June 8, 2018

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

Re: Docket No. FDA-2018-D-1201: FDA Draft Guidance on Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding FDA Draft Guidance, *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry*.

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BIO supports the FDA's work to develop the Draft Guidance titled *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry*. We see this as an important step in ensuring that information regarding the safety and efficacy of therapies that may be used by pregnant women is available to patients and providers. Below we have included general comments regarding the Draft Guidance as well as more detailed comments beginning on page three of this letter for the FDA's consideration.

General Comments:
BIO views the Draft Guidance as being applicable to how and when to include pregnant women in drug development clinical trials. We interpret clinical trials to mean controlled interventional studies (with one or more arms) for drugs, biologics, or devices that are subject to FDA regulation. We ask the FDA to indicate whether the guidance also applies to post-marketing registries. Furthermore, we also ask the FDA to clarify whether the Draft Guidance applies to open label trials (where treatment assignment is clear) as well as blinded studies, where a pregnant woman may be assigned to placebo. Finally, we ask the FDA to clarify the applicability of the Draft Guidance to multinational and non-U.S. studies.

Throughout the Draft Guidance BIO requests that the FDA clarify if they view the term "nonpregnant women" to be used synonymously with "women of reproductive potential". For example, depending on the drug being evaluated, nonpregnant women could include post-menopausal women, or women deemed clinically infertile (e.g., post-hysterectomy).

BIO believes that guidance from the Agency regarding issues pertaining to the inclusion of lactating women in clinical studies is also of high importance for industry Sponsors. To this end, BIO asks that the Agency either include information pertaining to the inclusion of

lactating women in this Draft Guidance or develop additional guidance that will specifically address issues pertaining to the inclusion of lactating women in clinical trials.

The number of pregnant women enrolled in clinical trials is expected to be small, except for medical products that are specifically indicated for pregnant women. BIO suggests the Agency provide guidance regarding how to analyse and interpret data obtained from pregnant women in clinical trials that are not indicated for pregnant women and how data obtained in pregnant women may be incorporated into the product label. Given that the number of pregnant women in clinical trials for products that are not indicated for pregnant women will be small, the Draft Guidance would also benefit from the inclusion of information regarding the use of innovative trials designs. For example, in Section C of the Draft Guidance, the FDA could provide information regarding the use of adaptive trial designs for the collection of pharmacokinetic data in pregnant women in cases where the product is not specifically indicated for pregnant women. In addition, given the small numbers enrolled in trials, the assessment of risk of a given product should also include information collected from off-label use of the product or from clinical experience with other products in the same class.

Finally, BIO also recommends that FDA consider including relevant statements in the Introduction and/or Background sections of the Draft Guidance regarding the use and importance of patient-focused drug development as it relates to clinical trials containing pregnant women.

As the Agency continues to develop considerations for research in pregnant women BIO encourages the FDA to provide clear opportunities for Sponsors to discuss such research with appropriate review divisions. BIO appreciates this opportunity to submit comments regarding FDA's Draft Guidance. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
Danielle Friend, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 38-40	The Draft Guidance indicates "Some of the information provided in this guidance applies to drugs indicated to treat pregnancy-specific conditions (e.g., preterm labor, pre-eclampsia), but the larger focus is on drugs indicated for conditions that occur commonly among females of reproductive potential." Elsewhere in the Draft Guidance it is stated that drugs may be studied in pregnant women for potential benefit to the fetus and/or neonate (e.g., lines 102-103).	BIO suggests the proposed change: "Some of the information provided in this guidance applies to drugs indicated to treat pregnancy-specific conditions (e.g., preterm labor, pre-eclampsia), **or to drugs which may have potential for benefit to the developing fetus or neonate**, but the larger focus is on drugs indicated for conditions that occur commonly among females of reproductive potential."
II. BACKGROUND		
Lines 69-71	This section states "the frequent lack of information based on clinical data often leaves the health care provider (HCP) and the patient reluctant to treat the underlying condition, which in some cases may result in more harm to the woman and the fetus than if she had been treated," however there is no reference for the statement.	BIO requests that a reference be added to the end of this sentence to support this statement.
Lines 72-74	This section states "In addition, pregnant women often use medically necessary drugs without a clear scientific understanding of the risks and benefits to themselves or their developing fetuses (Lyerly et al. 2008)," but the statement does not acknowledge circumstances under which a woman uses a medically	BIO suggests adding the following statement to acknowledge trials conducted for the purpose of benefiting the fetus or neonate: "**While nascent, some clinical trials are completed for the purpose of protecting the fetus or neonate (i.e., maternal vaccines).**"

