Biotechnology Industry Organization

October 15, 2015

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

Re: Docket No. FDA-2015-D-2306: Draft Guidance on Testicular Toxicity: Evaluation During Drug Development

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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the *Draft Guidance for Industry on Testicular Toxicity: Evaluation During Drug Development* (Draft Guidance).

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BIO appreciates the release of this Draft Guidance and we believe that the Draft Guidance will assist Sponsors to evaluate the potential for testicular toxicity. It would be helpful to Sponsors for FDA to include additional clarity regarding nonclinical safety margins, the conduct of clinical trials in men of reproductive age, and when to conduct a clinical trial to assess the impact of a drug candidate on the testes.

BIO notes that it is currently unclear if the content of the Draft Guidance applies to a stand-alone study (confirmatory nonclinical) or is relevant to general toxicology assessments that include reproductive assessments. Likewise, it is not clear if a stand-alone clinical trial in male humans (volunteers or patients) is required or if the recommendations apply to any clinical trial (*e.g.*, Phase 1 or 2) in which data could be collected for a subset of male participants. We think it would be helpful for FDA to provide additional clarity around these topics.

BIO asks FDA to ensure that this guidance does not conflict with any applicable ICH guidelines and provides references to these guidelines as appropriate. Specifically, we believe that Section III (Nonclinical Evaluation) of the final version of the guidance should specifically reference ICH *S6(R1)* and likewise should acknowledge that, for certain active pharmaceutical ingredients (API), the only relevant toxicology species may be the non-human primate. We offer further harmonization suggestions in the chart below.

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BIO believes that it is important that the guidance clarifies the acceptable safety margins to support clinical development as discussed in Section III. C. Specifically, the use of the phrase "reassuring safety margin" in this section is inadequate to describe an acceptable exposure-based safety margin. While we understand that speaking to many variables and a single margin applicable to all conditions is not realistic, it would be helpful to provide Sponsors with a defined targeted margin (*e.g.,* 10x). In the absence of a framework expressed in guidance and applicable across review divisions, individuals (or Divisions) may vary in their interpretations which often can result in inconsistencies. As a result of the lack of a frame of reference for acceptable safety margins, there is increased likelihood that development of new drugs may be terminated in the nonclinical phase before evaluating their potential in human clinical studies.

It remains unclear at what point in early clinical development the risk of testicular toxicity should be evaluated. Section IV of the Draft Guidance indicates that a plan for clinical monitoring for the risk of testicular injury should be in place early in clinical development for drugs that have a potential to cause human testicular toxicity but it is unclear whether Phase I first-in-human single ascending dose (SAD) or multiple ascending dose (MAD) studies would be allowed to progress if there is an appropriate safety margin, Additionally, as the need for monitoring depends on several factors (*e.g.*, patient population and indication) in addition to the nonclinical data, we ask the FDA to consider including a section describing the risk assessment process for determining the need for clinical monitoring in the Final Guidance.

On an editorial and clarity note, we have noticed that throughout the Draft Guidance the terms "histologic" and "histopathologic" have been used interchangeably. We recommend the use of "histopathologic" consistently within the document.

Finally, it would be helpful for the final version of the guidance to address special considerations when developing combination products.

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 on our comments, as needed.

Sincerely,

/S/

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Manager, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Line 21, Footnote 2:	The Draft Guidance states, "For the purposes of this guidance, all references to *drugs* and *drug products* include both human drugs and therapeutic biological products unless otherwise specified."	We assume that vaccines, blood products, cellular therapies, gene therapies, and excipients are excluded from the scope of the guidance, and suggest the text in footnote 2 is edited as follows: "[2] For purposes of this guidance, all references to *drugs* and *drug products* include both human drugs and therapeutic biological products unless otherwise specified; vaccines, blood products, cellular therapies, gene therapies, and excipients are excluded from the scope of this guidance."
Line 19-21:	The Draft Guidance states, "The purpose of this guidance is to assist sponsors who are developing drug products that may have potential adverse effects on the testes, which we refer to as testicular toxicity, based on findings in nonclinical studies."	BIO asks FDA to reference Olsen et al., 2000 (Reg Tox Pharmacol) indicating that animal to human translational aspect is not a 1:1 correlation. For clarification purposes, BIO also suggests adding the statement "The purpose of this guidance is not to assist sponsors who are developing marketed drug products."
Lines 30-31:	The Draft Guidance discusses the topics regarding drug products that may have potential adverse effects on the testes and states, "Clinical monitoring that can be employed when these drug products are initially administered to human subjects".	This sentence could be interpreted to indicate that clinical monitoring should be implemented for all APIs that have demonstrated adverse effects on the testes in non-clinical studies. BIO suggests editing the text to the following to add context: "Clinical monitoring ~~that~~ can be considered ~~employed~~ when these drug products are initially administered to human subjects".

