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

Re: Docket No. FDA-2009-D-0461: Draft Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies, REMS Assessments, and Proposed REMS Modifications

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Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Draft Guidance for Industry on "*Format and Content of Proposed Risk Evaluation and Mitigation Strategies, REMS Assessments, and Proposed REMS Modifications.*"

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.

BIO appreciates that the FDA has developed the Draft Guidance to provide additional information for industry on the processes for submitting, modifying, and assessing REMS programs. By definition, prescription drugs and biologics carry both benefits and risks that must be carefully evaluated by patients, healthcare providers, regulators, and industry. In 2007, Congress codified many accepted risk management practices through

the establishment of REMS under the *Food and Drug Administration Amendments Act of 2007* (P.L. 110-085, FDAAA).

We hope that the Draft Guidance and future REMS guidances continue to identify common processes and best practices for agreeing upon REMS and appropriate risk management tools. Based on the operational experience of BIO's member companies with REMS programs, our comments propose several recommendations on how to best:

1. Enhance FDA-Sponsor communication around REMS requirements and integrate REMS discussions into the Good Review Management Practices;
2. Facilitate minor, editorial, and non-substantive modifications to REMS; and
3. Assess the effectiveness of REMS programs.

We believe that as both FDA and industry gain greater experience with the challenges and nuances of REMS, there will continue to be opportunities to share experience to refine and improve REMS-related processes and policies.

I. FDA AND SPONSORS SHOULD COMMUNICATE ABOUT POTENTIAL REMS REQUIREMENTS ON A REGULAR BASIS

In the context of the initial approval of a REMS or substantive modification to a REMS as part of a company's risk management strategy, it is critical that FDA and Sponsors have a common understanding of when and how Sponsors should communicate with FDA regarding a potential REMS and how that discussion is integrated into the review process. In general, the Draft Guidance addresses the question of what to do after a REMS is required, but does not address how the decision to require such a program is reached. It is important that Sponsors understand when and how agreements are reached and what specific risk is to be mitigated. This critical decision that determines the nature and content of a REMS should be addressed in the Draft Guidance.

Additionally, the Draft Guidance does not sufficiently address the timing of REMS discussions between Sponsors and the FDA and how those discussions are integrated into the Good Review Management Practices (GRMPs). Best practices suggest that Sponsors should collaborate with regulatory authorities early and throughout the development lifecycle to discuss emerging safety issues and develop science-based risk management plans that will be effective. Through proactive risk management, it may be possible for sponsors to construct drug development plans that accelerate patient access to life-enhancing and lifesaving medicines with Sponsor commitments to actively monitor safety and benefit-risk balance on an ongoing basis.

For example, for drugs in a class for which a previous active moiety has a REMS, the FDA and the Sponsor should be able to discuss very early in development the need for a REMS given the targeted indication and the class of the new active moiety. Also, for drugs of a class with existing Elements to Assure Safe Use (ETASU), such as drugs with known teratogenic potential, Sponsors and FDA should be able to anticipate very early in development that ETASU will be expected should the drug be marketed. However, Sponsors will often develop a new product in an existing class because it may have a

superior safety profile. Therefore, in some situations even though a drug is in the same class as previously approved drugs with a REMS, there may be factors that obviate the need for a REMS. These factors should be discussed with FDA early in the process.

Importantly, for drugs needing a new REMS or a change to the approved REMS, both FDA and the Sponsor must be timely in the sharing of new safety information (regarding a serious or unexpected risk associated with use of the drug, or safety information about the effectiveness of the approved REMS (505-1(b)(3)). Identification of new safety information and discussions about the search methodology, strength of association, and validity of the analysis should be timely and transparent. If there is need for special expertise to be brought into the discussions, this should be recognized early on and obtained. There are numerous opportunities to apply good review management practices to the decision-making and review of REMS.

A. Integrating Risk Management Discussions into GRMPs:

For the REMS provisions to have their intended effect and to ensure a timely review and approval process, BIO recommends that FDA integrate risk management considerations and discussions, including REMS, into the GRMPs and not merely view it as an “add-on” obligation for Sponsors and FDA to discuss at the end of a review. One of the messages FDA has delivered consistently to Sponsors is the importance of submitting complete applications to FDA to avoid unnecessary delays caused by reliance on major amendments to applications. This message is undercut by FDA’s reluctance to discuss REMS until the end of the review process. It is impossible for Sponsors to submit complete applications to FDA if Sponsors do not know what FDA would consider to be complete.

FDA should agree that Sponsors could engage with the Agency during the product development process and that formal PDUFA meetings are appropriate during this stage of the process to discuss a potential risk mitigation strategy, including REMS. Since these meetings would be part of the development process for a filing, Type B meetings would be ideal.

We suggest that certain milestone interactions and discussion topics could be incorporated into the GRMPs to facilitate early discussion of REMS within the larger context of risk management planning. As noted in the chart in Appendix A (page 29), numerous opportunities exist during a product’s lifecycle for FDA and a Sponsor discussions of risk management activities. Many of these milestones should be formally integrated into established meeting and review practices, and where appropriate, communicated to the Sponsor in the 74-day letter consistent with the 21st Century Review Process.

