Biotechnology Innovation Organization

April 2, 2019

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

Re: Docket No. FDA-2018-D-4628-0001: REMS Assessment: Planning and Reporting

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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments to the Draft Guidance on REMS Assessment: Planning and Reporting.

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BIO applauds the FDA on the work done to develop this Draft Guidance - it offers clear, practical information to sponsors and other stakeholders who are involved in the design and effectiveness evaluation of REMS programs. This important Draft Guidance is well written and provides instrumental recommendations particularly on how the REMS program goals, objectives and REMS design may impact the selection of metrics and data sources, which will be used to assess whether the program is meeting its risk mitigation goals.

BIO appreciates the Agency's recognition that the "data sources, methodologies, and metrics used to assess the effectiveness of REMS continue to evolve" and that there are limitations to Sponsors' ability to accurately evaluate safety-related health outcomes as part of REMS assessment.[1] BIO suggests the Agency continue to keep the challenges of isolating the effect of REMS on health outcomes in mind when Sponsors are proposing metrics in the assessment category, "Health Outcomes and/or Surrogates of Health Outcomes." BIO would welcome the opportunity to partner with the Agency to define improved metrics to evaluate safety-related health outcomes.

Of note, it is not clear from the Draft Guidance how existing/well-established REMS for existing drugs will be addressed. BIO encourages the FDA clarify that existing REMS would be grandfathered, particularly regarding evaluation of burden on healthcare system and patient access.

[1] https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm629743.pdf

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BIO also recommends that the Draft Guidance address the unique challenges of conducting burden assessments of REMS, particularly regarding the dichotomy of challenges between conducting a burden assessment on REMS that have been required as part of an initial approval of a product, and REMS that have been required post-market as a result of an emergent safety signal. In the case of REMS that are required as part of an initial approval, there is no comparator group of patients who had access to the product without REMS. Without that comparator group, it is very difficult to measure the effect of the REMS program on patient access to the product. BIO suggests that the Draft Guidance acknowledge this difference in challenges and make suggestions for how to address burden in each case.

Regarding the assessment of effectiveness of "individual REMS requirements", the REMS elements are implemented as an integrated risk mitigation program. There are scientific challenges associated with attempting to isolate and independently assess the impact of an individual element of the program, and this point has not been addressed in the Draft Guidance. In the absence of baseline measurement (for instance in the case of REMS required as part of an initial approval as outlined above), evaluating the incremental value of a REMS component is even more difficult.

In the past, the FDA has conducted Webinars to discuss new guidance documents. BIO encourages the FDA consider conducting an educational Webinar once the Draft Guidance is finalized and would be happy to support the Agency as appropriate.

BIO appreciates this opportunity to submit comments on the Draft Guidance on REMS Assessment: Planning and Reporting. 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.

Sincerely,

/S/

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

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
General	General comment - multiple instances (e.g., lines 344 and 440) where the agency references conducting analysis "if feasible." Given the Agency is acknowledging challenges with feasibility of data analysis in some cases, it would be helpful if the Agency could describe examples of what might be feasible.	BIO suggest the Agency describe examples of what it refers to as "feasible" in various context of the Draft Guidance.
II. BACKGROUND		
Lines 55-63	It is unclear what the expectation for strategy assessments would be after year seven.	FDA should include additional clarification on how the Sponsors should proceed after year seven.
Lines 58-60	The section identifies the timetable for submission of the REMS assessment and lists two items. Currently, the FDA uses either the first option (18 months, 3 years and 7 years) or the second option (different frequency, e.g., 12 months). The use of the word 'and' suggests that both are applicable.	BIO proposed change: "- includes assessments submitted to the FDA by the dates that are 1)18 months, 2) 3 years after the strategy is initially approved, and 3) in the 7th year after the strategy is so approved, ~~and~~ **or"**
Lines 69-70	It is unclear if the statement regarding voluntary assessments of approved REMS, also would permit for sponsors to, based on a voluntary assessment, propose modification to approved REMS, i.e., reduce the burden of some or all of the original REMS requirements.	BIO suggests the Agency provide clarification
Lines 85-86	The word "management" is overly broad. BIO believes "clinical management or mitigation" is	BIO Proposed change: "…mitigate the risk of renal failure, the success of which may be measured by the

