December 11th, 2017

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

Re: Docket No. FDA-2009-D-0461: Format and Content of a Risk Evaluation and Mitigation Strategy Document

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments to the Draft Guidance on Format and Content of a Risk Evaluation and Mitigation Strategy Document.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO commends FDA on this Draft Guidance which provides recommendations to applicants on drafting proposed Risk Evaluation and Mitigation Strategy (REMS) documents and converting an already-approved REMS document to a new standardized format.

General Comments

- The Draft Guidance should include additional REMS Requirements for REMS programs run or administered through specialty pharmacy healthcare settings. Requirements should include enhanced/expanded communication with prescribers and/or patients, which is within the workflow for specialty pharmacies.

- The Draft Guidance should specify the following:
    - Who is responsible for storage and retention of certain REMS participant documents (e.g., completed forms)
    - Who is responsible for monitoring of patients (see lines 67 and 70) subject to REMS (see also lines 197 and 480, as well as parts of HCP and dispensing sections). On this issue, it is not clear from the guidance whether it is the HCP and/or pharmacy. Also, it is not clear whether line 197 refers to HCP/dispensing participants, and not patient participants. Clarification is requested.
    - The duration of retention of these participant materials

BIO appreciates this opportunity to submit comments on the Draft Guidance on Format and Content of a REMS Document. We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart.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.

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Sincerely,

/S/

Sesquile Ramon, Ph.D.
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
III. FORMAT AND CONTENT OF A REMS DOCUMENT		
B. REMS Goals		
Lines 118	This section should include a clear statement of the risk(s) to be mitigated.	BIO asks FDA to include a clear statement of the risk(s) to be mitigated.
Lines 119-125	This section should include other examples of intermediate measurable objectives, including those focused on education of participants, which is often a major component of REMS programs.	BIO suggests editing the text to read: "The REMS Goals section should describe the overall, safety-related health outcome(s) that the REMS is designed to achieve. Because risk mitigation goals cannot always be measured directly, it is important to also include one or more intermediate measurable objectives that, if achieved, indicate that the REMS is meeting its goals. For example, a REMS for a drug that causes renal toxicity may include a goal to mitigate the risk of renal failure, and the measurable objectives could be that patients undergo periodic testing of serum creatinine and that appropriate management steps are undertaken based on the test results. Another example could be to regularly test REMS participants' understanding of the proposed education program.""
Lines 119-125 and 306-316	In lines 162-163, FDA recognizes and differentiates between clinical (i.e., targeted risk which can be reduced in frequency or severity by a specific intervention) and administrative (i.e., educational) REMS goals: "[Requirement]: Participant requirements generally include clinical or administrative activities that the participant must comply with as part of the REMS."	BIO recommends that FDA: 1. Provide additional examples of clinical *versus* administrative REMS in Lines 119-125 2. That the REMS Document Template be reflective of the difference between clinical and administrative goals in lines 306-316 by including a category of "Administrative" and "Clinical" in addition to the

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	BIO believes that the delineation between clinical and administrative REMS goals is important since the former is often more measurable/quantifiable. Conversely, if the specific risk is one which cannot be reduced in frequency or severity, the goal of the REMS is primarily to educate/inform prescribers and patients about the risk. This differentiation is important for completion of REMS assessments and evaluating/determining the impact/success of the REMS as well as forming the basis for potential modification of an established REMS. We therefore recommend, in addition to providing additional examples of clinical *versus* administrative REMS in Lines 119-125, that the REMS Document Template in lines 306-316 include a category of "Administrative" and "Clinical" in addition to the "REMS objective".	"REMS objective". We propose the following edit/addition: II. REMS Goal(s) This section describes the overall, safety-related health outcome that the REMS is designed to achieve (e.g., mitigate the risk of a particular serious adverse event) and the intermediate, measurable objectives. In many cases, it is not possible to measure a risk mitigation goal directly; therefore, it is important to include one or more intermediate, measurable objectives that, if achieved, indicate that the program is meeting its goal(s). [Overall REMS goal] [Administrative] and/or [Clinical] 1. [REMS objective] 2. [Other REMS objectives, as needed]"
C. REMS Requirements		
Line 134 and 174	This section begins by describing the REMS Participant Requirements. The current order (REMS participant requirements described prior to REMS applicant requirements) makes sense for REMS with ETASU, but most simple REMS have fewer participant requirements.	BIO suggests placing the "REMS Applicant Requirements" section before the "REMS Participant Requirements" section.
Lines 135-136	The current text implies only REMS with ETASU can have REMS participants. However, there are many FDA-approved non-ETASU REMS, such as those with communication plans only.	As such, BIO suggests editing the text to read: "The REMS Participant Requirements are the activities that REMS participants must undertake in REMS with ETASU or with communication plan only REMS."

