September 27, 2020

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

Re: Docket No. FDA-2014-D-1551: FDA Draft Guidance, Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance, Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.

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 appreciates the Agency's inclusion of the pregnancy registry and the risk summary in the label to ensure awareness and encourage Health Care Provider (HCP)-patient conversations. BIO has two overarching comments on this guidance. Firstly, it is not clear from the guidance whether sponsors can utilize the pregnancy and lactation data as supportive safety data generated from other drugs that are in the same drug class or possess the same drug molecular structure with representative justification. It would be helpful if the Agency could provide clarification as to whether this data would be accepted to demonstrate safety for pregnant and lactating women. Secondly, since pregnancy studies and lactation studies are rarely conducted pre-approval and given the Agency's prioritization of initiatives focused on use of real world evidence, it would be helpful if the Agency could provide recommendations on utilizing post-marketing real world data to support labeling updates for pregnancy and lactation sections. BIO has included in this letter several comments and recommendations for FDA's consideration in finalizing this guidance.

Listing Non-Sponsor Registries

BIO believes that the registry's listed should be limited to those registries which are endorsed/sponsored or accepted by the sponsor. In some therapeutic areas, there are registries that are not endorsed or sponsored by the drug developer, but that capture drug exposure information. These registries that are not endorsed or sponsored by the drug

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

developer may be scientifically meaningful but uninformative in relation to the specific product concerns and therefore may be confusing to patients and providers if listed.

Specifically, data captured in registries that are not endorsed or sponsored by the drug developer is often not collected in a way that:

- Meaningfully or measurably informs understanding of benefit-risk profiles rendering the data uninformative to meet FDA needs/ requirements.
- Ensures/ enables rigorous and consistent application of inclusion criteria for patients/ pregnancies in a prospective manner consistent with the sponsor's registry.
- Enables data to be combined with patients from other registries with the same data elements and units of measures such that an analysis of data can occur with multiple sources.
- Ensures that consent for registry participation by registry participants and curators include the sharing, analysis, and reporting of data by a designated partner and with the product sponsor.
- Enables deduplication of patients in a multi-source analysis.

Listing non-sponsor registries in addition to the one for which the sponsor is accountable could mean the many patients unknowingly choose to enroll in a non-sponsored registry where data collected does not adequately inform the safety risk-benefit profile or is inaccessible for the necessary analysis. Third party registries also may have financial support/resourcing models that are not tied to the oversight of a sponsor and can be terminated (or qualitatively diminished) for reasons outside of the sponsor's control, potentially jeopardizing the sponsors ability to fulfill requirements or inform patients/ HCPs about pregnancy related safety.

For these reasons, BIO advocates for the presentation of only sponsored or "authorized" registries that are supported in a way that ensures fulfillment of regulatory commitments in a drug label. BIO encourages the Agency to keep inclusion of the sponsor's designated registry(ies)/study(ies) in the final guidance.

BIO appreciates this opportunity to submit comments regarding FDA's Draft Guidance, Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/
Camelia Thompson, Ph.D.
Senior Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

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

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 16-55	The guidance states, "This guidance is intended to assist applicants in complying with the content and format requirements for the *Pregnancy, Lactation,* and *Females and Males of Reproductive Potential* subsections of labeling for human prescription drug and biological products." The guidance does not address if sponsors will be required to update existing labeling to reflect the new recommendations.	BIO requests that the Agency clarify if sponsor companies will be required to update existing labeling to reflect the new recommendations.
II. BACKGROUND		
Lines 91-94	The guidance states, "Instead of pregnancy letter categories, under the PLLR, narrative summaries of the risks of a drug during pregnancy and discussions of the data supporting those summaries are required in labeling to provide more meaningful information for health care providers." This statement seems to apply to different sections throughout the guidance and not just the current section. It needs to be clarified that lactation is included in this statement.	BIO recommends the following edit to clarify that lactation is included: "Instead of pregnancy letter categories, under the PLLR, narrative summaries of the risks of a drug during pregnancy **and lactation** and discussions of the data supporting those summaries are required in labeling to provide more meaningful information for health care providers."
III. General Principles		
Revising Labeling		
Lines		
Formatting		
Lines		
Cross-Referencing		
Lines		
Omitted Information		
Lines 166-171	The guidance states, "In some circumstances applicants must omit certain subsections or specific	BIO recommends that the Agency consider including a Risk Summary statement as the information would assist in

