Biotechnology Industry Organization

August 11, 2015

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

Re: Docket No. FDA-2015-D-2001: Draft Guidance on Assessment of Male-Mediated Developmental Risk for Pharmaceuticals

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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the *Draft Guidance for Industry on Assessment of Male-Mediated Developmental Risk for Pharmaceuticals*.

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.

General Comments

BIO appreciates the release of this Draft Guidance. It provides clarity and insights on FDA's recommendations for the assessment of developmental risks associated with administration of pharmaceuticals to males.

BIO recommends that the Draft Guidance clearly differentiate between genotoxic and non-genotoxic agents in relation to developmental risk. While the potential risks mediated by genotoxins are well accepted, the risk from non-genotoxic agents is theoretical. Differentiation of these agents within the Guidance and inclusion of recent publications evaluating the likelihood of effects from non-genotoxic agents would provide a more scientifically balanced guidance.

In addition, the Draft Guidance does not distinguish between small and large molecules within the considerations and recommendations for assessing developmental risk. Given the differences in the approaches for non-clinical developmental/reproductive assessments of these classes of active pharmaceutical ingredients (APIs) and the differences in risk, separate discussions of small and large molecules within these sections would provide clarity.

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Additionally, the example calculation for monoclonal antibodies in Section IV.C does not account for the assumptions regarding seminal fluid concentration and vaginal uptake, thereby overestimating the concentration in circulation and underestimating the exposure margin. As mentioned in the chart below, we ask FDA to recalculate this example to take these into consideration.

Finally, BIO recommends the following changes for clarity on the topic of the Guidance and throughout the text. The current title implies that any developmental effects are mediated by the male, not by the API. BIO suggests changing the title of the Guidance to "Assessment of Developmental Risks from Administration of Pharmaceuticals to Males" to better represent the topic of the Guidance. BIO also notes that the terms "sperm," "semen," and "seminal fluids" are used throughout the text, sometimes interchangeably. We suggest FDA define these terms early in the Guidance and use them consistently throughout.

We provide specific, detailed comments to improve the clarity of the Draft Guidance in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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Biotechnology Industry Organization (BIO)

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SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Line 38:	Footnote 4 indicates that male reproductive toxicity includes genetic and nongenetic damage to the male germ cells. The topic of nongenetic damage and its relevance to male mediated developmental risk does not appear to be addressed by the recommendations in Section III.	BIO asks FDA to provide clarification on how non-genetic damage to germ cells could impact developmental risk.
Lines 51-55:	The Draft Guidance states that "this guidance does not address the potential risks to partners exposed to seminal fluid transfer of an API from men taking pharmaceutical products, nor does it discuss potential effects on embryo/fetal development resulting from exposure to pregnant women via any route other than seminal transfer." The reason for this exclusion is unclear. The calculations in Section IV.C. provide an estimation of the exposure to the partner, which could be used to assess the risk.	BIO suggests providing a short rationale explaining why partners are outside the scope of the Guidance as well as clarifying whether seminal transfer other than vaginal seminal transfer is also excluded from the Guidance, especially in light of Section IV.C. which provides information that could be used to assess the risk to partners but is limited to vaginal uptake.
II. BACKGROUND		
Lines 75-79:	The potential risk mediated by genotoxins is accepted. However, risks from non-genotoxic agents have not been clearly demonstrated.	This section would benefit from the inclusion of papers (*e.g.* Klemmt and Scialli, Birth Defects Research (Part B) 2005; 74:119-131, Collie, Reproductive Toxicology, 1993; 7:3-9) that evaluate the risk from non-genotoxic agents. BIO suggests FDA reference additional literature that provides information on the potential risk for non-genotoxic agents such as Klemmt and Scialli, Birth Defects Research