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II. DIFFICULTIES EVALUATING TESTICULAR TOXICITY IN HUMANS		
Lines 50-65:	The Draft Guidance states, "A thorough evaluation of a drug product's adverse effects on testes in humans is challenging for the follow reasons:"	The inherent inter- and intra-individual variability in semen parameters contributes to the difficulty evaluating testicular toxicity in humans and in interpreting changes in semen parameters (*e.g.*, Stewart et al., 2013 Birth Defects Res Part B). BIO suggests the guidance reflect subject variability as a significant challenge when interpreting data.
Lines 53-56:	The Draft Guidance states, "Only a few clinical markers can reliably monitor potential changes in human testicular function that might accompany drug exposure. Examples of measurements of testicular function include semen analysis, serum testosterone concentrations, and serum gonadotropin concentrations."	BIO notes that changes in inhibin B indicates testicular toxicity, additionally the guidance recommends inhibin B in line 243 of the Draft Guidance. As such, we recommend editing the text to read: "Only a few clinical markers can reliably monitor potential changes in human testicular function that might accompany drug exposure. Examples of measurements of testicular function include semen analysis, serum testosterone concentrations, inhibin B, and serum gonadotropin concentrations."
Lines 71-74:	The Draft Guidance states, "Sponsors of anticancer drugs that fall under the scope of the International Conference on Harmonisation (ICH) guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* should consult with the Office of Hematology and Oncology Products before initiating follow-up studies evaluating testicular toxicity."	BIO agrees with this suggestion for consultation in the context of oncology products, but believe it should be expanded to include considerations for sponsors of drugs intended to treat other serious and life-threatening diseases, by adding the following sentence: "Sponsors of drugs for other serious and life-threatening diseases should consult with the relevant Review Division before initiating follow-up studies to evaluate testicular toxicity."

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		Moreover, given that patient population and indication are important factors in determining the need for clinical monitoring in general, BIO suggests moving this sentence to a new section describing factors involved in the determination of the need for clinical assessment of semen parameters. Finally, we note that this statement could be interpreted to mean that anticancer drugs are not within the scope of this guidance and are instead covered under *ICH S9*; this should be clarified in the final version of the guidance.
III. NONCLINICAL EVALUATION		
Lines 78-111 and Lines 167-189:	BIO notes that much of the information in Section III Nonclinical Evaluation is in alignment with the relevant ICH *M3 (R2)* and *S5 (R2)* guidances. However, ICH is currently in the process of revising ICH *S5 (R2)*. In addition, the Draft Guidance does not reference ICH *S6 (R1)* and does not address active pharmaceutical ingredients (API) for which the only relevant toxicology species is the non-human primate.	Given the differences in the approaches for non-clinical reproductive assessments of these APIs and the current activity of the Expert Working Group for ICH *S5 (R3)* to revise *ICH S5*, BIO asks FDA to consider eliminating Sections A, B and E of this section and referring the reader to the appropriate guidelines.
A. INTRODUCTION		
Line 79:	In addition to the nonclinical examinations, the weight of evidence should also consider such things as pharmacological relevance, species specificity/sensitivity, etc.	BIO suggests FDA expand Section III.A. introductory text to include other contributors to the weight of evidence other than positive findings in a nonclinical study (*e.g.*, pharmacology, cross species potency, etc.).

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Lines 85-89:	"Testicular toxicity is routinely assessed using: • Repeat-dose toxicology studies with at least 4 weeks of drug exposure in two species • Assessment of male fertility in rodents • Comparative evaluation of pharmacokinetics in animals and humans"	This section does not address APIs for which the only relevant toxicology species is the non-human primate. In addition, while comparative evaluation of pharmacokinetics in animals and humans is utilized in the risk assessment, it is not a direct assessment of testicular toxicity. Additionally, ICH S5 (R2) states that repeat dose studies with 2-4 weeks of drug exposure are sufficient to assess testicular toxicity. FDA guidance should be consistent with ICH guidance. The Draft Guidance also does not reflect that, in some cases (*e.g.,* for biologics), repeat-dose toxicology studies generally are limited to one species. Accordingly, BIO suggests revising the section as follows: "Testicular toxicity is routinely assessed using: • Repeat-dose toxicology studies with ~~at least 4~~ 2-4 weeks of drug exposure in two species, when applicable, unless only one species is studied when based on pharmacological relevance • Assessment of male fertility in rodents (when applicable) • ~~Comparative evaluation of pharmacokinetics in animals and humans~~"
Line 89:	Footnote 4 points readers to ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*, *S5A Detection of Toxicity to Reproduction for Medicinal Products*, and *S5B Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility*.	As ICH *S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* addresses reproductive toxicity evaluations for biologic products, BIO suggests that the FDA include this guidance in the footnote. BIO also suggests FDA cite the Guidance for Industry: Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns (September 2011).