SECTION	ISSUE	PROPOSED CHANGE
	information otherwise required under the PLLR because it is clearly inapplicable or misleading. For example, if a drug is indicated for use only in neonates, an applicant must omit subsections *Pregnancy* and *Lactation* because this information is clearly inapplicable. The applicant should provide to the Agency the rationale and justification for any proposed PLLR labeling omissions of subsections, heading, subheadings, or specific information required under the PLLR." On the FDA website (https://www.fda.gov/drugs/labeling-information-drug-products/outline-section-81-83-drug-labeling), the agency indicates that, in Section 8.1 Pregnancy and 8.2 Lactation, the subheading "Risk Summary" is a required section under the PLLR, which seemingly contradicts what the guidance says may be omitted.	counseling patients appropriately when accidental or inappropriate exposure of a medicine occurs, including in a population different than that in which the medicine is currently indicated.
IV. SPECIFIC SUBSECTIONS		
8.1 Pregnancy		
Line 186	The guidance labels this section heading as, "1. Pregnancy Exposure Registry". It is unclear if this section also refers to other post-approval pregnancy safety studies.	BIO requests that the Agency clarify if the scope of this section includes other post-approval pregnancy safety studies (e.g., single arm pregnancy safety study) and whether the section heading needs to be changed if other post-approval pregnancy studies are discussed.
Lines 186-216	This section of the guidance includes listing of non-sponsor registries. Registries may be scientifically meaningful but uninformative in relation to the specific product concerns. Hence, patients could	BIO recommends that the Agency consider supporting only sponsored or "authorized" registries that are supported in a way that ensures fulfillment of regulatory commitments in a drug label.

SECTION	ISSUE	PROPOSED CHANGE
	unknowingly choose to enroll in a non-sponsored registry where data collected does not adequately inform the safety risk-benefit profile or is inaccessible for the necessary analysis. Similarly, third party registries have financial support/resourcing models that are not tied to the oversight of a sponsor and can be terminated (or qualitatively diminished) for reasons outside of the sponsor's control, potentially jeopardizing the sponsors ability to fulfill requirements or inform patients or Health Care Providers (HCPs) about pregnancy related safety. The guidance states that, "Applicants may also consider including the contact information for other pregnancy safety studies that are enrolling patients." It is not clear what 'other pregnancy safety studies' the guidance is referring to. It is also unclear as to what specific 'contact information' should be included.	BIO requests that FDA clarify the types of "other pregnancy safety studies" that the guidance is referring to and provide criteria for when sponsors should consider including these other studies. BIO recommends that the Agency cross-reference Footnote 15 FDA guidance *Postapproval Pregnancy Safety Studies (May 2019)* to highlight post-approval pregnancy safety studies. BIO also requests that the Agency provide specific details about the type of contact information that should be included, such as name, address, and contact phone number.
Lines 200-216	The guidance states that "Contact information for how to enroll in the registry or obtain information on the registry must also be included…" and that "Applicants may also consider including the contact information for other pregnancy safety studies that are enrolling patients." The guidance also highlights that the labeling should "…include a cross-reference to the *Pregnancy* subsection for the contact information for how to enroll." Finally, the guidance states that, "When a registry is closed or there are changes to the contact information of an existing registry, the labeling must be updated." The contact information is not available at the time of drug	BIO appreciates that the Agency has included contact information in the guidance. BIO recommends that the Agency consider adding a statement on the existence of a pregnancy registry requirement or commitment to be updated within a certain period of the protocol approval by FDA.

SECTION	ISSUE	PROPOSED CHANGE
	approval as protocols per Biologics License Application (BLA) requirements and subsequent operational details would not yet be established.	
Lines 218 – 276	The guidance states that, "If a drug is systemically absorbed, the labeling under the Risk Summary heading must include information about the background risk of major birth defects and miscarriage in the U.S. general population, regardless of drug exposure. Because there is no single comprehensive birth defect surveillance program in the United States, various population-based data sources have been used to estimate the overall prevalence of major birth defects, including the Metropolitan Atlanta Congenital Defects Program and the Texas Birth Defects Registry. These programs vary in methods of ascertainment and goals and objectives. Additional factors that may affect the birth defect rate include maternal age, race/ethnicity, and gestational age." For general and disease population, it is most helpful if this data is standardized by the FDA. Disease population pregnancy outcomes are relevant and often unavailable. The presentation of data from studies that are not population based may be misleading, which means significant context would need to also be presented in the label. The Center for Disease Control and Prevention (CDC) highlights other factors that may also affect the birth defect rate: certain medical conditions, such as being obese or having uncontrolled diabetes before and during pregnancy; family history.	BIO appreciates that the Agency has addressed requirements of the Risk Summary and that the background population risk must be included. BIO recommends that the Agency consider standardizing the background population risk information. BIO requests that the Agency standardize the background population risk information and provide the source as a reference for the information. BIO also requests that the Agency consider the location of the information - is the US label the optimal place to provide this information. BIO suggests the following edits: "Additional factors that may affect the birth defect rate include maternal age, race/ethnicity, ~~**and**~~ gestational age, **certain medical conditions such as obesity or uncontrolled diabetes before and during pregnancy, and family history**."