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Line 146	Clarification is needed	BIO suggests including a sample completed table.
Lines 152-157	To better align the definition of "REMS Participants" with the examples given in sections 196-200 and 363-366, which indicate certain requirements that need to be fulfilled by participants for REMS with ETASU.	BIO suggests editing the text to read: "[REMS Participant]: REMS participants are stakeholders who participate in the REMS and are described based on their role in clinical assessment, prescribing, dispensing, administering, or monitoring as well as the distribution process. For example, REMS participants can include health care providers who prescribe; patients who receive the drug; health care settings, practitioners, and pharmacies that dispense; and wholesalers/distributors. REMS Participants for REMS with ETASUs may also have certain requirements to fulfill as further illustrated in this guidance document."
Line 158	The document should be aligned with REMS Document Template	BIO suggests editing the text to read: Change [Timing] to [Timing Category] to align with REMS Document Template
Lines 192-195	Under REMS requirements, the guidance stated, "as well as distribution process" (Line 130). However, in the requirement section, there is no mention of distribution process.	BIO recommends the inclusion of distribution process as part of REMS operations requirement for clarity. BIO suggests editing the text to read: "Requirements related to operations can include requirements for the applicant to develop, establish, and implement systems and infrastructure (e.g., databases, websites, call centers, distribution process) to support the REMS requirements that enable access to and participation in the REMS"
IV. PROCEDURES		
A. Proposed REMS Submissions		

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Line 228-229	The term "scoring criteria" is not clear	BIO suggests editing the text to read: "e.g., why a REMS is necessary based on application of the statutory factors, how the REMS would ensure that the benefits of the drug outweigh the risks, implementation processes, compliance and enforcement policies and procedures, definitions, knowledge assessment ~~scoring criteria~~ analysis approach, and the REMS assessment plan."
Lines 219-220	Proposed language states that the Medication Guides does not need to be appended to the REMS document when it is part of REMS materials.	BIO asks FDA to please clarify whether this is also true for the Product Information, for REMS materials that would be distributed with Product Information appended.
D. Posting REMS Documents on the FDA Web site		
Lines 280-283	Supporting REMS documents describe the rationale for the various REMS elements, however, these are not posted. Making these rationales available may prompt better understanding among REMS stakeholders, as a result, better compliance by practitioners, patients, and pharmacies.	BIO asks FDA to consider recommending that each section in an approved REMS document include a brief sentence describing the rationale.
APPENDIX: REMS DOCUMENT TEMPLATE		
Lines 314	The REMS Objective section should clearly indicate the risk(s) to be mitigated.	BIO suggests that the REMS Objective section indicates the risk(s) to be mitigated.
Lines 324-328	In line with comments made above to Lines 134 and 174, it may make sense to re-order this section so that the Applicant Requirements (what has to be	BIO suggests FDA place the "Applicant Requirements" before the "Participant Requirements."

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	done) come before the Participant Requirements (who has to do it).	
Line 366	In Item 7, it is unclear if [topic] is considered to be the "particular serious adverse event" referenced in line 308.	BIO finds this section of the Draft Guidance unclear and asks for clarification.