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	clearer, particularly in the content of a REMS with ETASU.	objectives that all patients undergo periodic testing of serum creatinine and that appropriate ~~**management**~~ **clinical management or mitigation** steps are undertaken when laboratory values are out of range.
Line 99	This assessment is crucial to meeting program objectives especially in ETASU REMS and when assessing the burden of a REMS on the healthcare system, HCPs and patients	BIO suggested edit: "**Whether the REMS elements pose any digital or technology challenges, as well as the extent to which these elements interface with electronic health records, pharmacy systems, and whether they are compatible with stakeholders' use environment and data sources."**
III. REMS ASSESSMENT- OVERVIEW		
Lines 79-80	It is unclear what the specific timeframe that FDA would consider the "REMS design phase."	BIO requests FDA provide additional clarification.
Lines 81-82	It is unclear what intermediate measures are suggestive of achieving REMS.	BIO requests FDA provide additional clarification.
Lines 89-94	Critical discussions regarding a REMS may occur very late in the review period and can be inappropriately rushed due to efforts to meet the PDUFA date.	BIO suggest the Agency initiate REMS discussions earlier in the review to allow adequate time for dialogue and agreement.
Lines 99-100	The Agency should include the conduct of situational analysis when discussing Sponsor's considerations for inclusion in REMS programs.	BIO suggested including the following as a sub-bullet: "**Conduct a situational analysis that would describe the regulatory context; the healthcare system and specific targeted healthcare settings (e.g., clinical-patient workflow? prescribers? settings? typical care processes?); and the policy environment (e.g., existing clinical guidelines? legal or economic incentives or dis-incentives?)"**

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Lines 104-108	It is unclear what the "premarket testing" referenced in this text would encompass.	BIO requests FDA provide additional clarification.
Lines 126-129	It is unclear what the Sponsor's and FDA's responsibilities once burden data are available.	BIO suggest that it should be possible to have a data-driven dialogue with FDA about addressing goals of REMS that prove to be burdensome. In addition, the Agency should provide a comment on how existing ETASU REMS should incorporate metrics assessing the patient access into their assessment plan. Additionally, please clarify whether these data points would include a drug utilization study or survey, and whether FDA has a preference for one versus another.
Lines 150-153	BIO is encouraged by FDA's call for collaboration among stakeholders with the goal to advance the science of evaluation.	BIO welcomes additional details on how to best engage with the Agency to advance this important area.
Line 154-156	It is unclear if each element of the REMS programs needs to be separately evaluated as well as the overall impact of the program	FDA should clarify that each element does not need to be separately evaluated.

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Lines 185-189	It is unclear whether these types of outcomes in an assessment of knowledge, attitudes and behavior (KAB) would be adequate, or if an additional study will be required to obtain the health outcomes being referred to. In addition, in regard to the reference to a reduction in the number of serious outcomes associated with a particular adverse event), it is unclear how this would be captured in the assessment report.	BIO requests FDA provide additional clarification.
Lines 194-195	In regards to the text: "Applicants should provide a rationale for all metrics selected and state whether the metric has been validated." It is not clear how the metric can or would be validated.	BIO suggests the FDA provide additional thinking for how it believes these metrics would/could be validated and provide literature or guidance references for validation methods
IV. DEVELOPING THE REMS ASSESSMENT PLAN		
A. Assessment Categories		
Lines 199-223	There are a variety of metrics provided in this section and it would be useful if the Agency could provide examples for how these metrics could be feasibly calculated.	BIO suggests the Agency provides relevant examples for how these surrogate outcomes could be measured, especially in the absence of patient registries
Line 190	*Sustainability* is not included as part of the aspect to assess within the assessment categories.	FDA should include *sustainability* as part of the aspect to assess within the assessment categories.
194-195	It is unclear what the Agency means by 'validated' as it is used differently across the document.	BIO suggests FDA provide additional clarification
Lines 181-183; 214-217	Section IV.A. (Assessment Categories) provides limited scope and examples of metrics to consider	FDA should provide further clarification on the scope and additional examples to consider for safe use behaviors.

