationships, exposure or exposure-response relationships, if available, may be more informative than dose or dose-response relationships. BIO suggests including references to exposure and exposure-response relationships in a consistent manner throughout the Guidance.

BIO believes that the Agency should consider a general statement about background risk should go with the *Risk Summary*, and the specific risk data should be included within Clinical Considerations so the risks with pregnancy and the risk associated with a specific population are tied together for the reader/prescriber.

C. Background Risk and Birth Defects

The Draft Guidance requires the Sponsor to state the background risk for major birth defects and miscarriage in the general population in order to establish a basis for comparison to data collected on the drug. BIO believes that there should be guidance for

references on background prevalence for specific birth defects rather than major birth defects overall only. The Agency should consider including information about both background risk of major birth defects overall and risk of specific birth defects of interest.

The statement on background major birth defects occurring in 2-4% of the general population does not address the occurrence of increases in rare drug-related malformations that do not increase the overall major birth defects rate above 2-4%. Additionally, low birth weight and functional deficits, two additional manifestations of developments toxicity, are not addressed relative to background rates in the Risk Summary. The Agency should also address background rates for low birth weight and functional deficits in the general population and how to handle increases in rare malformations that do not raise the overall major birth defect rate above background.

Furthermore, the Draft Guidance asks Sponsors to "periodically review the birth defects and miscarriage data to ensure that the information in labeling is accurate." BIO believes that when to update the label should be based on new information that is significantly different, as opposed to simply additional or slightly changed information. We request further clarification on the Agency's thinking on this topic.

Finally, the Draft Guidance references the "U.S. general population," suggesting that data should be sourced and analyzed from only U.S. patients. BIO requests clarification on whether or not data included should be only from U.S. patients.

D. Considerations for Vaccines

The only example provided regarding vaccines is rubella and the paragraph concludes that "pregnant women may be advised to avoid vaccination during pregnancy," which inadvertently may appear to be a default recommendation. We suggest either that the text is modified to become vaccine-specific (for example, "pregnant women may be advised to avoid vaccination with the rubella vaccine during pregnancy"), or that care is taken to ensure that the Guidance does not imply that vaccination should generally be avoided during pregnancy.

E. Class Labeling

The Draft Guidance notes that FDA "may consider developing class labeling for known maternal and/or embryo/fetal risks." BIO welcomes further guidance indicating the depth of information required for this new format. Additionally, it would be helpful to the Sponsors to state where new class labeling will be posted in the future.

F. Consistent Use of the Drug Name

Throughout the Draft Guidance, "(name of drug)" is mentioned in several places (*e.g.*, where the Sponsor would insert the name of the drug into particular statements). However, it is unclear whether the name of the drug refers to the product's tradename or to the

generic name of the drug. It appears that either would be applicable, depending on the statement. For example, Lines 174-175 state "There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to <TRADENAME> during pregnancy" while Lines 237-238 state "<Generic name of drug> is not absorbed systemically following (route of administration), and maternal use is not expected to result in fetal exposure to the drug." To clarify, we recommend the Guidance specify that either the "tradename or generic name" of the drug would be used as applicable or specifically state "tradename" or "Generic name of drug" for each statement throughout the Guidance.

G. Discontinued Products

In both the PLLR and the Draft Guidance document, it is unclear if the rule/guidance applies to product labels that are no longer marketed in the U.S. BIO requests clarification on this matter. BIO suggests that the guidance applies to the labels for products that are marketed in the United States beyond June 30, 2018.

H. Additional Formatting Considerations

In some cases throughout the Draft Guidance, sections are referenced only by name, while others are mentioned by both section number and name. For consistency and clarity, BIO recommends including both the section number and section name.