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Lines 91-92:	The scope of the guidance appears to be drug products that may have potential adverse effects on the testes when administered to male subjects. As such, it is unclear how effects in embryo-fetal development (EFD) studies or pre- and postnatal development (PPND) studies would affect the risk assessment or provide confirmation of testicular toxicity for exposed men.	We suggest the removal of Lines 91-92.
B. NONCLINICAL STUDY DESIGN CONSIDERATIONS		
Line 94:	It is not clear whether Section B (page 3), applies to the studies described on Lines 85-92 or is specific to a stand-alone male animal fertility study.	BIO asks FDA to clarify the applicability of Section B.
Line 96-97:	Even if testicular toxicity is identified in a repeat-dose toxicity study, additional studies to investigate this finding may not be warranted in certain cases. Consideration should be given to the duration of drug use in patients, the patient population and the indication.	BIO suggests adding the following text: "A rationale should be provided for the choice of doses, duration of exposure, and species used to investigate male reproductive toxicity in nonclinical studies. A decision on whether a nonclinical study, to further investigate testicular toxicity, is needed is dependent upon such factors as the chronic use of the drug, the patient population, and drug indication." It is also unclear as how this is different from the rationale used to select appropriate doses, duration of exposure, and species for toxicology studies in general.
Lines 99-105:	The Draft Guidance states, "Unless studies are intended to support dosing in pediatric patients, the use of sexually immature animals in acute/subchronic	The early non-rodent toxicology studies are sometimes performed using juvenile/adolescent animals, especially for APIs that are only active in non-human primates.

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	toxicity studies is not recommended because histology findings in immature animals may incorrectly suggest that fertility is impaired. Histological evaluations of the reproductive organs is considered the most sensitive endpoint for evaluating testicular injury in animals."	Additionally, while histological assessment is a sensitive endpoint, it may not be the most relevant endpoint depending on the criteria being assessed. Moreover, we note that acute studies are no longer a regulatory requirement under ICH *M3(R2)*. Further, it is unlikely that testicular damage would occur after a single dose of a drug. BIO suggests the following revision: "~~Unless studies are intended to support dosing in pediatric patients, the use of sexually immature animals in acute/subchronic toxicity studies is not recommended because histology findings in immature animals may incorrectly suggest that fertility is impaired.~~ Histological evaluations of the reproductive organs of sexually mature animals is considered ~~the most~~ an appropriately sensitive endpoint for evaluating testicular injury in animals."
Lines 105-107:	The Draft Guidance states, "Toxicology studies should include an examination of the histopathology of the testes, seminal vesicle, epididymis, and prostate with appropriate fixation and staining of the testes."	BIO notes that the male mammary glands can also exhibit histological effects indicative of toxicity to reproduction. As such, BIO suggests adding male mammary glands to this list.
Lines 105-107 and citation 5:	Citing more recent literature would reflect the current best practice regarding histological procedures.	We recommend the citation of *Proliferative and Nonproliferative Lesions of the Rat and Mouse Male Reproductive System Toxicologic Pathology, 40: 40S-121S, 2012* by D. Creasy et al. as a reference which refers readers to the trimming protocols in goRENI (Kittel et al. 2004) and Boorman, Chapin, and Mitsumori (1990); Boorman, Elwell, and Mitsumori (1990); Foley (2001); and Suwa et al. (2001,

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		2002). And additional current reference is Creasy DM, Chapin RE. Male reproductive system. In: Haschek WM, Rousseaux CG and Wallig MA, editors. Haschek and Rousseaux's handbook of toxicologic patholgy, 3rd ed. London: Academic press; 2013. p.2541-2542.
Lines 107-109:	The Draft Guidance states, "Histopathology assessment of reproductive tissues in the nonclinical male fertility study/studies is recommended if adverse findings in gonadal tissues were observed in repeat-dose toxicity studies."	If dosing regimen is similar in the male fertility study, the benefit of repeating the histology is unclear. BIO suggests the editing the statement to read: "If adverse findings in gonadal tissues were observed in the repeat-dose toxicity studies, histopathology assessment of reproductive tissues in the nonclinical male fertility study/studies may provide additional information to inform the human risk assessment ~~is recommended if adverse findings in gonadal tissues were observed in repeat-dose toxicity studies~~."
Lines 109-111:	The Draft Guidance states, "Assessing the persistence versus the reversibility of adverse effects on the reproductive system after drug withdrawal in the repeat-dose toxicology and male fertility studies is an important consideration in the risk assessment."	For certain toxicities, reversibility can be assessed based on the type, extent and severity of the pathology finding and the regenerative capacity of the organ. In these cases, demonstration of complete recovery should not be essential. Additionally, the final version of the guidance should clarify that the persistence (rather than the assessment of persistence) is a consideration in the risk assessment. BIO suggests revising this sentence to the following: "~~Assessing t~~The persistence versus the reversibility of adverse effects on the reproductive system ~~after drug withdrawal in the repeat-dose toxicology and male fertility studies~~ is an important consideration in the risk assessment."