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	for assessing safe use behavior. Current examples cited are laboratory tests, prescribing patterns and patient counseling.	
B. Selecting Metrics		
Lines 199-201	BIO appreciates FDA's desire to understand the open and read rate of communications. However, FDA has historically recommended U.S. mail as a first approach to be followed by email. Email is the only feasible means of tracking open and read rate. We suggest that the guidance be updated accordingly.	BIO proposed change: "Metrics in the Program Outreach and Communication assessment category may include numbers of specific REMS materials that were distributed ~~to, and the proportion of these that were subsequently opened or read by, the targeted audiences.~~"
Lines 203-207	This recommendation will be challenging for large-scale REMS programs or well-established programs.	BIO suggests FDA include "grandfathering" guidance for well-established REMS programs.
Lines 219-223	Metrics in the health outcomes assessment and/or surrogates of health outcomes assessment, can be limited by the degree of under-reporting or general reporting bias and is not necessarily something the Sponsor could mitigate. This is addressed later in the document but should also be noted here in this discussion.	BIO suggest that this portion of the document include a cross-reference to Section 4 (lines 332-368). In addition, BIO request clarification on whether the metrics referred to in this text correlate to the number of AEs reported post-marketing
C. Selecting Sources of Assessment Data		
Lines 234	The Draft Guidance states applicants are encouraged to identify complementary data sources that provide a combination of qualitative and quantitative information about the REMS. This section does not state when these Assessment Data should be considered part of the REMS or assigned as a PMR.	FDA should provide clarification on when the Assessment Data should be included as part of a REMS or assigned as a PMR.

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Line 236	The discussion in this section on use of complementary data sources is important and relevant, however some of these data sources will require additional time to extract meaningful data (in particular considering that they generally are not real-time databases, but rather will lag behind).	BIO suggest timelines for the sponsor to provide interim progress reports to FDA (and final commitment date) be adjusted accordingly.
Lines 298-301	The example given in the Draft Guidance of healthcare professionals reporting of compliant behaviors may potentially lead to biased data as providers may face liability when self-reporting non-compliance with a required risk intervention.	BIO suggest the Agency to revise the example to one where surveys strictly assess the knowledge that the healthcare professionals provides to the patient during the counseling session. This may provide a more accurate representation of safety message mastery and possibly represent a surrogate endpoint for impact of safety messaging on patients.
Lines 303- 305	Knowledge, Attitude, and Beliefs (KAB) surveys that measure "attitudes and beliefs" can be useful as a process indicator in some REMS assessment categories, however we note that associating changes in behavior (i.e., specific monitoring criteria or counseling recommendations) or outcomes with data from KAB surveys is not accurate and therefore not always an ideal measure, particularly for evaluating safety-related health outcomes.	BIO would welcome the opportunity to collaborate with the Agency to clarify when KAB surveys are appropriate and to develop more sensitive measures to get at REMS efficacy when they are not.
Line 309-330	This section is about drug utilization studies and there is ample literature on how to do a drug utilization study and the sources of data to be used, mostly secondary data sources such as prescription	The Agency should include additional information on how to use real world data. Please also clarify the requested timeframe for the submission of the drug utilization study protocol (i.e.,

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	claims. The Agency should reference these resources, in particular how to use real world data	will this be submitted in the same timeframe as the KAB survey?)
Line 356 - 357	Post-marketing adverse event data are in general not suitable for use to quantify the occurrence (frequency / incidence) of an adverse event. Reporting rates will likely increase after a REMS program is introduced, not necessarily due to an increase in true incidence of the adverse event of interest, but potentially due to increased awareness of the issue (if the REMS communications are accomplishing their intended objective) and/or increased ascertainment (for REMS programs that include augmentation of safety data collection and/or REMS assessments that involve outcome studies or direct interactions between the Sponsor and customers such as surveys).	The Draft Guidance should recognize that for new drugs, it is likely that the REMS program will be introduced at the time when the product is launched. For many products, therefore, there will be no valid comparator.
Lines 339-403	It is unclear whether FDA expects sponsors to include post marketing AEs reported in the Assessment Report.	BIO suggests FDA provide additional clarification
Lines 423-424	The guidance refers to seeking input from key stakeholders affected by REMS. It is unclear whether FDA's expectation is that market research studies be conducted, or whether this information should be obtained from other means.	BIO suggests FDA provide additional clarification
Line 439	It is not clear what an acceptable performance threshold for a health outcome of interest is.	BIO suggests the FDA include in what the FDA considers acceptable. For example, 70-80% threshold for knowledge assessment.