CONCLUSION:

BIO appreciates this opportunity to comment on the *Draft Guidance for Industry on Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products*. 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 J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

Biotechnology Industry Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
II. BACKGROUND		
Lines 73-78	The Draft Guidance makes mention of the complexity of risk-benefit decisions regarding use of a drug during pregnancy and the move to narrative summaries and data supporting those summaries as a labeling requirement. It may also be appropriate to acknowledge the complexity of interpretation of clinical and nonclinical pregnancy data in formulating the risk assessment.	BIO suggests that FDA clarify whether or not this reflects a general expectation that more data will be required overall to support the label.
Lines 95-96, 191	"…contraception is required or recommended before, during, or after drug therapy or when there are human or animal data that suggest drug-associated fertility effects." "…based on all relevant human data, animal data, and the drug's pharmacology…"	FDA should change "or" to "and/or" to match the text in the Regulation: "…contraception is required or recommended before, during, and/or after drug therapy or when there are human and/or animal data that suggest drug-associated fertility effects." "…based on all relevant human data, animal data, and/or the drug's pharmacology…"
III. GENERAL PRINCIPLES		
A. REVISING LABELING		
Lines 103-106	"Consistent with this requirement, when revising existing labeling…applicants should evaluate labeling content to ensure that it accurately reflects current knowledge."	BIO suggests revising the sentence to state: "Consistent with this requirement, when revising existing labeling…applicants should evaluate labeling content to ensure that it accurately reflects current knowledge based on systematic review of the available evidence."

SECTION	ISSUE	PROPOSED CHANGE
C. CROSS REFERENCING		
Lines 127-136	This Draft Guidance does not mention updating Section 17 – PATIENT COUNSELING INFORMATION except for in lines 182-184. When updating for PLLR, this is a section that the Sponsor should consider updating, along with HIGHLIGHTS, if applicable.	"Cross-referencing follows the general principles of the PLR. In most situations, the PLLR subsections of labeling will contain the detailed and most important information relevant to prescribing in the patient populations at issue. Other sections of labeling (e.g., CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS) may briefly present a topic addressed in the PLLR subsections and will cross-reference the more detailed discussion(s) in the PLLR subsections. For example, if a clinically significant drug-associated adverse developmental outcome warrants a contraindication in pregnancy, the CONTRAINDICATIONS section will list pregnancy as a contraindication with a brief description of the observed or anticipated consequences of using the drug during pregnancy and will cross-reference to USE IN SPECIFIC POPULATIONS (8.1) for details. The sponsor should also consider updating PATIENT COUNSELING INFORMATION as necessary when updating the label for the PLLR."
Lines 140-141	The cross-reference example "(*e.g.*, (*see Data*))" may be confusing since there may be two "Data" subheaders in the label: one under "Pregnancy" and one under "Lactation."	BIO suggests that the cross-reference should be more specific, *e.g.*, "See Pregnancy, Data" or "See Data relevant to clinical decision-making." (see comment below)
IV. SPECIFIC SUBSECTIONS		
A. 8.1 PREGNANCY		
Line 153	• "*Data*"	BIO recommends renaming this section "Data relevant to clinical decision-making." BIO also recommends clarifying that this section refers to study results, and providing an example. Finally, there

SECTION	ISSUE	PROPOSED CHANGE
		should be mention that this refers to both nonclinical and clinical data.
Lines 155-156	The statement "For the purposes of the PLLR…that are regulated as drugs" is noted as footnote 2 on page one of the Guidance.	BIO suggests deleting this sentence: "~~For the purposes of the PLLR and this guidance, the term drug or *drug* product is used to refer to human prescription drug and biological products that are regulated as drugs.~~ Because some drugs…"
1. PREGNANCY EXPOSURE REGISTRY		
Lines 163-165	"The purpose of including information on a scientifically acceptable pregnancy exposure registry in the **Pregnancy** subsection is to inform health care providers of the availability of a pregnancy exposure registry for a product."	BIO recommends appending this sentence as follows: "…exposure registry for a product, if applicable."
Lines 170-172	Pregnancy exposure registries for a particular drug are usually the result of a post-marketing commitment. However, many pregnancy exposure registries are diseased-based and not specifically sponsored by a particular drug (*e.g.*, anti-retroviral pregnancy registry, autoimmune disease registry). As the FDA endeavors to encourage participation in registries to improve their usefulness, a disease-based registry could help accomplish that goal.	"If there is a scientifically acceptable pregnancy exposure registry for the drug or disease/condition, the following statement…"
Line 180	"Where there is no pregnancy exposure registry, this subheading should be omitted." It is unclear if this section can be omitted if the registry is now closed.	If the intent for this section is to include open pregnancy registries, BIO recommends revising the sentence as follows: "Where there is no active or open pregnancy exposure registry, this subheading should be omitted."
Lines 182-184	The Draft Guidance here describes pregnancy exposure registries.	BIO believes that, if applicable, this section should include a reference to the Patients Information/Medication Guide.