SECTION	ISSUE	PROPOSED CHANGE
	necessary drug for the purposes of protecting the infant.	
Lines 88, 152, 163, 285	The term "hold out the prospect" is used several times throughout the Draft Guidance (lines 88, 152, 163 and 285).	For clarity, BIO requests that the FDA replace the phrase "hold out the prospect" with "**has the potential to demonstrate**".
Lines 94-95	This section states "There are multiple reasons for considering the inclusion of pregnant women in clinical trials, including the following…" and provides multiple reasons but does not address circumstances in which the purpose of the clinical study is to develop medicines that reduce infant mortality.	BIO requests that the FDA acknowledge circumstances under which the purpose of the clinical trial is to demonstrate reduce neonate mortality. BIO suggests making the addition: "**Development of effective treatment options for the pregnant population that can reduce neonatal mortality is a significant public health issue**."
Lines 94-106	Treatment of pregnant women often relies upon "off-label" use of medication so recruiting subjects and discussing studies such as those included in a pregnancy registry with either patients or healthcare providers can be interpreted as "promoting" off-label use. However, the goal of a pregnancy registry is to capture exposures that are occurring regardless of participation in the registry. These ethical considerations likely negatively impact recruitment into the studies.	BIO requests that the FDA address the issue of "off-label" use as it applies to pregnancy surveillance studies to promote enrolment.
III. Ethical Considerations		
FDA Regulations that Govern Research in Pregnant Women		
Lines 148-150	This section states "1. Where scientifically appropriate, nonclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been	We request that the FDA clarify the nature and extent of clinical trial data on nonpregnant women that should be available before clinical trials in pregnant women are initiated. A cross-reference to Section IV may be helpful.

SECTION	ISSUE	PROPOSED CHANGE
	conducted and provide data for assessing potential risks to pregnant women and fetuses;", however there is not any information regarding the nature/extent of clinical trial data on nonpregnant women that should be available before clinical trials in pregnant women can be initiated.	Additionally, later in the guidance (lines 266 to 268) the Draft Guidance indicates that information from medical literature and/or other sources regarding use in pregnant women may provide ethically justifiable evidence for including pregnant women in clinical trials. BIO request that lines 148 to 150 also include references to "preliminary safety data from the medical literature and/or other sources regarding use in pregnant women".
152-153	This section states "The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means; The above text recounts the Department of Health and Human Services (HHS) 45 CFR part 46 regulation, subpart B which requires that the research involving pregnant women directly benefit either the pregnant woman or the fetus.	BIO requests that the Draft Guidance clarifies that the regulation would be met even if the benefit to the fetus only occurs after birth (when it is no longer a fetus), as would be the case for a maternal vaccine.
Line 163-167	The Council for International Organization of Medical Sciences (CIOMS) (Guideline 19) indicates that some research involving pregnant women may be directed at the health of the fetus. In such cases, the role of the woman remains the same, she is the decision-maker for any interventions that affect her. This does not exclude the possibility of the woman consulting with the father of the fetus, if she wishes.	BIO requests the FDA to consider the CIOMS guidelines in reference to circumstance when an intervention benefits the fetus but when the intervention may impact the woman. BIO also requests that the FDA consider referencing cases when there may be risk for the woman and benefit for the fetus.

SECTION	ISSUE	PROPOSED CHANGE
169-170	In this section neonates are specifically identified for ethical consideration, but nowhere else in the Draft Guidance are neonates specifically identified.	BIO recommends including neonates in other sections of ethical considerations.
Research-Related Risks		
General Guidelines for Including Pregnant Women in Clinical Trials		
Line 259	This section details circumstances when it is ethically justifiable to include pregnant women with a disease or medical condition requiring treatment in clinical trials. There are 3 conditions listed and the last requires at least one of 3 conditions, all three are part of the original third bullet and should be indented for clarity.	BIO requests the proposed change: In the postmarketing setting (i.e., FDA-approved drugs) • Adequate nonclinical studies (including studies on pregnant animals) have been completed and • There is an established safety database in nonpregnant women from clinical trials or preliminary safety data from the medical literature and/or other sources regarding use in pregnant women and one of the following: • **Efficacy cannot be extrapolated** **and/or** • **Safety cannot be assessed by other study methods** • **Pharmacokinetics cannot be assessed by other methods**
Lines 266-268	This section indicates "There is an established safety database in nonpregnant women from clinical trials or	Given that data submitted for approval of the drug would have included safety data from nonpregnant women, BIO