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		In addition, BIO suggests moving this sentence to a separate section on risk assessment (see comment under F. conclusion, line 191).
Lines 109-111:	FDA guidance should be consistent with ICH guidance (*e.g.*, *M3*, *S5A*).	BIO suggests FDA add a reference to ICH guidance as applicable along with recommended sample sizes. Additionally, BIO suggests the guidance use "recovery group" to distinguish from "drug withdrawal."
C. NONCLINICAL FINDINGS THAT RAISE CONCERN FOR MALE FERTILITY		
Lines 115-117:	The Draft Guidance states, "In general, reproductive toxicity findings in male animals that increase concern for impaired fertility include, but are not limited to, testicular atrophy, seminiferous tubule degeneration or necrosis, or other pathology that may suggest impaired reproductive function."	BIO suggests expanding the list of relevant findings to include degeneration, necrosis, or hypocellularity of the testes. In addition, there are background incidences of seminiferous tubule degeneration. By stating "increased seminiferous tubule degeneration" this better describes test article-related findings from background incidences. Finally, we recommend noting that findings in other associated male reproductive organs (*e.g.,* prostate, seminal vesicles, and epididymis) could present additional concerns for testicular toxicity. As such, BIO suggests editing the text to read: "In general, reproductive toxicity findings (above background incidence) in male animals that increase concern for impaired fertility include, but are not limited to, testicular atrophy, degeneration, necrosis, or hypocellularity of the testes, increased seminiferous tubule degeneration or necrosis, germ cell depletion, or other pathology that may suggest impaired reproductive function. In addition, findings in other associated male reproductive organs (*e.g.,* prostate, seminal vesicles, and epididymis) may be suggestive of

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		testicular toxicity.”
Lines 119-152:	The text and the table are redundant and do not contain all of the same information.	BIO suggests that the FDA consider revising this section to include only the text or the table. However, if the Final Guidance will include both the text and table, we suggest ensuring that the sections are consistent. Additionally, we believe it would be helpful to reorganize this information into three categories: 1) Weight of evidence 2) Increased concern 3) Contributing factors.
Line 127:	The Draft Guidance states, “The adverse histopathology correlates with effects on reproductive organ weight”	This sentence does not acknowledge the effect of decreased body weight gain as a covariate for decreased male accessory organ (prostate/seminal vesicle) weight. It also does not acknowledge the confounding effect of stress on testicular weight/function, especially in non-human primates. BIO suggests including information on these factors.
Line 129-130:	The Draft Guidance states, “A finding does not resolve after a period of one spermatogenic cycle following the last drug dose”	While BIO agrees that there can be greater concern if a finding requires more than 1 cycle to resolve, resolution and recovery is possible at periods much longer than 1 cycle. Critically, the rat seems more resistant to recovery after full atrophy than mice or humans or dogs (see Meistrich review, 2013, and Dube et al., 1987). Therefore, a delayed recovery in the rat does not necessarily mean delayed recovery in other species. This has been shown in both the cancer recovery literature (van Dorp et al., Eur. J. Cancer 49: 1280-1286) and for DBCP, the nematocide which caused testicular toxicity in agricultural workers in the 1970’s (rev. by

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		Potashnik and Yanai-Inbar, 1987). In addition, for APIs with a long half-life, one spermatogenic cycle may not be sufficient to allow for drug clearance. BIO suggests revising this sentence as follows: "A finding does not show a trend toward reversibility ~~resolve after a period of one spermatogenic cycle~~ following the last drug dose."
Line 132:	The Draft Guidance states that the significance of the findings increase if "The adverse findings occur at all of the doses evaluated"	BIO suggests deleting this bullet, as it is inconsistent with Table 1.
Lines 134-135:	The Draft Guidance states, "The adverse findings are seen at pharmacokinetic exposures that do not provide a reassuring safety margin compared to clinical exposure."	For clarification, BIO suggests editing the text to read: "~~The adverse findings are seen at pharmacokinetic exposures that do not provide a reassuring safety margin compared to clinical exposure.~~ The NOAEL for testicular toxicity occurs at a systemic exposure that does not provide a sufficient margin to the systemic clinical exposure." If FDA does not edit the text as recommended, BIO recommends striking the term "reassuring" and adding, after "clinical exposure" the statement "that is adequate in light of clinical benefit to the intended indication." This additional language would help to clarify that safety margins only are relevant in the context of clinical benefit. We also suggest cross-referencing the 2011 FDA guidance "Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns," which provides helpful guidance on criteria that would increase/decrease level of concern.

