BIOTECHNOLOGY INDUSTRY ORGANIZATION
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November 8, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2010-D-0451: Draft Guidance for Industry on Suicidality: Prospective Assessment of Occurrence in Clinical Trials

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Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Draft Guidance for Industry "Suicidality: Prospective Assessment of Occurrence in Clinical Trials." BIO supports the overarching goals of the Draft Guidance to reduce the potential for suicidal behavior, ideation and attempts during drug treatment. BIO encourages further validation of the Columbia Classification Algorithm for Suicide Assessment (C-CASA) and requests additional guidance on when this or alternative tools may be used.

BIO represents more than 1,100 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.

1. The Columbia Scale should be Further Validated

BIO is concerned that there is no mention in the Draft Guidance of how the Columbia Classification Algorithm for Suicide Assessment (C-CASA) scale and the Columbia Suicide Severity Rating Scale (C-SSRS) have been validated under various conditions, such as differing

study populations or cultures, or how the psychometric properties have been established. BIO is aware of a handful of studies that have assessed this tool[1], but it is unclear if the Columbia Scale has been adequately evaluated in a controlled, prospective fashion. Further, we are not aware of studies evaluating the scale in the context of all indications recommended for use in the Draft Guidance.

Additionally, using the C-CASA scale may generate extraneous information that is difficult to interpret in a useful manner. Experience suggests that that if a researcher purposefully asks about a specific side effect, they will tend to find it since the power of suggestion will elicit the response. There has been considerable research conducted on the potential bias introduced by using a checklist versus spontaneous reports, including Wallin et al. (1981), Barber and Santanello (1995), and Bent et al. (2006).

BIO encourages FDA to discuss in the Draft Guidance how the tool has been validated and whether it appropriately captures and classifies suicidal ideation and behavior. In addition, to minimize the potential for bias or confusion resulting from widespread use of this tool, we encourage the research community to further evaluate the Columbia Scale empirically through independent, peer reviewed study across all relevant indications discussed in the Draft Guidance.

2. Single-Source Assessment Tools May Limit Widespread Adoption

Currently, there are no alternate vendors for this specific product and the Draft Guidance is unclear as to how other assessments may be approved for substitution. Given the specific identification of C-SSRS as the assessment instrument acceptable to the FDA, we suggest that FDA and the Columbia University Research Institute for Mental Hygiene work together to ensure that the C-SSRS becomes publicly accessible in an open source format.

Since the scale has not been conclusively validated, it is also difficult for Sponsors to determine what measures would be necessary to validate an alternative instrument. The guidance states that "Sponsors can use other appropriate prospective suicidality assessment instruments, but should discuss alternative instruments with the appropriate review division." (Lines 140-142) More guidance addressing this point is needed. For example, the Sheehan Suicidality Tracking Scale has been discussed as another potentially appropriate assessment instrument.

3. The Draft Guidance may Underestimate Reporting Requirements

Use of the tool may be warranted to enhance patient safety and increase knowledge about the benefit/risk profile of a product, but should be administered in the most effective and efficient means possible. The Draft Guidance states that "Although the screening questions should be completed at baseline and at every visit for every patient, they are not by themselves

[1] Posner et al. American Journal of Psychiatry, "Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants", 2007;167:1035-1043

burdensome." (Lines 136-137) However, BIO questions whether the Draft Guidance accurately assesses the reporting burden associated with use of the scale. The experience of BIO member companies suggests that the C-CASA tool can be a time consuming process, as it contains numerous questions and can be complicated. As the Draft Guidance recommends that C-CASA be administered at baseline, at every study visit and also in some cases after the study is complete, use of the tool potentially increases the time and complexities of studies, which can be compounded across development programs with multiple studies.

Additional clarifications in the Draft Guidance may enhance the efficiency of administering the tool and maximize the benefits to patient safety. For example, the reporting burden may particularly be great during Phase 1 trials. The Draft Guidance indicates that for an inpatient Phase 1 study, suicidality assessments would ordinarily be done at the same times as other clinical assessments. However, inpatient Phase 1 studies frequently have daily assessments. As such, the addition of suicidality assessments at every assessment would greatly increase the time needed during Phase 1 trials. BIO requests additional clarification regarding the expectations for the frequency of assessments in Phase 1 trials under these conditions and administration of the C-SSRS on a daily basis to healthy volunteer subjects.

4. It is Unclear When Suicidality Assessments Should be Included or Omitted

Additionally, it is unclear which trials would or would not utilize this tool under the Draft Guidance. The Draft Guidance states that, "Other than the exceptions noted, prospective suicidality assessments should be carried out in all clinical trials involving any drugs being developed for any psychiatric indications, as well as for all antiepileptic drugs and other neurologic drugs with central nervous system (CNS) activity, both inpatient and outpatient, including Phase 1 trials involving healthy volunteers." (Lines 338-332) More clarification is needed regarding what would be considered evidence of CNS activity for neurologic drugs. For example, it remains unclear how drugs will be handled which are being developed for neurologic conditions and primarily target the immune response.

The Draft Guidance also states that a Sponsor considering the omission of standard suicidality assessments from a particular clinical trial in a particularly challenging population should discuss this omission with the FDA to gain prior agreement. Please clarify if the populations listed (Alzheimer's disease, other dementias, mental retardation, and autism) for which it is stated that it is reasonable to omit such assessments, require explicit prior agreement to omit prospective suicidality assessments from clinical studies.

Additionally, there are concerns beyond psychiatric and other central nervous system drugs as there are already a small-handful of drugs named as needing suicidality assessments and this list can be added to at any time. For example, the Draft Guidance recommends that prospective suicidality assessments be carried out in all clinical trials for all drugs that are pharmacologically similar to the following drugs: isotretinoin and other tretinoins, beta blockers (especially those entering the brain), reserpine, drugs for smoking cessation, and drugs for weight loss. (Lines 337-340) It is anticipated that this list may evolve over time and information is needed regarding how revisions in these recommendations would be conveyed to clinical trial Sponsors. Drugs on

this list include molecules that drug developers may not have anticipated as at risk and it thus becomes hard to scientifically rationalize when suicidality assessments need to be included in studies.

5. Rationale for Capture of Various C-CASA Coding Categories

Although reference is made to an anticipated separate guidance addressing the analysis of the data derived from prospective assessments of suicidality, some indications of preferences in data analysis are indicated. For example, the Draft Guidance states that *Code 7 / Self-injurious behavior without suicidal intent* represents a nonsuicidal event, but should nevertheless be captured because it has some predictive value for future suicidality. On the other hand, the Draft Guidance indicates that *Code 5 /Self-Injurious Behavior Intent Unknown* is unnecessary. However, even with intense effort, subjects may be lost to follow-up or important information may remain unavailable at the end of a study. Also it is indicated that Code 8 events need not be captured. More direction is needed regarding the handling of missing data and the rationale regarding the varying importance attached to certain C-CASA codes such as Codes 7 vs 5.

CONCLUSION:

BIO appreciates this opportunity to present our views on the Draft Guidance for Industry "Suicidality: Prospective Assessment of Occurrence in Clinical Trials" and we would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)