SECTION	ISSUE	PROPOSED CHANGE
		(Part B) 2005; 74:119-131, and Collie, Reproductive Toxicology, 1993; 7:3-9 as mentioned above. We also suggest that FDA clarify that the conceptus can be affected by direct, local exposure after seminal transfer as well as systemic exposure after vaginal uptake. There may be differences in the effect of direct, local exposure versus systemic exposure that are important to consider.
III. CONSIDERATIONS AND RECOMMENDATIONS FOR ASSESSING MALE-MEDIATED DEVELOPMENTAL RISK		
Lines 107-109:	This section does not consider the ADME properties within the pregnant partner.	BIO suggests editing the text to read: "The absorption, distribution, metabolism, and excretion (ADME) properties of the drug (e.g., distribution to and/or accumulation in male reproductive tissues or partitioning into semen, degree of vaginal absorption, and placental transfer)"
A. UNKNOWN GENOTOXIC, REPRODUCTIVE AND/OR DEVELOPMENTAL RISK POTENTIAL		
Lines 124-127:	The Draft Guidance states, "Until the genotoxicity and reproductive and/or developmental risk potential of an API have been adequately characterized in nonclinical studies, male subjects in clinical trials should take precautions to prevent pregnancy of a partner and/or exposure of a conceptus during and after the period of pharmaceutical exposure."	BIO notes that small and large molecule therapeutics are not differentiated in this section. For large molecules that are not pharmacologically active in rodents or rabbits, non-clinical reproductive/developmental toxicity assessments may be deferred until later stage clinical development per ICH M3(R2) and S6(R1). Given the specificity of these pharmaceuticals, significantly reduced seminal fluid concentrations, and decreased vaginal uptake, precautions to limit exposure of pregnant partners should not be the default recommendation for these molecules. As such, BIO suggests FDA consider exempting large

SECTION	ISSUE	PROPOSED CHANGE
		molecule therapeutics from this section.
B. KNOWN GENOTOXIC, REPRODUCTIVE, AND/OR DEVELOPMENTAL EFFECTS IN NONCLINICAL STUDIES		
Section 1 **Lines 146-147:**	The recommendation for "appropriate contraception for males who are administered any API identified as genotoxic" could be interpreted to indicate that any observation of genotoxocity in the battery (ICH S2 R1) would warrant contraception. Contraception should not be required in cases where there are observations of clastogenicity *in vitro* and appropriate *in vivo* studies show no evidence of clastogenicity. Contraception should also not be required for aneugens with an adequate safety margin for the no-observed-adverse-effect-level / lowest-observed-adverse-effect level (NOAEL/LOAEL) in an in vivo micronucleus assay relative to the clinical exposure.	BIO suggests FDA recommend appropriate contraception for males who are administered API in cases where genotoxicity occurs via 1) a mutagenic mechanism of action; 2) a clastogenic mechanism of action within unknown relevance *in vivo*; or 3) a clastogenic mechanism of action with established relevance in vivo. Additionally, BIO suggests that contraception should also be considered for males who are administered API which is genotoxic via an aneugenic mechanism of action. In cases where an adequate safety margin for an *in vivo* micronucleus assay relative to the anticipated clinical exposure can be established, contraception may not be needed.
Section 2 **Lines 151-153:**	The cited papers (Safarinejad 2008; Lewis and Aitken 2005) describe DNA damaging agents and the references would be more appropriate in the genotoxic agents section (lines 132-147).	BIO suggests moving the text of lines 151-153 to the genotoxic agents section.
Section 2 **Lines 153-157:**	The Draft Guidance states, "In the event that an API has been identified as having the potential to affect male reproduction based on either the mechanism of action or through demonstrated animal toxicity (*e.g.,* in a repeat-dose toxicity study or study evaluating fertility), appropriate contraception should be	As Section III.B.1 addresses genotoxic agents, it appears that this section is addressing APIs that affect fertility through non-genotoxic mechanisms. However, it is unclear how an agent that affects fertility via non-genotoxic sperm damage can lead to abnormal fetal developments.