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Lines 137-140:	The Draft Guidance states, "Although histology is the most sensitive way to detect testicular and sperm quality toxicities, findings of reduced fertility, impaired mating behavior, and reduced capacity to mate in male fertility studies are concerns in and of themselves. These findings are especially concerning if they are corroborated by repeat-dose toxicity studies."	As the endpoints assessed in a male fertility studies are not routinely assessed in repeat-dose toxicity studies, it is unclear how the findings would be corroborated by the repeat-dose toxicity studies. BIO suggests revising the text to read: "Although histology is the most sensitive way to detect testicular and sperm quality toxicities, findings of reduced fertility, impaired mating behavior, and reduced capacity to mate in male fertility studies are concerns in and of themselves. These findings are especially concerning if they are corroborated by evidence of effects on reproductive tissues in repeat-dose toxicity studies."
Lines 140-143:	The Draft Guidance states, "The level of concern increases if reproductive toxicity occurs following exposures during multiple stages of life (e.g., fetal, peri/postnatal, juvenile, and/or adult stages)."	As toxicities at multiple stages of life may simply reflect a common mechanism, it is unclear why this would automatically increase the level of concern. BIO suggests editing the text to read: "The level of concern may be increaseds if reproductive toxicity occurs following exposures during multiple stages of life (e.g., fetal, peri/postnatal, juvenile, and/or adult stages)."
Line 142-144:	The Draft Guidance states, "Findings that are suggestive of perturbations of the endocrine system are also a concern because endocrine disruptions may adversely affect male (and female) reproductive physiology and performance."	This sentence suggests that all endocrine disruptions are of equal concern. However, some endocrine perturbations (*e.g.*, thyroid hormone) are unlikely to result in direct effects on reproductive physiology and performance. BIO suggests revising this sentence to reflect perturbations of reproductive hormones.

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Line 151, Table 1:	Table 1 reads, "Finding is dose-dependent"	It is unclear how dose-dependency increases the level of concern as this is the basis for establishing safety margins. BIO suggests deleting this line.
Line 151, Table 1:	Table 1 reads, "Finding persists or increases in severity with increasing duration of exposure"	"Finding persists" should be very different from "finding increases in severity with increasing duration of exposure" and it is not considered as an increased concern if the severity is not increased with increasing duration. BIO suggest removing "persists or": "Finding ~~persists or~~ increases in severity with increasing duration of exposure"
Line 151, Table 1:	Table 1 reads, "Finding persists after drug withdrawal, especially if withdrawal period is an entire spermatogenic cycle"	While BIO agrees that there can be greater concern if a finding requires more than 1 cycle to resolve, resolution and recovery is possible at periods much longer than 1 cycle. Please refer to our previous comments on lines 129-130. BIO suggests editing the text to read: "Finding persists after drug withdrawal. ~~especially if there is no exposure during withdrawal period is an entire spermatogenic cycle~~"
Line 151, Table 1:	Table 1 reads, "Maximum dose without adverse effect occurs at exposures that are clinical relevant"	BIO suggests revising the text to read: "~~Maximum dose without adverse effect occurs at exposures that are clinical relevant~~ The finding occurs at clinically relevant exposures"

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Line 151, Table 1:	Table 1 reads, "Anti-androgenic signs - reduced body weight, decreased weight and maturation of male sexual organs, clinical signs suggestive of reduced aggressiveness (e.g., lethargic or reduced mating behavior)"	BIO suggests removing "reduced body weight" and "lethargic" because these signs are often associated with general toxicity and may have no effect on male fertility. We also suggest adding feminization of males to the examples provided, as follows: "Anti-androgenic signs - ~~reduced body weight,~~ decreased weight and maturation of male sexual organs, clinical signs suggestive of reduced aggressiveness (e.g., ~~lethargic or~~ reduced mating behavior or feminization of males)."
Line 151, Table 1:	Table 1 reads, "Androgenic signs – masculinization of females (decreased fertility, female sexual organ pathology, or estrus cyclicity), decreased testes size, and impaired spermatogenesis"	It is unclear how masculinization of females in the absence of findings in male animals increases the level of concern for men. BIO suggests deleting the reference to masculinization of females.
Line 151, Table 1:	Table 1 reads, "Confounding Issues"	Confounding issues is also addressed in the following section (Section D, Lines 153-165). BIO suggests deleting this from the table to avoid redundancy in separate sections. Additionally, BIO suggests adding common background findings in the testes and pharmaceuticals that modulate reproductive hormones to the list of confounding issues.
Line 151, Table 1:	Table 1 lists "Decreased male fertility and impaired mating behavior" under findings that increase the level of concern and "Pharmaceuticals that impair mating behavior or neuromuscular function" under confounding issues.	BIO suggests revising these sections to provide clarity/consistency on the difference between these factors.

