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March 29, 2010

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA–2010–D–0026-0001: Draft Guidance for Industry, Assessment of Abuse Potential of Drugs

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, Assessment of Abuse Potential of Drugs.*

BIO represents more than 1,200 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, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS

BIO is concerned that several definitions of terms found in this guidance are inconsistent with other relevant guidance documents. We recommend that the FDA work with the Industry Working Group (IWG) developing the Opioid class REMS to arrive at a consensus regarding the definitions of the terms “misuse” and “diversion” used in this guidance.

BIO is also concerned that there is a lack of clarity around abuse potential assessment recommendations for new formulations of drugs with well-established abuse potential, and/or drugs with abuse potential that work through novel mechanisms of action. We note the draft guidance indicates the need to submit an abuse potential assessment as a section in the New Drug

Application (NDA) or supplement. This statement implies that abuse potential assessments will need to occur multiple times. We request clarification that the abuse potential assessment should typically only be done once, *i.e.*, prior to NDA submission, and thereafter only under specific circumstances, such as the development of an extended-release dosage form of a drug with abuse potential when an immediate release form of this drug is already available.

Additionally, as written, the Guidance would require an abuse potential assessment for any drug that affects the Central Nervous System (CNS) or has an effect on sedation and mood. This would include anticonvulsants, antipsychotics and antidepressants, and compounds with no known abuse potential. BIO considers this scope too broad. We recommend that FDA revise the Guidance to state that if there are no signals of abuse potential in either preclinical testing or clinical trials, no further testing is required and there is no need to include an abuse potential assessment in the NDA.

BIO also requests clarification as to the criteria FDA will use for requiring a human abuse liability study in recreational drug users. Additionally, for clarity, we request that FDA revise the Guidance to include a single section that addresses sponsor consultation with the Agency to discuss abuse potential issues throughout all stages of development. As drafted, the Guidance addresses this topic in separate sections. (Please see lines 222-227, 457-459, and lines 520-522.)

Lastly, BIO is seeking clarification of the relationship, if one exists, between the need for a scheduling determination and the determination at the FDA that a Risk Evaluation and Mitigation Strategy (REMS) will be required.

SPECIFIC COMMENTS

BIO has provided specific comments on sections of the draft guidance in the chart below. In the left column of the table, we identify the page in the draft guidance; the next column contains the relative impact we view the item to have (C for a critical concern that must be addressed, M for a minor concern that should be addressed, and E for an editorial comment to the text); the next column contains BIO's comments and rationale to support our position; and the right column carries our suggested changes, where applicable. We would be pleased to provide further input or clarification of our comments, as needed.

*** Relative Impact** **C** = A critical concern that must be addressed
M = A minor concern that should be addressed
E = Editorial comment to text (change not necessarily required)

Specific Comments			
Citation Location Section/Page	**Relative Impact ***	**SPECIFIC Concern (short explanation)**	**Proposed Change / Suggestions for Rewording (if applicable)**
17-18	M	One cannot know the potential for abuse unless that has been determined after assessment of all data available/required.	Please revise to read"...drug products that may have potential for abuse..." rather than "...drug products with

			the potential for abuse...”
19-24 and 161-165	C	The description of the type of drugs/formulations to be assessed is unclear; 161-165 is broader than 21-24.	Please make descriptions consistent between the 2 sections.
19-24 and 161-165	C	Studies on abuse potential should not be required for NCEs belonging to a class with documented absence of abuse potential.	
93-116	C	It would be helpful if there were information given concerning when in the review of the NDA the Controlled Substance Staff (CSS) performs its review. The draft guidance does not identify the target timing for when the Sponsor may expect to receive FDA’s assessment and proposal for scheduling before it is posted in the Federal Register.	Please consider adding time frame when each of these steps may occur. Please indicate when FDA’s assessment and proposal for scheduling would be provided to the sponsor.
110	E	Please replace “In” with “If” to provide clarity.	Please revise to read, “If accepting …..”
120-121	C	The Guidance advises sponsors to contact the Drug Enforcement Administration (DEA) early in the development process if they believe their development candidates have abuse potential.	Please consider modifying the Guidance to elaborate on this consultation with DEA, and indicate whether the appropriate CDER review division is involved in this interaction with the DEA (and if so, how), and what kind of information should be provided in the submission package to the DEA.
136	C	The definition for addiction has a proper accepted reference. However, there is no reference for the definition of “abuse potential”.	We recommend utilizing the definitions in DSM IV-TR.
136-137	E	This definition is not accurate; it would be useful to adopt definitions similar to those used by the European Medicines Agency (EMA) or in Canadian guidances.	Please revise the definition to read, “Abuse potential is the likelihood that a drug product could be subject to user-initiated, non-therapeutic self administration.”