SECTION	ISSUE	PROPOSED CHANGE
Lines 248-249	The guidance states that, "The risk statement(s) based on animal data may differ from the risk statement(s) based on human data." This statement seems out of place.	BIO suggests deleting this sentence since details are further addressed in the guidance in lines 349-356. ~~**"The risk statement(s) based on animal data may differ from the risk statement(s) based on human data."**~~
Lines 254-256	"When use of a drug is contraindicated during pregnancy, this information must be stated first under the Risk Summary heading. A brief description of the observed or anticipated consequences of the contraindicated use should also be included." It is unclear if the contraindication will cross-reference section 8, like a Warning.	BIO requests that the Agency clarify if the contraindication will cross-reference section 8.
Lines 304-306	The guidance states, "A well-documented case series may also support a statement about fetal risk in particular situations, such as detection of a structural abnormality that is rare in the general population but occurs with relatively high frequency among exposed fetuses and infants." The presence of a well-documented case series is not equivalent to strong evidence of an association or causality. Case series are often with the absence of the presentation of patients with the exposure lacking the identified outcome. The risks remain uncharacterized.	BIO recommends that the Agency consider adding language that specifies the quality, quantity, and general recommendations for inclusion of case series in the label that would apply to all suggestions of inclusion of case series reports.
Lines 322-324	The guidance states that, "When risk information is not available for women with these condition(s), the risk for the specific outcome in women exposed to the drug during pregnancy must be compared to the rate at which the outcome occurs in the general population." Presenting general population data	BIO recommends that the Agency consider requiring that the label state that disease-specific risk information is not available. BIO also requests that the Agency clarify if these comparisons to unexposed patients with disease can be derived from rates found in the literature as well.

SECTION	ISSUE	PROPOSED CHANGE
	comparisons may mean that outcomes (whether favorable or unfavorable) among patients exposed to the product may be inappropriately viewed as related to product. A lower frequency of an outcome in product-exposed pregnancies does not mean that the product may have a protective effect.	
Line 343	The guidance states, "Animal doses expressed in terms of human dose or exposure equivalents". It is much more scientifically robust to perform comparison of animal dose to humans based on exposure only (not dose equivalents).	BIO suggests the following edit: "Animal doses expressed in terms of **human** ~~**dose or**~~ exposure equivalents"
Lines 414-424	The guidance states, "The labeling under the Maternal Adverse Reactions subheading must provide a summary of drug-associated adverse reactions that are unique to pregnancy or occur with increased frequency or severity in pregnant women, and should include appropriate cross-references to other sections of labeling (e.g., WARNINGS AND PRECAUTIONS, ADVERSE REACTION) for additional information. If clinical interventions are available to help monitor or mitigate drug-associated maternal adverse reactions, these interventions must be described under this subheading of labeling (e.g., monitoring blood glucose for a drug that causes hyperglycemia in pregnancy). If known, the effect of dose, timing, and duration of exposure on the maternal risk of these adverse reaction(s) must be included." Maternal and fetal adverse reactions can become part of the safety profile and impact inclusion of safety sections in the overall product profile.	BIO requests that the Agency clarify that maternal and fetal adverse reactions can become part of the safety profile and impact inclusion of safety sections in the overall product profile.

SECTION	ISSUE	PROPOSED CHANGE
Line 498	The guidance states, "Dose, duration, and timing of exposure". Timing of exposure may not always be known; it may be more appropriate to state extent of exposure and include plasma concentrations (at least maternal).	BIO suggests the following edit: "Dose, duration, **and ~~timing~~ extent** of exposure, **(at least maternal concentrations) ~~plasma concentrations~~**"
8.2 Lactation		
Lines 529	The guidance states, "The PLLR uses the term lactation to refer to the biological state during which a woman's body produces and **excretes** milk." Rather than "excretes" milk this should state "secretes" milk. Unlike urine and feces, milk is not a waste product.	BIO suggests the following edit: "The PLLR uses the term lactation to refer to the biological state during which a woman's body produces and **~~excretes~~ secretes** milk."
Lines 579-581	The guidance states, "The actual or estimated infant daily dose must be calculated for an infant fed exclusively with human milk and compared to the labeled infant or pediatric dose (if available) or the labeled maternal dose." There are several methods for estimating or calculating infant doses, some more accurate than others. It would be good to state that maternal area under the curve, AUC, value should be used when available to calculate the amount of drug in milk. Maximum concentration, Cmax, has previously been used, but this can overestimate the amount of drug that is delivered to the infant. The relative infant dose compared to maternal dose is can also be provided in percent, and a general rule of thumb is that a drug with a relative infant dose < 10% of the maternal dose is safe to use, the relative infant dose	BIO recommends the following edit: "The actual or estimated infant daily dose must be calculated for an infant fed exclusively with human milk and compared to the labeled infant or pediatric dose (if available) **~~or~~ and** the labeled maternal dose **(relative infant dose, RID). The average value of milk ingestion for exclusively breastfed infants of 150 ml/kg/day can be used to calculate relative infant dose. The area under the curve, AUC, of drug in maternal milk/plasma, rather than the Cmax, is recommended to be used to get the most accurate estimate of amount of drug delivered to the infant."**