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Line 151, Table 1:	Table 1 lists "Use of immature animals" under confounding issues.	BIO suggests the language be clarified as follows: "Use of sexually immature animals."
D. CONFOUNDING FACTORS		
Lines 155-156:	The Draft Guidance states that "Numerous factors can confound apparent male reproductive toxicities. The use of immature animals…"	BIO suggests the language be clarified as follows: "Numerous factors can confound apparent male reproductive toxicities. The use of sexually immature animals…"
Line 158-160:	The Draft Guidance states, "When azospermia or decreased spermatogenesis is detected in testicular histopathology examinations it is important to document the reproductive age of the nonclinical model."	Azospermia is defined as the absence of sperm in the seminal fluid and, therefore, cannot be diagnosed in testicular histopathology examinations. BIO suggests removing azospermia from the sentence.
Line 160-162:	The Draft Guidance states, "If animals were immature at the beginning of treatment but should have attained maturity by the end of the study, then it is important to determine if the drug can have temporary or permanent effects on testicular development and spermatogenesis."	The need to conduct follow-up studies to determine permanence will be dependent on the nature of the findings and the context of intended use. Accordingly, BIO suggests the language be clarified to be less prescriptive and allow case-by-case determinations, as follows: "If animals were immature at the beginning of treatment but should have attained maturity by the end of the study, then it may be ~~is~~ important to determine if the drug can have temporary or permanent effects on testicular development and spermatogenesis."
Line 163-165:	The Draft Guidances states, "Clinical evaluation of testicular function should be considered only for direct-acting testicular toxicants, where decreased	This is important guidance and should be included in a section on risk assessment and determining the need for clinical monitoring, not a section on confounding factors.

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	reproductive function is accompanied by adverse histopathology."	
E. FOLLOW-UP INVESTIGATIONS		
Line 170-171:	The Draft Guidance states, "Omission of follow-up studies to further characterize adverse findings should be justified."	This sentence implies that follow-up studies should be performed irrespective of the overall risk assessment. As the non-clinical reproductive assessments generally performed during development can provide a thorough assessment of the potential for testicular toxicity and allow for an adequate risk assessment, follow-up studies may not be required. BIO suggests removing the requirement to provide a justification for not performing follow-up studies.
Line 174:	The Draft Guidance states, "A demonstration of the reversibility of the adverse finding after cessation of dosing"	In some cases it is clear that the testicular toxicity is not reversible, and in this case there is no need to conduct a reversibility study. In cases where it is needed, for clarification reversibility is described to include partial resolution because complete reversibility may not occur in 1 spermatogenic cycle. In addition, we recommend revisions for consistency with the wording in other ICH Guidances (such as ICH *M3R2 Q&A*). Accordingly, BIO suggests the text be clarified as follows: "If needed, ~~A~~ a demonstration of ~~-~~a trend toward reversibility (including partial resolution trending towards resolution) of the adverse finding after cessation of dosing"
Lines 176-177:	The Draft Guidance states, "A reproductive hormone analysis, although hormone concentrations can vary between animals and over time"	BIO recommends this language be clarified as follows: "A reproductive hormone analysis, although hormone concentrations can vary between animals, as a result of the

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		time of day, and over ~~time~~ the course of the study." BIO also notes that due to the high degree of variability, reproductive hormone assessments are of limited benefit, unless effects are relatively profound, in which case it is more of a confirmatory test. Careful design of hormonal type studies is a key consideration. BIO suggests adding a footnote to reference Stanislaus et al. 2012 (Toxicol Pathol) regarding key hormone study considerations.
Lines 184-185:	The Draft Guidance discusses adding fertility and/or sperm quality analysis in "select cases."	It is unclear what is meant by "in select cases." It would be more helpful if FDA provided more specificity on this topic.
Lines 185-187:	The Draft Guidance states "The length of dosing in the premating period of the male fertility study could be increased to cover an entire spermatogenic cycle (for example, 63 days in rats) to determine the extent of expected or observed toxicities in previous studies."	BIO recommends this language be clarified as follows: "The length of dosing in the premating period of the male fertility study could be increased to cover an entire spermatogenic cycle (for example, 63 days in rats) to determine the expected functional effects based on toxicities observed ~~extent of expected or observed toxicities~~ in previous studies."
Lines 187-189:	The Draft Guidance states, "A confirmatory study in a second species may be useful in cases where the finding is suspected to be species dependent."	It is not clear what confirmatory study is being referred to. Since the general toxicology studies typically assess rodent and non-rodent testes via histopathology, it is not clear how the statement on Line 187-188 provides guidance. Additionally, BIO believes it would be helpful to add an example where the use of a second species might be helpful (*e.g.*, when effects are hypothesized to be due to a