SECTION	ISSUE	PROPOSED CHANGE
	preliminary safety data from the medical literature and/or other sources regarding use in pregnant women."	asks the FDA to clarify whether this not be sufficient to serve as the 'established safety database'?
Line 272	This section states "efficacy cannot be extrapolated," but does not indicate to which population the efficacy cannot be extrapolated.	BIO recommends the addition: "Efficacy **in pregnant women** cannot be extrapolated"
Line 276	This section states "safety cannot be assessed by other study methods," but does not indicate to which population the safety cannot be assessed.	BIO recommends the addition: "Safety **in pregnant women** cannot be assessed by other study methods"
Lines 285-288	This section indicates "the clinical trial holds out the prospect of direct benefit to the pregnant woman and/or fetus that is not otherwise available outside the research setting or cannot be obtained by any other means (e.g., the pregnant woman may not have responded to other approved treatments or there may not be any treatment options)" however in some cases while the benefits could be obtained it may be prohibitively expensive and not recommended outside the context of prematurity or other high risk factors. An impractical but theoretically possible alternative way to obtain the benefits of a therapy may exist, but should not stand in the way of testing an alternative that could deliver the benefits to a far greater number of patients.	BIO suggests the addition: "cannot be obtained **or is impractical to obtain** by any other means (e.g., the pregnant woman may not have responded to other approved treatments or there may not be any treatment options)"
Lines 293-307	This section indicates "Women who become pregnant while enrolled in a clinical trial", but the section does not indicate whether this applies to all phases of drug development (e.g., Phase 1 studies) or just to later phases (phase 2 or 3).	BIO asks the FDA to clarify to which phases of the drug development lifecycle this section applies. BIO also requests that this section cross-references Section IV, as appropriate and useful.

SECTION	ISSUE	PROPOSED CHANGE
Lines 293-307	This section indicates "When a pregnancy has been identified during a clinical trial, unblinding should occur so that counseling may be offered based on whether the fetus has been exposed to the investigational drug, placebo, or control. The risks and benefits of continuing versus stopping investigational treatment can be reviewed with the pregnant woman. Pregnant women who choose to continue in the clinical trial should undergo a second informed consent process that reflects these additional risk-benefit considerations." but little guidance is providing regarding how to best proceed with the unblended clinical trial participant. Additionally, the term "unblinding" typically means disclosure of the blinded study treatment assignment of an individual subject, a group of subjects, or all subjects at any time during the conduct or reporting of a clinical study. However the second part of this paragraph refers to pregnant women who choose to continue in the clinical trial should undergo a second informed consent process. It is ambiguous whether "unblinding" in this paragraph refers to termination.	BIO asks for further clarity regarding whether women who become pregnant while enrolled in a clinical trial should be unblinded and remain in the study. Specifically we ask that the FDA clarify whether or not the FDA refers to "unblinding" in this case as termination of study participation. To this end, BIO requests the addition: "**Unblinding, while possibly necessary, may require removal from the trial.**" BIO also recommends that FDA indicate that dosing is suspended until the activities discussed in this section have occurred and a new informed consent has been performed. BIO also suggests that the counselling and risk to the pregnancy be discussed prior to unblinding drug assignment, as the participant may elect to continue in the study and it would be best to continue in a blinded manner. If the participant elects to discontinue the study drug then they could be unblinded and informed of their treatment assignment.
Lines 295-300	For vaccines, some reported pregnancies in clinical trials (i.e., non- maternal immunization trials), unblinding has no impact on the management of the patient but may impact the validity of the study results. Although there are circumstance when unblinding would be ethically warranted, unblinding in the absence of a direct impact on management of the patient could bias the outcomes reported.	BIO asks the FDA to clarify that unblinding is recommended only in cases when the treatment assignment is necessary to appropriately direct management of the subject.