SECTION	ISSUE	PROPOSED CHANGE
2. RISK SUMMARY		
Line 186	"2. Risk Summary" There appears to be a lack of language throughout this section referring specifically to post-marketing events. An additional concern is that the Draft Guidance does not address second and third generation effects of drugs.	BIO suggests including language around post-marketing events. We also recommend that language be included that addresses late-onset (generational) events and how they are to be labelled.
Line 189-191	Adequate human experience in terms of exposure in pregnancy and/or lactation should take precedence over available animal data in providing the basis of the risk assessment.	BIO requests clarification for the Risk Summary overview section on this issue.
Lines 195-196	"'Structural abnormalities' describes dysmorphology, which includes malformations, variations, deformations, and disruptions"	We recommend including definitions of malformations, variations, deformations and disruptions required agreement, especially deformations and disruptions which may not be common terminology, under structural abnormalities,.
Lines 199-200	In the description of functional impairment, broad categories of impairment are described (*e.g.*, endocrinopathy and neurodevelopment effects) along with the inclusion of a specific finding (deafness). The inclusion of a specific diagnosis (deafness) representing a sensory deficit seems out of place and less informative than if the broader category of "sensory deficit" was used.	BIO suggests "deafness" is replaced by "sensory deficits" or "sensory impairment."
Lines 201-202	"'Alterations to growth' describes such outcomes as growth restriction, excessive growth, and delayed and early maturation"	BIO suggests the Agency expand on this to include prior long latency fetal and generational abnormalities.

SECTION	ISSUE	PROPOSED CHANGE
	Considering we have seen prior long latency fetal abnormalities which have affected sexual maturity in the offspring, growth development may too narrow of a category.	
Lines 229-230	"When use of a drug is contraindicated during pregnancy, this information must be stated first in the Risk Summary."	BIO believes that this statement should be placed at the beginning of the section on Risk Summary, similar in placement to the Lactation section. Additionally, BIO requests additional guidance on how and why Sponsors would provide observed consequences for contraindicated drugs.
Lines 230-231	"A brief description of the observed or anticipated consequences should also be included."	For consistency, "consequences" should be changed to "adverse developmental outcomes": "A brief description of the observed or anticipated ~~consequences~~ adverse developmental outcomes should also be included."
Lines 233-234, 527-529	There are some routes of administration for which systemic exposure is expected to be very low, especially for large molecule therapeutics (*e.g.*, intraocular administration). Although systemic exposure may be so low as to not be clinically monitorable, it is difficult to prove that it has been completely prevented. These considerations may also apply for secondary exposure of partners of patients through genital contact/intercourse	BIO asks FDA to clarify the burden of proof in establishing a lack of systemic exposure.
Lines 251-257	"Determining whether pregnancy exposure data can establish a drug associated risk is a complex process that requires an assessment of the quality and quantity of available data. Human data may come from any of the following sources, depending on the particular study design:	BIO proposes including a positive confirmatory statement regarding that inclusion of human data meeting quality criteria, but is not from the USA, is acceptable for use in these new labels: "…Human data may come from any of the following sources,

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	• Clinical trials, • Pregnancy exposure registries • Other large scale epidemiologic studies"	depending on the particular study design: • Clinical trials, • Pregnancy exposure registries • Other large scale epidemiologic studies The human data need not be from US population provided it can be assessed to be of adequate quality (§314.106)." We also propose defining "other large scale epidemiologic studies" to include cohort, case-control, systematic reviews and meta-analyses.
Line 268	"Its incidence" True incidence of developmental outcomes may not be available.	BIO suggests changing "incidence" to prevalence or occurrence
Line 271	"The effect of gestational timing of exposure"	"Gestational timing of exposure" to be explicitly defined, (*e.g.*, by week, trimester, and/or critical period of organogenesis)
Lines 273-276	"If human data indicate that there is an increased risk for a specific adverse developmental outcome in infants born to women exposed to the drug during pregnancy, this risk must be quantitatively compared to the risk for the same outcome in infants born to women who were not exposed to the drug but who have the disease or condition for which the drug is indicated to be used."	BIO recommends specifying whether this is for either treated or untreated disease. Additionally, further guidance on risk for patients treated with other medications in combination with medication of interests would be helpful.
Lines 282-283	"Where there are no human data or the available human data do not establish the presence or absence of drug-associated risk, this must be stated in the Risk Summary."	BIO asks that FDA provides guidance on how drug-associated risk should be ascertained.