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		metabolite found in one animal species but not humans).
F. CONCLUSION		
Lines 191-200:	This Conclusion section describes the risk assessment process for determining the need for clinical monitoring.	As this is a critical component of this Draft Guidance, we suggest that the FDA consider elevating this paragraph to a separate section (*e.g.*, Section IV), combining it with the information in lines 205-218 and inserting into the guidance prior to the currently Section IV. Monitoring of the testes during clinical trials.
IV. MONITORING OF THE TESTES DURING CLINICAL TRIALS		
Line 203:	As Sponsors may not have all information as the same time, interactions are likely to take place throughout drug development.	It would be helpful to group information about when and how to interact with FDA as varying types of information become available and plans are made for further development.
Lines 207-209:	The Draft Guidance states, "This plan can be discussed with the appropriate review division as part of a pre-investigational new drug application (IND) meeting or be developed by the sponsor and included with the original IND."	The Draft Guidance is unclear in regards to the timing of the testicular toxicity studies. BIO suggests FDA provide additional clarity if these studies are to be started in Phase 1, 2 or 3.
Lines 221-222:	The Draft Guidance states, "For example, the drug could be initially investigated only in females, vasectomized men, or men with no interest in future procreation."	It is not clear why it would be acceptable to evaluate a potential testicular toxicant in vasectomized men or men with no interest in future procreation while the potential for testicular toxicity is still under nonclinical evaluation; moreover, this language implies that procreative interest is permanent and cannot change over time. BIO asks FDA to either delete this reference, or provide additional clarity on the reasoning for recommending this evaluation.

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Lines 222-225:	The Draft Guidance states, "Initial use in females and vasectomized men will not contribute any clinical data relevant to testicular toxicity, but will make initial pharmacokinetic, safety and efficacy evaluations of a drug possible while additional nonclinical testicular safety data are obtained."	This statement is inconsistent with prior statements indicating the value of monitoring effects on hormones and libido, which should be the same in vasectomized and non-vasectomized men, and also suggests that additional nonclinical studies can clarify the risk to humans. In some cases, including nonclinical safety studies limited to NHP, the identification of a testicular effect, and its reversibility, may be the only data available to inform the human risk assessment. BIO suggests editing the text to read: "Initial use in females and vasectomized men will not contribute any clinical data relevant to semen quality, but assessment of reproductive hormones could be considered. This approach will make initial pharmacokinetic, safety and efficacy evaluations of a drug possible while additional nonclinical data are obtained if relevant."
Lines 228-230:	The Draft Guidance states, "During the clinical trial in these subjects, information should be gathered on the effect of the drug on the testes."	This section implies that semenology be included in all studies for drugs with a potential effect on the testis and inclusion of men who may desire future fertility. Given the difficulties in collecting and interpreting these data in humans, especially in relatively small trials, this may not be feasible other than as a monitoring option that can be offered to individual patients. BIO suggests revising the text to read: "During the clinical trial ~~in these subjects~~ consideration should be given to offering individual monitoring to subjects who may desire future fertility. ~~should be gathered on the effect of the drug on the testes.~~"

SECTION	ISSUE	PROPOSED CHANGE
Lines 241-243:	The Draft Guidance states, "In addition, other biomarkers of testicular injury (such as serum concentrations of testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), and inhibin B) should be assessed."	Diurnal variation of testosterone and inhibin has been well documented and should be factored into any sampling scheme during clinical trials. BIO suggests adding a footnote to reflect that hormone sampling needs to consider diurnal and episodic nature of hormone secretion.
V. DESIGN OF A CLINICAL TRIAL TO EVALUATE THE EFFECT OF A DRUG ON THE TESTES		
Lines 249-251:	The Draft Guidance States, "Based on the nonclinical findings, the results from initial human testing, and the intended use of the drug being considered, it may be appropriate to conduct a dedicated clinical safety trial having as its primary purpose an evaluation of the effect of the drug on testicular function."	This section does not provide guidance on when a separate study may be warranted. BIO suggests the addition of such guidance into either this section or a separate section on the risk assessment process. This should include guidance on when such a study may not be warranted, such as if there are other anticipated toxicities, or if the drug class and mechanism is consistent with established effects on the testes (*e.g.*, radiomimetics, androgens, anti-androgens) or if sufficient information can be obtained in Phase II clinical trials. Additionally, BIO notes that the age of the patient population is also a key consideration in deciding whether or not a clinical study is required and we recommend this be added to the Draft Guidance.
A. SUBJECT SELECTION		
Lines 256-257:	The Draft Guidance states, "Trial subjects should be men considered to have normal potential for fertility as reflected by semen parameters."	The Draft Guidance is unclear on the types of male subjects to be enrolled in the clinical trial. BIO suggests FDA specify if these studies are to be conducted in healthy volunteers or in subjects with the condition under study.