		We note that abuse potential and abuse liability are not interchangeable terms.	
153	E	Abuse potential should also be differentiated from actual abuse, which is an outcome (rather than probability assessment), and is referred to in the last section of the document related to post marketing data.	
155	C	"...other information..."; please specify.	Please specify what is meant by "other information".
155-159	C	A proposal for scheduling should not be mandatory just because a drug produces psychoactive effects. Currently, there are psychoactive substances that are not scheduled.	Please revise to read, "or produces psychoactive effects such as euphoria". Also, we suggest that the Guidance be modified to read, "A sponsor may need to submit in the NDA an assessment of studies and other information…"
157-159	C	This text suggests that a proposal for scheduling should also be completed for drugs that show no evidence for abuse potential, but do affect the CNS and/or are similar to other drugs of concern. We do not agree.	Please clarify the rationale for this statement.
161-165 & 169	C	These lines suggest that an abuse potential assessment must be submitted as a section of the NDA or a supplement. This statement could be taken to imply that an assessment on a compound will occur multiple times, *i.e.*, every time a supplement is submitted (see general comment above). This is in contrast to the current practice where scheduling occurs once. FDA has revisited the scheduling of compounds; however, it has not been the practice to do this with each supplement filed.	We request clarification that the abuse potential assessment should typically only be done once, *i.e.*, prior to NDA submission, and thereafter only under exceptional circumstances.
186-197	E	We recommend reorganizing the	Specifically, we recommend

		contents of the abuse section of the NDA, to enhance clarity.	renaming "Preclinical Pharmacology" to "Nonclinical Pharmacology" and placing items c, d, and e under that heading. We recommend including a new heading "Clinical Assessment" and including items e, f, g, and h under that heading. In addition, under the "Clinical Assessment" section we recommend including a section for "human PK", and we recommend that an "epidemiology" subsection be included under item h.
186	E	Recommend adding "If applicable".	Please revise to read, "If applicable, all primary ..."
201-209	E	We recommend being more specific as to where in Module 1 and 2, respectively, the proposal for scheduling and proposed labelling should go.	
222-227	C	As drafted, the Guidance addresses sponsor consultation with the Agency to discuss abuse potential issues in several separate sections of the document.	For clarity, please revise the Guidance to include a single section that addresses sponsor consultation with the Agency to discuss abuse potential issues throughout all stages of development.
237-238	E	In "... results of *other* animal and human...", the word "other" should be deleted.	Please revise to read, "results of animal and human..."
241-242	M	Please elaborate on what is meant by the term "active metabolite", as animals may have different metabolites from humans.	
246	M	Please clarify the distinction between "direct" and "indirect".	
247	M	Please clarify the distinction between "actions" and "effects."	
279	C	Section B alludes to the necessity to prepare an assessment when there is a new	Please revise the draft guidance to recommend that the abuse potential

		formulation of a drug substance rather than drug product. Please see our comments on line 169.	assessment should typically only be done once, *i.e.*, prior to NDA submission, and thereafter only under significant circumstances, such as the development of an extended-release dosage form of a drug with abuse potential when an immediate release form of this drug is already available.
307-308	M	Please modify the draft guidance to include a reference to additional guidance from the DEA or another appropriate agency/entity as to what process to follow in order to safely dispose of the products referred to in lines 307-308 (transdermal and transmucosal drug products in which excess, unused drug substance remains after use) as well as abuse-deterrent/tamper-resistant formulations.	
347-349	C	We note that while the request for epidemiological data appears simple, we believe that presently, no U.S. databases are sufficiently credible for FDA/CSS to make valid conclusions on relative actual abuse of one compound vs. another.	
356	M	Results of abuse potential studies in animals may not suggest the need for further abuse potential assessments.	Please revise this portion of the Guidance to read, "... guide the sponsor and FDA in determining whether and what additional ..."
362	C	The requirement is inconsistent with the position taken by the International Conference on Harmonisation (ICH) and EMA on the issue of animal abuse potential studies and species selection.	Please revise to read, "Animal abuse potential studies can use several species, usually rodents and primates. Studies should be conducted preferably in rodents unless there is a rationale that justifies the use