SECTION	ISSUE	PROPOSED CHANGE
Line 293	"b. Risk statement based on animal data"	BIO asks that FDA provide more clarity and an example on what is expected in this section. Additionally, we ask the Agency to provide specific descriptions of the expectations for the narrative Risk Summary wording. It is unclear whether there is an expectation to integrate non-clinical data in the manner suggested in the *Reproductive and Developmental Toxicities – Integrating Study Results to Assess Concerns* guidance.
Lines 299-302		BIO recommends the following additions to acknowledge a reasonable and feasible approach to animal testing that is also consistent with ICH S6(R1): • "The number and type(s) of pharmacologically relevant species affected • Timing of exposure (or indicate if continuous) • Animal doses expressed in terms of human dose or exposure equivalents • Outcomes for pregnant animals and offspring" Additionally, BIO suggests adding a footnote to indicate that studies would be limited to pharmacologically relevant species for highly targeted molecules with no expected off-target effects.
Lines 304-306	"The risk statement must state when animal studies do not meet current standards for nonclinical developmental toxicity studies, or when there are no animal data (§201.57(c)(9)(i)(B)(2)." It is unclear what is meant by meeting "current standards for nonclinical developmental toxicity studies." There could be circumstances in which a portion of a relevant study did not meet the	BIO recommends the Agency clarify and provide an example to help Sponsors understand this overly broad statement.

SECTION	ISSUE	PROPOSED CHANGE
	standards outlined in the cited references, and yet the study outcome could be meaningful in evaluating risk. It is also unclear how in-depth this risk statement needs to be.	
Line 308	"Toxic drug exposure may manifest as one type of developmental effect (*e.g.* embryo-lethality) in an animal species, but a different type of developmental effect (*e.g.*, structural abnormality) in humans."	BIO suggests modifying the sentence as follows: "Toxic drug exposure may manifest as one type of developmental effect (or no effect) (e.g. embryo-lethality) in an animal species, but a different type of developmental effect (e.g., structural abnormality) in humans."
Lines 310-313	Adverse developmental toxicity outcomes are generally more concerning where there is an absence of maternal toxicity or when they occur in more than one animal species.	BIO requests clarity around the statement "FDA does not believe it is possible to conclude that a drug causes an increased risk of a particular type of developmental effect based on animal data alone." For example, combination of animal data and/or pharmacology data alone may be sufficient to determine human risk. Additionally, BIO suggests including the following: "An adverse developmental outcome is more concerning when the outcome occurs in more than one animal species, especially if the outcome is consistent across species and occurs in the absence of maternal toxicology." We also recommend additional wording that clarifies that findings in one species may still be a concern. Less experienced sponsors may be led to believe that more developmental toxicity studies are better. Finally, we recommend including mechanism of action as a basis for concluding that a drug may cause a particular developmental effect (*e.g.*, VEGF-inhibitor acting as an anti-

SECTION	ISSUE	PROPOSED CHANGE
		angiogenesis agent may cause "physeal dysplasia" in fetal development.
Lines 315-328	The Draft Guidance states that "When the drug has a well-understood pharmacologic mechanism of action that may result in adverse developmental outcomes, the Risk Summary must explain the mechanism of action and the potential associated risk…For other drugs, the concern may be based on biologic plausibility…" By the time of marketing approval, most drugs will have a well understood pharmacologic mechanism of action. The use of phrases such as "may result in" and "biologic plausibility" are overly broad and will likely result in most drugs falling into this category and requiring a risk statement based on pharmacology, even when animal data is negative for developmental toxicity. If the developing embryo/fetus contains the drug target, which would have to be assumed without data confirming otherwise, and there is placental transfer of the drug, it would be biologically plausible that the drug "may cause" an adverse developmental outcome. Furthermore, without sufficient human data confirming a lack of developmental toxicity, it would be prudent to assumed that a new drug "may cause" an adverse developmental effect. If most drugs require a pharmacology risk statement communicating a theoretical risk, the value of this risk section will be limited and counter to the goal of	BIO recommends that FDA provide clarifying guidance on when a pharmacology risk statement is required, definition and application of phrases such as "may result in," and application of this section in light of nonclinical developmental toxicity data indicating no adverse developmental findings. BIO also asks for additional clarity on whether to include or exclude pharmacology information when the pharmacology suggests no predicted risk, and an example of specific wording would be beneficial. Much of the text in the first two sentences of the paragraph is redundant. We suggest editing the second sentence (Lines 319-322) to read: "When the drug or drug class has a well-understood pharmacologic mechanism of action that may result in drug or drug class-associated adverse developmental outcomes, the Risk Summary must explain the mechanism of action and the potential associated risks. ~~In addition, the Risk Summary should explain the mechanism of action and potential associated risks when there is a well-understood pharmacologic mechanism of action that may result in drug-class associated adverse developmental outcomes.~~" BIO also suggests the following change in Line 326: "If applicable, a cross-reference should be provided to CLINICAL PHARMACOLOGY…"