SECTION	ISSUE	PROPOSED CHANGE
	considered until the possible implications for developmental risk have been assessed."	BIO asks FDA to clarify the scope of this section and provide scientific basis for the concern and the subsequent recommendation for appropriate contraception.
Section 3 Lines 162-164:	The Draft Guidance states, "A number of developmental toxicants present in seminal fluid have been reported to affect pregnancy outcomes adversely in animals by this mechanism (Robaire and Hales 1994)."	BIO notes that several recent publications indicate that manifestation of this theoretical risk is unlikely at clinically relevant exposures (*e.g.* Klemmt and Scialli, Birth Defects Research (Part B) 2005; 74:119-131, Reproductive Tox 2014, v.48: 115-137 Hui, p. 115-123, Breslin, p. 124-131, Moffat p. 132-137). As such, BIO suggests including discussion and references on the potential risk from exposure through seminal fluid at clinically relevant exposures.
Lines 164-170:	The Draft Guidance states, "For example, the presence of thalidomide in semen was associated with evidence of developmental toxicity, including fetal malformations, in the progeny of treated male rabbits (Lutwak-Mann, Schmid, et al. 1967)."… "Thalidomide has been measured in human semen after oral dosing, with an apparent correlation between semen and plasma levels."	These sentences imply that clinically relevant doses of thalidomide may result in developmental toxicity in pregnant partners. However, a recent publication (Hui et al, Reproductive Tox, 2014, 48: 115-123) indicated that intravaginal administration of thalidomide at a dose >10,000-fold higher than the expected amount of thalidomide in human semen did not result in any developmental abnormalities. As such, BIO suggests that current references assessing the clinical relevance of exposure to thalidomide through semen should be included or these examples should be deleted.
Lines 166-168:	The Draft Guidance states, "…increased preimplantation loss after mating cyclophosphamide-treated male rats with untreated females was attributed to the presence of the drug in seminal fluid	Cyclophosphamide is an alkylating agent (*i.e.* genotoxic); therefore, this example would be more appropriate in the "Genotoxic Agents" section. As such, BIO suggests deleting this reference from Section III.B.3.

SECTION	ISSUE	PROPOSED CHANGE
	(Hales, Smith, et al. 1986)."	
Lines 172-175:	The Draft Guidance discusses the need for precautions to prevent pregnancy or exposure.	BIO believes this section should reference Section IV. for guidance on assessing effects. Additionally, the term 'significant developmental risk' should be further explained with regard to the class of developmental toxicity and safety margin considerations should be included either in this paragraph or in a glossary. As such, we recommend editing the text to read: "Therefore, when a significant developmental risk such as structural malformations/teratogenicity at clinical relevant exposures, has been identified in nonclinical studies in which the pregnant female is dosed, precautions to prevent pregnancy or exposure of a conceptus in partners of a treated male should be considered until the potential for ~~male-mediated~~ effects has been fully assessed (see Section IV ~~e.g., determination of API levels in human seminal fluid ejaculate~~)."
IV. NONCLINICAL STUDIES RELEVANCT TO ASSESING DRUG-INDUCED MALE-MEDIATED DEVELOPMENTAL EFFECTS IN ANIMALS		
A. IN VITRO STUDIES		
Lines 185-186:	The Draft Guidance discusses in vitro studies relevant to the assessment of potential developmental toxicity from administration to males.	BIO notes that "miscellaneous studies of pharmaceutical effects on sperm" is unclear. If this type of study is to be included in the Guidance, we ask FDA to provide additional description of the study and its relevance to genotoxicity and/or developmental toxicity.