			of non-human primates (NHPs). NHPs should be reserved only for limited cases where there is clear evidence that NHPs would be predictive of human abuse potential and the rodent is inadequate."
363	C	Please clarify what is meant by "Sponsors should provide (1) justification for the selection of an animal model..."; it is unclear whether this refers to the selection of an animal species or a specific test, or both.	
363-364	C	Please clarify what is meant by "Sponsors should provide ... (2) the prior drug history of the animals selected". Specifically, please clarify whether this refers to the training drug alone or any type of drug history prior to testing. We note that the latter requirement would be difficult to satisfy for NHP testing in Clinical Research Organizations (CROs) due to confidentiality concerns.	
369-372	C	The Guidance reads, "Route of administration can significantly affect behaviour...the proposed clinical route of administration as well as other routes should be tested when feasible."	Please revise to read, "The proposed clinical route of administration should be used in preclinical abuse potential studies, where feasible. Additional routes of administration commonly abused by individuals should also be considered for these studies. The route of administration in preclinical abuse potential studies should produce drug levels that are consistent with the clinical PK/PD profile and mimic the plasma exposure levels observed in humans."
382-384	C	Negative controls have no added	Please revise the Guidance to

		value: - For the tests as such - For the comparison with existing drugs for treatment of the same condition (often complete data is not available for the marketed drug and the new drug in development will have another mechanism of action)	state that incorporation of a negative control drug group is only required when its addition can be justified. Please also clarify what negative control compound should be selected when a drug is intended to treat a new indication where no approved treatment exists, or where no drug known to be devoid of abuse potential is available.
391-397	C	Please provide clarity regarding the expected dose limits for abuse potential investigation. As drafted, the recommended dose-range is unclear. Please also provide additional information regarding self-administration models and parameters, as the Guidance is unclear as drafted with regard to the preferred schedule of reinforcement (whether the training drug can be used as the comparator, or whether it is acceptable to use any drug of abuse as a training drug provided it produces levels of self-administration that are significantly different from placebo).	Please revise to read, "Generally, studies should explore the behavioural effects of a range of doses, including those that yield plasma exposure levels associated with the therapeutic dose up to the maximum tolerated dose based on safety/toxicity data. Doses related to nonspecific behavioural effects that might confound interpretation of the data should be avoided." And, "When technically feasible, intravenous self administration should be conducted to assess rewarding properties of the drug in a model with highly predictive validity unless solubility of the drug and intravenous administration is a concern. Conditioned place preference (CPP) can be an alternate model to evaluate rewarding properties when self-administration is not feasible."
391	M	The Guidance is unclear whether lower doses should be tested when doses several times the	

		therapeutic dose do not show signals of abuse potential.	
396-397	C	Please clarify whether the animal tests should be conducted up to the MTD.	
418	C	We agree with the example (same for neuroleptics) but the sentence as such (a negative result does not mean there is no drug abuse potential) can be misunderstood.	A negative result in one test design does not ...
424	M	Sponsors are advised to rely on "other behavioral tests" to assess abuse potential for drugs with effects broadly characterized as psychedelic.	Please revise the Guidance to indicate which behavioural tests are valid to test for psychedelic effects.
452-453	C	The Guidance states demonstration of dependence in animals can influence the human safety and abuse potential evaluations.	Please describe the relationship between animal findings and human abuse potential evaluations. In particular, it would be helpful to learn how negative animal findings (*i.e.*, no evidence for abuse potential) influence human abuse potential evaluations. Inclusion of a flowchart with decision time points, describing when in development certain kinds of abuse potential studies are needed, would be useful.
470-472	C	Section IV D of the Guidance states that GLP principles described in the ICH S7A Guidance and in 21 CFR part 58 apply to abuse potential studies in animals. Please note that to date, we are not aware of any CRO that performs conditioned place preference tests that are GLP-compliant.	
492-495	C	We are not aware of any direct measures that can precisely assess misuse. For example, pill counts/drug accountability may/may not be indicative of	We request that the guidance provide some endpoints/measures for assessing misuse.

		misuse and therefore is not an exact measurement of misuse.	
502-503	C	It is unclear why a single positive study, if conducted correctly and thoroughly, would not be sufficient for abuse potential assessment.	Please revise the Guidance to be more specific about meeting FDA's expectations in this regard.
504	C	The draft guidance puts a lot of emphasis on human abuse liability studies and clinical trial data and suggests that if the human abuse potential studies as well as adverse event profile from phase 3 trials are negative, then a recommendation for scheduling would be unlikely.	Please clarify the role of animal studies in the overall context of abuse potential assessment. Particularly, it would be helpful for FDA to clarify whether data from animal studies are required if a sponsor plans to conduct human abuse liability studies and review adverse events (AEs). We would also be interested in FDA's perspective on whether clinical studies would be required if preclinical data are clean and no AEs typical of abuse potential are reported. Please also provide guidance on how to proceed when there is a discrepancy between animal and human data (animal studies are positive but human abuse potential studies are negative).
519-521	M	Modification for clarity	Please consider adding a timeframe by which FDA would review and provide comments on the protocol.
526-528	C	The requirement for a "current history" of using a drug seems to conflict with the suggested exclusion criteria.	Please avoid the use of the term "recreational" drug user because this implies that subjects might not be experienced with the drug class that is relevant to the mechanism of action of the study drug. The exclusion criterion of "current abuse" seems