SECTION	ISSUE	PROPOSED CHANGE
	informing patients and physicians. In situations where the nonclinical animal data are negative for developmental toxicity, a positive pharmacologic risk statement based on vague criteria for "may result in" or based on biological plausibility, could lead to confusion. More clarity on the course of action when there is adequate information on the pharmacology of the drug and there is little or no predicted risk is needed, such as whether this section needs to be omitted or included. If there is no signal in animal data and no predicted pharmacologic risk, this would aid in overall characterization of risk to humans.	Finally, BIO recommends adding one or more drug class example that includes class knowledge for antibody therapeutics at the end of the paragraph: "For example, monoclonal antibodies are known to cross the human placenta during development and fetal exposure should be expected; potential developmental effects may be anticipated based on the understanding of the target biology during development. While we acknowledge an expected low transfer during organogenesis, we cannot say the fetus is not exposed to therapeutic antibodies during pregnancy."
3. CLINICAL CONSIDERATIONS		
Line 331	"3. Clinical Considerations"	BIO suggests that FDA include statements on where this information should come from (*e.g.*, types of studies, published only, etc.)
Line 335	"Considerations subheading is presented under the following five headings…"	For consistency, we suggest the following change: "Considerations subheading is presented under the following five subheadings…"
Lines 344-345	"Headings should be omitted if there are no data to inform them or the available data are not informative."	BIO believes it would be helpful to discuss the criteria being used to determine whether there are no available informative data, and the criteria should be consistent with Line 282. BIO also suggests the following edits: "Subheadings should be omitted if there are no data to inform them or the available data are not informative."

SECTION	ISSUE	PROPOSED CHANGE
Lines 372-377	The Guidance recommends including information in the label if the drug is primarily metabolized by a P450 enzyme with well-documented activity changes in pregnancy. However, P450 changes alone may not be clinically relevant or require a dosage change. Other pharmacokinetic changes in pregnancy (*e.g.*, altered Vd, intrinsic clearance, etc.) could impact the overall PK of the drug.	BIO recommends removing this example, or to provide additional guidance on when to include P450 changes (*e.g.*, only if a dosage alteration should be considered).
Lines 377-378	In some cases, drug levels may be measured in plasma or blood instead of serum in order to determine systemic exposures.	BIO suggests modifying the sentence as follows: "...this subsection should include this information and inform the prescriber that this change may affect ~~serum~~ systemic drug levels in the pregnant woman."
4. DATA		
Lines 429 to 443	"Labeling must describe the data regarding adverse developmental outcomes, adverse reactions, and other adverse events, and must include the following elements…exposure information (timing, duration, and dose of exposure)" This can be interpreted that both negative and positive results be included. In the context of multiple clinical trials, inclusion of all such data might be voluminous.	BIO recommends that the Guidance allow the sponsor to best determine the appropriate data to be included in the label.
Lines 434-442	"This portion of labeling must describe the data regarding adverse developmental outcomes, adverse reactions, and other adverse effects, and must include the following elements…"	BIO suggests including the following text as an additional bullet: "Description of comparison group (treated or untreated controls, general population, etc.)" Additionally, the bullet on "Data Source" (Lines 437-438)