SECTION	ISSUE	PROPOSED CHANGE
	compared to the maternal dose should be stated – as this is a standardized method of relating the infant dose to the maternal dose and is a clinically useful value (rather than comparing to the labeled infant or pediatric dose). FDA should clarify preferred methods of measurements.	
Lines 605-610	The guidance states, "If only animal lactation data are available, the labeling under the Risk Summary heading must state only whether or not the drug and/or its active metabolite(s) were detected in animal milk and specify the animal species, with a cross-reference to the Data heading within the Lactation subsection. Drug levels from 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." This paragraph suggests that collection of animal lactation data is encouraged. However, drug concentrations in milk from animal studies is rarely measured anymore (e.g. for biologics the answer is routinely the same <0.1%).	BIO recommends that the Agency clarify the limitations of using animal lactation data to predict whether a drug and/or its active metabolite(s) will be present in human milk.
Lines 630-631	The guidance states, "The labeling under the Risk Summary heading must describe the effects of a drug and/or its active metabolite(s) on human milk production, if such data are available." This does not account for drugs that can increase milk production due to the physiological mode of action, e.g., drugs that increase prolactin will result in increased milk production.	BIO recommends that following edit: "The labeling under the Risk Summary heading must describe the ~~effects~~ **increase or decrease** of a drug and/or its active metabolite(s) on human milk production, if such data are available."

SECTION	ISSUE	PROPOSED CHANGE
Lines 697-699	The guidance states, "A description of available interventions for monitoring and mitigating drug adverse reactions in the breastfed child, which were described in the labeling under the Risk Summary heading, must be provided in the labeling under the Clinical Considerations subsection." This statement as written is ambiguous for sponsors.	BIO recommends that the Agency clarifies what interventions the Agency is referring to.
8.3 Females and Males of Reproductive Potential		
Lines 769-772	The guidance states, "If there are pharmacokinetic studies of semen that inform contraception recommendations, a summary statement of pertinent findings and recommendations should be included under the Contraception heading, followed by a cross-reference to the *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section for a more detailed study description." Based on FDA's response to comment 89 in the final PLLR rule, information about partner exposure should be included in section 8.3.	BIO recommends that the Agency provide further clarification and include maternal exposure via partner during pregnancy and lactation.
Lines 787-788	The guidance states, "The availability of human data that demonstrate adverse effects of drug exposure on male or female fertility must be described under the Infertility heading." Potential drug effects on fertility can be negative or positive, and drugs that are not indicated for infertility treatment can still have positive effects on fertility and thus potentially increase chance for pregnancy, e.g. weight loss with GLP-1RAs can lead	BIO recommends that the Agency provide clarification on if and where information on any potential increase in fertility potential should be included. If the information is to be included, the Agency should also provide clarification on the inclusion of a statement on the potential need for contraception when using the drug in question.

SECTION	ISSUE	PROPOSED CHANGE
	to improved fertility and ovarian function, leading to increased risk of (wanted or unwanted) pregnancy.	
V. PROCEDURAL INFORMATION		
Applications Covered by the Final Rule and Implementation		
Lines		
Submitting Draft Labeling to FDA for Review		
Lines 868-884	The guidance states, "If applicants believe the information is not applicable, they should provide justification. Otherwise, this information should be in Module 1 of the eCTD." It is unclear whether the information should be provided in a specific format.	BIO recommends that the FDA clarify if the justification for change should be submitted in a specific format, e.g., a white paper or clinical overview.
Waivers and Extensions		
Lines		
Appendix A: Organization and Format for Pregnancy, Lactation, and Females and Males of Reproductive Potential Subsections		
Lines		
Appendix B: Pregnancy and Lactation Labeling Rule (PLLR) Implementation Plan		
Lines		