			contradictory with the need for subjects to have a "current history" with the drug class of interest. If the goal is to distinguish "current history of use" vs. "current abuse", then we request that a more well-developed definition for abuse be provided to help sponsors make the distinction.
540-541	M	BIO does not support the use of drug naïve healthy subjects in pivotal abuse potential studies, as the inclusion of these subjects may increase chances of making a Type II error.	
545	C	It cannot be assumed that the test drug (*i.e.*, new chemical entity) has CNS effects in humans. It is quite possible that the new drug has no distinguishable effects.	Please revise to read, "Study subjects should be able to demonstrate that they can discriminate the effects of the positive control and similar drugs from the placebo."
549	C	As we note immediately above, it cannot be assumed that the test drug (*i.e.*, new chemical entity) has CNS effects in humans. It is quite possible that the new drug has no distinguishable effects.	Please revise to read, "Some investigators may consider prescreening subjects for the ability to detect and report subjective effects of the appropriate positive control."
557-561	C	This paragraph is incorrect. Human abuse studies do not measure single dose administrations over time. Rather, these are single dose studies with multiple post dose assessments conducted over a period of time, determined by the time course of the drug's effects.	We recommend revising the text to indicate that the human abuse study measures repeated assessments over a period of time after a single dose administration.
563-564	C		Please provide recommendations for what trends would signify abuse potential. Please also provide guidance on positive control dose

			ranges.
566-567	M		Please clarify whether the phrase "significant difference" used in lines 566-567 refers to a clinical difference, statistical difference or both.
568	C	If there are many treatment arms, if the drug and/or its active metabolites have long half lives necessitating lengthy washout periods, or if carryover effects are anticipated for other reasons, a complete crossover design study may not be feasible.	Please revise the Guidance to read, "In some cases, a complete crossover design study may not be feasible, for example, if there are many treatment arms, if the drug and/or its active metabolites have long half lives necessitating lengthy washout periods, or if carryover effects are anticipated for other reasons." In these cases, we recommend that the Guidance urge sponsors to utilize a balanced incomplete crossover design in which subjects are randomized to receive placebo and a subset of the active treatments under crossover conditions.
573-574	C	What parameters/how many parameters are needed for each measure? How should one adjust for multiple comparisons?	Please elaborate.
604	C	The Guidance is unclear regarding the control that should be used in the case of a drug with a new MoA.	We suggest language similar to that at lines 526-529 (drugs in same pharmaceutical class or with similar psychoactive properties regardless of the pharmacological MoA).
618-619	C		Please provide a reference for the standardized questionnaire describe in this section.
625-630	M	Monetary value is not present in	We recommend that

		the list of measures most directly related to likelihood of abuse in lines 625-630.	monetary value be added to this list.
634-638	M	Please address PK analysis which can assist with outliers.	We suggest that pharmacokinetic analysis be performed for reviewing plasma levels of subjects who react differently from the majority of subjects in the study.
635	M		Please provide examples of behavioral and cognitive performance assessment methods.
642-651	M		Please provide guidance for those cases in which the study hypothesis/primary objective is to have no significant difference for the active drug, in comparison to the positive control.
744	C	Regarding post marketing surveillance, FDA recommends using databases such as Treatment Episode Data Set (TEDS), Monitoring the Future (MTF), Drug Abuse Warning Network (DAWN), etc. However, we note that some or all of those databases may not capture information on a new drug that is not on the market yet or even a new drug where the name may not be commonly known to those using the drug on the street.	
747	C	The Guidance recommends the use of DAWN Emergency Department (ED) to characterize and monitor risks associated with the misuse and abuse of certain drugs under development. Given the current problems that this database is experiencing with new site recruitment and response rates of	

		participating sites, it is unclear whether DAWN ED can be considered sufficiently robust as a surveillance source.	
754-762	C	Experience with both the FDA/CSS and Substance Abuse and Mental Health Services Administration (SAMHSA) has shown that it is very difficult to draw substantive and persuasive conclusions regarding relative abuse of various formulations containing the same active molecule. So, with the type of epidemiology data presently available, this paragraph suggests an approach that may not be feasible.	
764-757	M	We note that some of the sources, *e.g.*, abuse clinics and poison control centers, do collect data systematically, contrary to the statements in the draft guidance here.	

Conclusion

Thank you for this opportunity to comment on the draft Guidance for Industry, Assessment of Abuse Potential of Drugs. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

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