SECTION	ISSUE	PROPOSED CHANGE
		should be consistent with examples provided on Line 257.
Line 444	"Individual case reports"	BIO recommends FDA to articulate in what case(s) case report would be appropriate for inclusion in this section.
Lines 465-468	"Descriptions of maternal and offspring findings must include dose-response and severity of adverse developmental outcomes (§201.57(c)(9) (i)(D)(4)). However, for vaccines, developmental toxicity studies do not include dose-response evaluations and, therefore, the descriptions of maternal and offspring outcomes will be different for such products." For vaccines, no dose response is required. Many biopharmaceuticals with a long half-life and essentially continuous exposure during pregnancy may fall in a grey zone resulting in no clear dose-response at the dose levels tested. In some cases, a single dose level may be tested in a single species. It may not be feasible or appropriate to define an no-observed-adverse-effect level in pregnancy, especially if it requires going below clinically relevant exposures.	BIO suggests modifying the sentence as follows: "Descriptions of maternal and offspring findings must include dose-response or relationship when present and severity of adverse developmental outcomes (§201.57(c)(9)(i)(D)(4)). However, for vaccines and potentially other more advanced therapies such as cell therapies, developmental toxicity studies do not include dose-response evaluations and, therefore, the descriptions of maternal and offspring outcomes will be different for such products."
Lines 470-488	It is confusing to include the interpretive guidance that derives the risk assessment under 'Animal Data' section. This section should only include the data that derives the risk statement. It is more appropriate to include the interpretive guidance within the section of the 'Risk Statement Based on Animal Data' as that section needs an interpretive narrative of the non-clinical data.	BIO suggests moving the information on how to interpret non-clinical data for risk assessment to the section on "Risk Statement based on animal data" (Line 293)

SECTION	ISSUE	PROPOSED CHANGE
Lines 470-471, 482	"In evaluating and interpreting nonclinical data, various factors may affect the level of concern raised by a positive signal."	BIO also suggests that the Agency clarify the term "positive signal."
Line 471	"These factors include…"	BIO suggests including "Cross-study concordance" to the bulleted list (Lines 473-483)
Line 479	Lines 317-319 state "When the drug has a well-understood pharmacologic mechanism of action that may result in adverse developmental outcomes, the Risk Summary must explain the mechanism of action and the potential associated risks (§ 201.57(c)(9)(i)(B)(3))." However, Line 479 only asks for "Similarity between pharmacologic and developmental toxicologic mechanisms"	For clarity and agreement between Line 479 and Lines 317-319, BIO proposes the following change: "~~Similarity between pharmacologic and developmental toxicologic mechanisms~~ Pharmacological mechanism(s) of action and potential associated risks on development."
Line 482	"Presence or absence of maternal toxicity"	BIO suggests the following change: "Presence or absence of maternal toxicity in the presence of developmental toxicity.
Lines 487-488	"…see FDA's guidance for industry, *Reproductive and Developmental Toxicities – Integrating Study Results to Assess Concerns*.	BIO suggests including a footnote reference to the guidance.
B. 8.2 LACTATION		
Lines 504-505	The current wording of the last sentence suggests that studies providing human breast milk concentration data for all forms of drug are required. It could be interpreted to mean that measurement of all moieties of drug-related material (i.e., parent drug, prodrug, and active metabolite(s)) in human breast milk is required.	BIO suggests changing the sentence to read as follows: ~~"It is assumed that drug levels in human breast milk will be collected on the drug, prodrug and the active metabolite(s).~~ When measurement of drug-related material in human breast milk is performed, it is assumed the analysis will include detection of the pharmacologically important forms of the drug (*e.g.*, parent drug, prodrug, and active metabolite(s))."