SECTION	ISSUE	PROPOSED CHANGE
Lines 271-272:	The Draft Guidance states, "If feasible, subjects should be representative of the population for whom the drug is intended."	It is unclear if the Draft Guidance is not recommending a healthy volunteer study based on the study size and treatment duration but only a study with target indication patients with healthy sperm condition.
B. TRIAL DESIGN		
Lines 276-278:	The Draft Guidance states, "A randomized, double-blind, placebo-controlled, parallel-arm trial is recommended. We recommend that the trial randomize approximately 200 men in a 1:1 ratio to receive either the investigational drug or placebo."	It is not clear as to whether the 200 subjects refer to healthy volunteers or patients. Recruitment for this type of study is extraordinarily challenging. Healthy volunteers may see no benefit from participation and even benefits for patients may be limited if the study is focused on safety (testicular toxicity). Furthermore, the choice of a study population may be complicated by the disease state that the drug is proposed to treat (*e.g.*, chronic vs. acute, mortality associated, etc.). BIO asks FDA to clarify if this study is to be done in healthy volunteers or in patients. Additionally, it is unclear what the timing of this trial is. Knowing the expectations for timing will help in designing the overall assessment program. ICH *M3* doesn't speak to this type of trial except for the fertility testing by Phase 3.
Lines 283-284:	The Draft Guidance states, "In general, for drugs intended for chronic use, the drug should be administered for at least two human spermatogenic cycles, which is 26 weeks."	BIO notes that the duration of a human spermatogenic cycle is 10 weeks, rather than 13 as stated by the Draft Guidance. As such, we ask FDA to edit the text to read: "In general, for drugs intended for chronic use, the drug should be administered for at least two human spermatogenic cycles, which is ~~26~~ 20 weeks."

SECTION	ISSUE	PROPOSED CHANGE
Lines 295-297:	The Draft Guidance states, "A single central laboratory should process and analyze all semen samples for the purposes of consistency and quality assurance."	As assessments of sperm motility need to be performed on fresh samples, the use of a central laboratory is may not be practical for these evaluations. As such, BIO suggests removing this from the Draft Guidance.
Lines 299-302:	The Draft Guidance states, "The primary endpoint of the trial should be the percentage of subjects in each group who experience a 50 percent or greater decline in sperm concentration, compared to baseline, 13 weeks after starting the investigational drug (short-term use or intermittent re-treatment drugs) or after 26 weeks of drug exposure (chronically administered drugs)."	As outlined in the WHO Laboratory Manual for the examination and processing of human semen (4th edition, 2000), semen parameters have significant variability within each subject. The criteria for establishing how the above change represents as adverse is unclear. We ask FDA to add further justification and clarification for use of this endpoint.
Line 306-309:	The Draft Guidance states, "Therefore, changes from baseline in sperm concentration, ejaculate volume, total sperm per ejaculate, motility, and morphology should be evaluated as secondary endpoints."	As semen parameters demonstrate both intra- and inter-individual variability as well as cultural/ethnic and disease population variability, comparisons to the WHO reference values and population specific values could also be considered as secondary endpoints.
Lines 316-322:	The Draft Guidance discusses the re-evaluation of affected individuals.	BIO notes that re-evaluation of only the affected individuals may not be feasible as it could introduce bias.
C. PRESENTATION OF RESULTS		
D. EVALUATION OF RESULTS		
Line 376-378:	The Draft Guidance states, "Ultimately, the acceptability of the adverse effects of a drug on testicular function should be based on the overall risk-benefit assessment of the particular drug and indication being sought."	BIO believes this is a key statement and should be reflected in the introduction, or in a separate risk assessment section, not at the end of the clinical trial design section.

SECTION	ISSUE	PROPOSED CHANGE
VI. CONCLUSION		
	The Draft Guidance does not contain a conclusion section.	BIO recommends including an overall conclusion to the Draft Guidance.