SECTION	ISSUE	PROPOSED CHANGE
Line 302	For clarity, because any of the conditions could lead to a favorable benefit-risk justification for continued exposure, we suggest to replacing the "**and/or**" condition with **"or"**.	If fetal exposure has already occurred, a woman who becomes pregnant while enrolled in a clinical trial should be allowed to continue on the investigational drug if the potential benefits of continued treatment for the woman outweigh the risks 1. of ongoing fetal exposure to the investigational drug**,** ~~**and/**~~or 2. of discontinuing maternal therapy, ~~**and/**~~or of exposing the fetus to additional drugs if placed on an alternative therapy.
IV. Other Considerations		
Disease Type and Availability of Therapeutic Options in the Pregnant Population		
Timing of Enrollment		
Lines 343-344	This section indicates "Nonclinical reproductive and developmental toxicology studies generally should be completed before enrolling pregnant women in clinical trials." Although this section cites ICH M3(R2), the above could lead to some confusion regarding study expectations. For example, the ICH guidance specifically states that "female reproduction studies" (and genotoxicity) should be completed prior to	BIO requests that the FDA provide information regarding which studies should be expected (e.g. whether it includes pre-and postnatal development studies).

SECTION	ISSUE	PROPOSED CHANGE
	enrollment of pregnant women. However, the specific studies are not described.	
Pharmacokinetic Data		
Safety Data Collection and Monitoring		
Lines 384-391	This section indicates that "When pregnant women are enrolled in a clinical trial, data collection elements should include, at a minimum: gestational age at enrollment; gestational timing and duration of drug exposure; and pregnancy outcomes including adverse maternal, fetal, and neonatal events. Enrolled pregnant patients should also receive obstetrical care that meets the recognized standards of care. Infants born to mothers who were exposed to the investigational drug should have follow-up safety information collected. Systemic drug exposure to the fetus/newborn can be evaluated by collecting cord blood or neonatal levels of drug and/or metabolites, depending on the timing of exposure to the drug and its half-life," however this section does not address issues pertaining to biologics.	BIO request the following addition: "**For drugs with a long half-life, adverse events past the neonatal period should be reported**". BIO also requests that more detail be included in the Draft Guidance regarding the duration of follow-up for the safety outcomes as well as the what information should be collected, including specific examples regarding what is meant by "follow-up safety information."
Line 393	The term "consultant" is not defined.	BIO requests that a definition be included for the term "consultant."
Lines 393-395	Because pregnancies can occur in any clinical trial that enrolls women of childbearing potential, there should be some threshold for absolute inclusion of investigators or consultants who have expertise in obstetrics and/or maternal/fetal medicine. In addition, it is prudent for sponsors to have access to teratology experts to assess human and animal toxicology data to counsel pregnant trial participants.	BIO suggests the below changes: Clinical trials that **primarily** enroll pregnant women should include investigators or consultants who have expertise in obstetrics and/or maternal/fetal medicine, **or teratology**, depending on the underlying conditions treated by the investigational drug.

SECTION	ISSUE	PROPOSED CHANGE
Line 395	This section indicates "Clinical trials that enroll pregnant women should include investigators or consultants who have expertise in obstetrics and/or maternal/fetal medicine, depending on the underlying conditions treated by the investigational drug."	BIO suggests the addition: "**Rates of emergent safety events may benefit from a comparison to expected rates in a similar trial population to evaluate whether the emergent event should be considered a potential risk to the mother or the fetus/neonate**."
Stopping a Clinical Trial that Enrolls Pregnant Women		
Lines 412-415	This section details situations when it would be appropriate to stop a randomized, controlled clinical trial that is enrolling pregnant women, we ask that the items included in the list are prioritized based upon the most important reason for stopping a trial.	BIO suggests reordering the bullets such that safety and adverse events are placed first in the list of bullets.
Lines 412-415	This section indicates "There are documented serious maternal or fetal adverse events that can be reasonably attributed to drug exposure and are deemed to exceed the potential benefits of drug treatment. This determination should include consideration of alternative effective treatments and the risks of the underlying condition." The statement could benefit from clarifying that is applies to clinical trials that enroll pregnant women.	BIO recommends the below change: "There are documented serious maternal or fetal adverse events that can be reasonably attributed to drug exposure and are deemed to exceed the potential benefits of drug treatment **in clinical trials that only enroll pregnant women**."
References		
	It is not clear if other recognized guidelines/standards in this topic area have been considered in the development of this Guidance.	BIO asks the FDA to consider referencing the CIOMS guidelines, fully or partially in the Draft Guidance. Specific references are suggested in the sections that follow: • guideline 19 Pregnant and breastfeeding women;

SECTION	ISSUE	PROPOSED CHANGE
		• guideline 3 Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research; • guideline 15 Research involving vulnerable persons and groups; • guideline 18 Women as research participants