SECTION	ISSUE	PROPOSED CHANGE
1. RISK SUMMARY		
Lines 543-546, 574-575	"The Risk Summary must state whether the drug and/or its active metabolite(s) are present in human milk (§ 201.57(c)(9)(ii)(A)(2)(i)), and should include a brief description of the available data. If there are no data to assess the presence or absence of a drug and/or its active metabolite(s) in human milk, the Risk Summary must so state (§ 201.57(c)(9)(ii)(A)(2)(i))." For drugs that are of a known class/platform, a Sponsor may have data from previous compounds that allow them to draw conclusions for new molecular entities. For example, monocloncal antibodies that are of the same IgG subtype would be expected to end up in human milk similarly. The use of such data on earlier compounds should be encouraged. In addition, is pharmacologic modeling adequate to predict the presence of the drug and/or its active metabolites in human milk? (see the above example of the IgG subtype being expected to be present in milk)	BIO suggests FDA provide more clarity around the presence of the drug or its active metabolites in human milk, such as whether or not this is a qualitative or quantitative assessment, or both? BIO also suggests FDA consider the acceptability and encourage Sponsors to use data from earlier compounds to help them draw conclusions for NMEs. Additionally, clinical pharmacology modeling would be a good tool for predictability.
Lines 552-556	"…the Risk Summary must include the concentrations in human milk and the actual or estimated infant daily dose (§ 201.57(c)(9)(ii)(A) (2)(i))." Rather than referencing the section of the rule in which the infant milk dose calculations are presented, it would be helpful if the calculations for infant milk	BIO recommends that FDA includes the calculations for and estimations of infant milk dose in the text of the Guidance.

SECTION	ISSUE	PROPOSED CHANGE
	dose are presented in the Guidance.	
Lines 583-586	"If only animal lactation data are available, the Risk Summary must state only whether or not the drug and/or its active metabolite(s) were detected in animal milk and specify the animal species (§ 201.57(c)(9)(ii)(A)(2)(i)), with a cross-reference to the Data portion of Lactation (§ 201.57(c)(9)(ii)(A)), where the data are fully described (§ 201.57(c)(9)(ii)(C)). Due to species specific differences in lactation physiology, animal lactation data do not reliably predict levels in human milk; however, animal lactation data can be helpful in predicting whether a drug and/or its active metabolite(s) will be present in human milk." For some molecules, there may be plasma exposure data in suckling pups, but no milk excretion data from the maternal animal. The Draft Guidance infers that these suckling pup data are not to be included in the lactation subheading; however, in some circumstances, such data may be important for detecting a potential risk for the breastfed child.	BIO suggests the Guidance include instruction on whether and how to include such data. Additionally, BIO suggests the addition of the following: "Due to species specific differences in lactation physiology, animal lactation data do not reliably predict levels in human milk; however, when not already established for a drug class, animal lactation data can be helpful in predicting whether a drug and/or its active metabolite(s) will be present in human milk."
Lines 590-602	The Guidance discusses the effects of the drug on the breastfed child.	In the absence of any information on breastfed children, BIO suggests including available animal data, including suckling pup exposure and adverse effects detected in those pups.
Lines 595-596	"Pediatric age-related differences in absorption, distribution, metabolism, and elimination of the drug should also be include."	BIO suggests amending the sentence as follows: Pediatric age-related differences in absorption, distribution, metabolism, and elimination of the drug should also be included when available.

SECTION	ISSUE	PROPOSED CHANGE
3. DATA		
Lines 674-675	"The Data subheading must describe the data on which the Risk Summary and Clinical Considerations are based (§ 201.57(c)(9)(ii)(C))."	For concordance with Lines 514-516, we suggest the following edit: "The Data subheading must describe the human and/or animal data on which the Risk Summary and Clinical Considerations are based (§ 201.57(c)(9)(ii)(C))."
C. 8.3. FEMALES AND MAKES OF REPRODUCTIVE POTENTIAL		
Line 680	If class labeling (such as with antiretrovirals) regarding avoiding transmission of disease by advising to not have sex without protection is present, it is unclear if Section 8.3 should be omitted. Additionally, as this section is referring to contraception, it is logical to cross reference to appropriate sections that include information on drug-drug interaction with birth control options.	BIO asks for further clarification on the relevance of Section 8.3
Line 682	The information on the new "8.3 Females and Males of Reproductive Potential" section should have further clarification, especially for drugs with a contraindication to pregnancy and/or a black box warning.	BIO requests further clarification, especially on whether or not summary statements or any specific instructions should be given in these sections of the label.
Line 684-686	"…(2) there are human and/or animal data suggesting drug-associated effects on fertility and/or pre-implantation loss effects (§ 201.57(c)(9)(iii)."	BIO suggests appending the sentence as follows: "…(2) there are human and/or animal data suggesting drug-associated effects on fertility and/or pre-implantation loss effects (§ 201.57(c)(9)(iii). Note that if fertility data are only available from nonhuman primates (e.g., for biotechnology-derived products where there is a lack of pharmacologic relevance in rodents), there will be limited to no animal data regarding pre-implantation loss effects."