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Lines 447-453	As drafted, the recommended approach is highly biased. We believe using a range of values is a better way of taking these biases into account.	BIO suggest deleting the following language: ~~In lieu of prespecifying performance thresholds, applicants could consider providing alternatives such as: (1) a comparison of an adverse event for a drug with a REMS to a similar drug without a REMS, (2) a comparison of the reporting rate of an event from data obtained in a REMS registry to a background rate of that event in a similar patient population from a representative database, or (3) a comparison of the reported rate or the event rate from observational studies to the rate that was observed in the clinical trials. Each of these comparisons has limitations and should be interpreted with caution."~~
D. Specifying Thresholds for REMS Effectiveness		
V. CONSIDERATIONS FOR MEASURING BARRIERS TO PATIENT ACCESS AND BURDEN ON THE HEALTH CARE DELIVERY SYSTEM		
Line 457-459	Including ETASU in REMS allows patients safe access to drugs with known serious risks that would otherwise not be approved or would be withdrawn. Section 505-1(f)(2) of the FD&C Act 459 states that such ETASU shall, considering the risk, not be unduly burdensome on patient access, and, to the extent practicable, minimize the burden on the health care delivery system.	BIO suggest referencing the below guidance and describe how it applies to assessing impact on healthcare delivery system and patient access "A Framework for Benefit-Risk Counseling to Patients About Drugs with a REMS" (https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM577883.pdf)
A. Assessing Burden on the Health Care Delivery System		
General	Assessment of burden on the healthcare system: current state-of-the art regulatory science has not identified valid and robust methodologies to quantify burden on healthcare systems, prescribers	BIO suggests that assessing burden on health care system and patient access be optional as it is not clear how it can be assessed.

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	or patients. While practitioner- and patient-reported perceptions of burden can be collected to support a holistic impression that REMS elements are considered burdensome, it is not clear how these data can be compared to measures of risk mitigation for the purpose of understanding when a REMS element is "too burdensome" to justify the potential patient safety benefits of the intervention. Given the exploratory state of research in this area, it may not be reasonable to mandate formal assessment of burden as an element of REMS assessment.	It would be useful for the Agency to clarify what is considered unduly burdensome. By their nature, REMS with ETASU will be burdensome to the health care system and are supposed to introduce elements to assure safe use.
B. Assessing Barriers to Patient Access		
Lines 526-528	It is unclear what the types of patient interviews and focus groups FDA is referring to here.	Please describe the types of patient interviews and focus groups FDA is referring to here, and any parameters in planning those engagements, to ensure that patient feedback is considered by FDA to be valid and usable.
APPENDIX 1: EXAMPLE - ASSESSMENT CATEGORY AND METRICS		
Line 687	BIO believes the table should provide metrics in all REMS assessment categories rather than limiting the table to "Program implementation and operations" and "safe use behaviors."	BIO suggest the Agency to consider further building out the table and include example metrics for the assessment category "Health Outcomes and/or Surrogate Health Outcomes," BIO suggests that FDA reference Lines 219 through 223, where the Agency has already described example metrics and surrogate metrics (i.e., rates of serious bleeds and neutropenia, and inadvertent fetal exposures and number of prevented fetal exposures to the teratogenic drug). BIO would also be grateful for an example outcome metric based on a baseline comparison to events from real-world data/clinical trials versus post-approval events.

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		With regards to REMS assessment more generally, it would be useful of the table included example metrics that incorporate: • Assessment of REMS risk messaging effectiveness and alignment with current standard of care (clinical trial guidelines, HCP CME content, etc.) • Proportion of HCP knowledge about the risk over time • proportion of HCPs who understand the dosing/administration and patient monitoring considerations (and sources of information - app, CME, med practice guidelines, other)
APPENDIX 2: EXAMPLE REMS ASSESSMENT PLAN OVERVIEW		
General	BIO believes that having an example of REMS and REMS assessment plan in the Appendix is of great benefit. It would also be helpful to provide an example of REMS assessment report.	BIO suggests adding an Appendix with an example assessment report.