SECTION	ISSUE	PROPOSED CHANGE
Lines 187-189:	The Draft Guidance states, "Based on the strength of an in vitro signal, precautionary measures or follow-up in vivo studies may be warranted using reproductive outcome as a more definitive measure of paternally mediated effects."	An in vivo study using reproductive outcome may not be the appropriate follow-up for all of the types of studies listed in lines 184-187. Specifically, there are in vivo genotoxicity tests described in ICH S2R1 that appropriately evaluate in vitro signals of potential heritable damage. For in vitro developmental toxicity studies, an embryo-fetal developmental study may be more appropriate to evaluate potential signals. In addition, for APIs that are only active in primates, a study evaluating reproductive outcome is not feasible. As such, we suggest editing the text to read: "Based on the strength of an in vitro signal, precautionary measures or follow-up in vivo studies may be warranted ~~using reproductive outcome as a more definitive measure of paternally mediated effects~~."
B. IN VIVO STUDIES		
Lines 193-196:	The Draft Guidance discusses in vivo nonclinical studies of interest for assessment of potential developmental toxicity mediated by administration to males.	BIO asks FDA to consider including in vivo genotoxicity studies in this section as they are the primary source of in vivo data for heritable changes to germ cells that would inform this assessment.
Lines 201-203:	The Draft Guidance states, "For most pharmaceuticals, the only standard in vivo study that evaluates potential paternally mediated developmental effects is the fertility and early embryonic development study, with a direct effect assessed when only males are treated."	BIO notes that this section does not address APIs which are not pharmacologically active in rodents and rabbits. As noted in section 5.2 of ICH S6, for biopharmaceuticals where the only pharmacologically active species is the non-human primate, fertility is acceptably assessed by histopathological evaluation of gonadal tissue from general toxicology studies lasting at least three months. In addition, effects of NHP-only active biopharmaceuticals on embryonic development are sufficiently assessed by the enhanced peri-postnatal

SECTION	ISSUE	PROPOSED CHANGE
		development study where only females are dosed. We suggest editing the text to read: "~~For most pharmaceuticals~~For most small molecules, the only standard in vivo study that evaluates potential paternally mediated developmental effects is the fertility and early embryonic development study, with a direct effect assessed when only males are treated. For biopharmaceuticals where the non-human primate is the only active species, sponsors should refer to sections 5.2 and 5.3 of ICH S6(R1)."
Lines 201-205:	The Draft Guidance discusses when to conduct studies to determine the roles of treated males versus treated females.	This section notes that a study pairing treated males and females with untreated males and females should be conducted if an effect is observed in a study when only males are treated. However, this appears to be repetitive, since the study with treated males and untreated females should have already occurred if the effect is observed. BIO recommends that this section indicate a study of treated males paired with treated females and then a follow up study of treated/untreated male-female pairs if an effect is observed in the treated-treated pairings.
Lines 206-209:	It is assumed that additional studies should only be conducted if there is a signal for developmental toxicity at clinically relevant exposure.	BIO suggests editing the text to read: "Because standard fertility and early embryonic development studies may be inadequate to identify the full range of potential ~~male-mediated~~ developmental effects, additional studies in which pregnancies are followed to term should be considered if there is a signal for developmental toxicity at clinically relevant exposures following mating of treated males to untreated females."

SECTION	ISSUE	PROPOSED CHANGE
C. ADME INFORMATION		
Lines 213-215:	The Draft Guidance states, "For potent developmental toxicants in animals or humans, considerations should be given to ascertaining the API levels in ejaculated material in an attempt to quantify the potential levels that may reach the conceptus."	As indicated in lines 197-199, when developmental toxicity has been identified a risk assessment should be performed to assess the potential for exposure to fetuses through seminal transfer and vaginal uptake. If this is done using appropriately conservative assumptions for biodistribution, then actual quantification of ejaculate concentrations are not likely to alter the risk assessment. As such, BIO suggests editing the text to read: "For potent developmental toxicants in animals or humans, considerations should be given to ~~ascertaining~~ estimating the API levels in ejaculated material in an attempt to quantify the potential levels that may reach the conceptus."
Lines 217-218:	The Draft Guidance states, "Fetal exposures can be modeled using the following assumptions (Banholzer, Buergin, et al. 2012)".	BIO notes that recent papers have generated data which, in general, are consistent with the assumptions in Banholzer. However, in some cases, the data indicate that the assumptions are conservative (*e.g.* placental and vaginal transfer of large molecules). BIO suggests FDA include references to recent papers that have substantiated these assumptions and underscored their conservative nature (*e.g.,* Reproductive Tox 2014, v.48: 115-137 Hui, p. 115-123, Breslin, p. 124-131, Moffat p. 132-137.)
Line 247:	The Draft Guidance gives calculations for monoclonal antibodies and Fc-conjugated pharmaceuticals.	BIO recommends that proteins and peptides be included in these calculations as well. Absorption of peptides/proteins via the vaginal wall or peptide/proteins ascending via the female reproductive canal is extremely unlikely, since the