SECTION	ISSUE	PROPOSED CHANGE
Lines 693-694	"As applicable, the information required under this subsection must appear under the following subheadings, in the following order: • Pregnancy Testing • Contraception • Infertility"	BIO suggests including subsections for males and females under "contraception" and "fertility": "As applicable…in the following order: • Pregnancy Testing • Contraception o Females o Males • Infertility o Females o Males"
Lines 696-697	"If data suggest no adverse effects on fertility, this information should be presented under Infertility." It would seem that if there are no adverse effects on fertility that should not be associated with infertility.	BIO asks that the Agency provides more clarity on whether "no adverse effects on fertility" is referring to human, animal data or on predictive information based on pharmacology.
Lines 699-700	"If data from animal studies raise concerns about mutagenesis or impairment of human fertility in females or males…"	BIO suggests the following change: "If data from animal and/or human studies raise concerns about mutagenesis or impairment of human fertility in females or males…"
Line 704	In all the previous sections, the Draft Guidance clarifies the situations in which subheadings can be omitted (for example, when there is no pregnancy exposure registry or no data). This is not the case for section 8.3. It is implied that if there is no requirement for pregnancy testing or contraception, these subheadings can be omitted, although this is not stated.	"~~A~~ relevant subheading should be omitted ~~if not applicable. Subsection 8.3 should be omitted if none of the subheadings are applicable~~ if there are no recommendations or requirements for pregnancy testing and/or contraception before, or no data on fertility."

SECTION	ISSUE	PROPOSED CHANGE
	It is not clear what should be stated in the infertility subsection if there are no data on fertility, or if there has been no systematic evaluation of the effects on fertility. If these apply, should this subsection be omitted? The Draft Guidance indicates that a statement on infertility should be included if there are effects or the data suggest there are no effects on fertility, so the circumstances in which this subheading should be omitted are not clear.	
Lines 704-705	When section 8.3 is omitted, the following sections numbered should still begin with 8.4	"Subsection 8.3 should be omitted and not listed, if none of the subheadings are applicable."
V. PROCEDURAL INFORMATION		
A. APPLICATIONS COVERED BY THE FINAL RULE		
Lines 721-722	The requirements for labels that were approved prior to June 30, 2001, but were voluntarily converted to PLLR (those not subject to PLLR) are unclear.	BIO suggests the Agency provide a statement that outlines the PLLR requirements for labels voluntarily converted according to PLLR.
Lines 721-723, 753-756	The text in these two places is redundant.	BIO suggests deleting Lines 721-723
B. SUBMITTING DRAFT LABELING TO FDA FOR REVIEW		
Lines 733-734	Additional clarity would be helpful to understand whether the Agency prefers that these submissions generally not be combined with other supplements/labeling updates.	BIO asks that the Agency provide additional clarity.
Line 741	"Labeling in the old format"	BIO suggests deleting this bullet, as this would be the current approved label and is available to reviewers as well as can be viewed in the marked-up version
Line 746	"Microsoft Word versions of all the above"	BIO suggests deleting this bullet, as Sponsors will continue to make submissions as usual practice and this does not

SECTION	ISSUE	PROPOSED CHANGE
		allow for annotated pdfs which are often provided.
Lines 747	Structured Product Labeling is usually submitted with the prior approval supplements.	BIO suggests including the following as the final bullet: "Structured Product Labeling that complies with the PLLR content and format requirements"
C. WAIVERS		
Line 759	"C. Waivers"	BIO asks that the Agency elaborate on what sorts or situations would allow for a waiver.
APPENDIX A. ORGANIZATION AND FORMAT FOR PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCIVE POTENTIAL SUBSECTIONS		
Lines 781, 803	"Risk Summary (required subheading)"	BIO asks FDA to clarify whether a risk summary may be applicable based only on expected pharmacology and established drug class effects even in the absence of product-specific human or animal data for pregnancy and/or lactation.
Line 807	"Data (omit if not applicable)"	BIO recommends FDA specify human and/or animal data.
APPENDIX B: IMPLEMENTATION PLAN		
Line 819	"Implementation Plan" Table	For completeness, BIO suggests amending the table to include products not subject to the PLLR, but still have the requirement to remove the "Pregnancy" category within three years