SECTION	ISSUE	PROPOSED CHANGE
		vaginal mucus originating from the cervix contains a wide range of peptidases (Acatürk et al. 2001). Also, the degree of proteolytic degradation of peptides in the vagina is comparable to the degradation in the ileum (Lee and Yamamoto 1990, Yamamoto 1990). In addition, absorption and pharmacological activity of peptides administered via the vagina is negligible, unless absorption enhancers are added (Yamamoto et al. 1987, De la Cruz et al. 1975, Richardson et al.1992, Okada et al. 1982, 1983a, b, 1984, Morimoto et al. 1982). Finally, direct exposure of the conceptus to peptides in seminal fluid or adhering to spermatozoa that ascend locally via the female reproductive canal is extremely unlikely, since the cervical mucus becomes impermeable as the glucoprotein frame tightens under progesterone dominance (Sobero and MacLeod 1962, Speroff and Fritz 2005).
Lines 256-267:	The example given does not account for the assumptions regarding seminal fluid concentration and vaginal uptake; overestimating the concentration in circulation and underestimating the exposure margin.	BIO asks that FDA account for the 1% seminal fluid concentration and the 10% vaginal uptake in the calculation and adjust the exposure multiples based on the revised concentration in circulation. It also appears that the factors of 10 or 100% of placental transfer are missing from the calculation.
Lines 270-271:	The Draft Guidance discusses fetal exposure to API and potential risk.	BIO suggests clarifying the need for contraception if there is an adequate margin in the most sensitive species by editing the statement to read: "Using this model, when potential fetal exposures to the API are less ~~greater~~ than 10-fold ~~lower than~~ the NOAEL in the most sensitive species in the animal ~~reproductive and~~ developmental toxicity studies, no further evaluations ~~are~~

SECTION	ISSUE	PROPOSED CHANGE
		~~recommended~~ or contraception is necessary."
V. CONCLUSION		
Lines 294-296:	The Draft Guidance highlights that these recommendations also apply to vasectomied men.	BIO notes that sperm donors and women utilizing donated sperm are other populations who may not realize that the recommendations in this Guidance are relevant.
Lines 298-304:	The Draft Guidance discusses the use of male contraception.	This section does not differentiate between genotoxic and non-genotoxic agents. The scientific basis for the additional 90 days for non-genotoxic agents is not clear as clearance of unejaculated sperm should not be necessary for agents that do not directly affect sperm. In addition, a clear recommendation for biologics is not included and lines 301-304 may imply a longer duration for these APIs. As such, BIO suggests editing the text to read: "~~For most small molecules,~~ For agents that directly affect sperm (*e.g.*, genotoxic agents), use of male contraception for a period of time equal to 5 half-lives plus 90 days (the duration of one spermatogenic cycle in men and residence time for unejaculated sperm) after pharmaceutical exposure should be sufficient to avoid risk to the conceptus of a female sexual partner. Use of male contraception for 5 half-lives should be sufficient for agents that do not directly affect sperm. However, other considerations, including pharmacodynamic activity and pharmacokinetics, may influence the recommended duration of contraceptive use following cessation of therapy~~, especially for biologics~~ (Peou, Moinard, et al. 2009)."