We believe that FDA’s implementation of the REMS provisions would benefit from the development of internal procedures and a Manual of Policies and Procedures (MaPP) around REMS, similar to internal procedures that already exist for other statutory obligations. In addition to addressing how REMS should be incorporated into the

GRMPs through the REMS draft guidance, we suggest that several existing MaPPs and Guidelines should be revised accordingly.^{1, 2, 3, 4, 5}

B. Establishing a Methodology for Determining if a REMS is Appropriate:

To date, REMS discussions have usually been initiated by FDA only after labeling is determined or at an advisory committee meeting. This is too late in the review process and leads to unnecessary delays. BIO proposes that after Phase II of product development, Sponsors and FDA should discuss and formally agree on the methodology to evaluate potential or identified safety risks during the Phase III studies, such as frequency of laboratory tests, adjudication of adverse events, the high level design of post-marketing studies and any additional risk management strategies including REMS. This agreement by both FDA and Sponsors would be analogous to an agreement on efficacy endpoints between FDA and Sponsor resulting from a Special Protocol Assessment (SPA) process, but would address a safety signal and would not be binding.

This risk management discussion, which could be incorporated into the end-of-phase II meeting, would need to involve the Office of Surveillance and Epidemiology (OSE) as well as the Office of New Drugs (OND). A plan to address any new safety signals identified in Phase III should also be discussed. Newly identified risks would require further discussion and possible modification of the safety assessment along with risk mitigation strategies. If no new safety issues arise during or after Phase III, Sponsors would expect that the agreed upon risk mitigation plan would support timely product approval with the agreed-upon risk management activities, including REMS, as applicable. Thereafter, at the time of issuance of the 74-day letter, FDA should meet with the Sponsor to address REMS and discuss whether there are new safety concerns that warrant additional REMS planning.

¹ MaPP 6010.1 Review Management/Pre-approval Safety Conferences
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm079940.pdf>

² MaPP 6025.1 OND/Good Review Practices
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm082016.pdf>

³ MaPP 6700.1 Review Management/Risk Management Plan Activities in OND and ODS
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm082058.pdf>

⁴ MaPP 6020.4 OND/Classifying Resubmissions
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm082002.pdf>

⁵ Guidance to Review Staff and Industry: Good Review Management and Review Practices for PDUFA Products, April 2005
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079748.pdf>

C. Documenting and Communicating Criteria for a REMS:

There continues to be uncertainty regarding FDA's criteria for determining if a REMS is necessary, particularly if the REMS needs to include ETASU. Often, Sponsors and FDA disagree as to the necessity of a REMS and the REMS elements. To advance the dialogue between Sponsors and FDA and facilitate mutual commitment to implementation of a beneficial REMS program, we request that the Agency commit to providing a formal written explanation to a Sponsor regarding the need for a REMS, including an explanation of the rationale for each REMS element. Such a document is needed for the sponsor to create the content of its REMS and draft its REMS supporting document. For consistency, clarity and transparency, we recommend that such considerations be standardized by a guidance to reviewers or a CDER MaPP and CBER Standard Operating Procedures and Policies (SOPP), and that this document be made available with the drug approval package on the FDA web site.

D. Discussion of Risk Management Strategies Outside of the Scope of REMS

In addition, sponsors may wish to seek FDA review and comment on risk minimization strategies even if they are not necessary to ensure the benefits outweigh the risks. A Sponsor can propose risk minimization activities outside of a REMS (in section 4 of an EU format RMP) that will help optimize the benefit/risk balance but are not essential to ensure a positive benefit/risk balance. Such a proposal would be considered a risk minimization commitment whereas a REMS would be considered a risk minimization requirement.

FDA should also define a much more streamlined program for communication-only REMS programs consistent with the legal threshold and spirit of REMS, which is to impose substantial risk minimization only on products that would not otherwise be approved (i.e., risk would outweigh benefit). Communication-only REMS should have more narrow goals and streamlined documentation and data collection. Alternatively, if FDA believes it does not have the statutory flexibility to permit streamlined programs for some REMS, then we ask the Agency to consider how to permit communication elements such as MedGuides to be implemented outside FDAAA.

E. Communicating REMS Information Regarding an Off-Label Use

There is also uncertainty regarding FDA's requirement in certain instances that a Sponsor comply with REMS labeling requirements that address an off-label use of the Sponsor's approved drug. For example, an FDA requirement that a Sponsor warn against a specific risk or adverse event associated with a drug may encompass approved uses as well as off-label use of a drug. This could occur where a recognized off-label use of a drug, such as a use that represents a medically accepted standard of care, is deemed by FDA to present a specific risk that can be addressed and mitigated by a REMS requirement. However, in this same instance it is not clear that FDA would permit the required information regarding the risk of the off-label use to be accompanied by information regarding the safe, appropriate use of the drug for that off-label indication. Accordingly, it appears that

physicians may receive incomplete information: a warning regarding an off-label use without the information regarding how to properly use or administer the drug, proper dosing, and other adequate directions for use of the drug.

BIO is concerned about the resulting knowledge gap and imbalance of information that can result from supplying one-sided information to a physician. A Sponsor is the primary source of product information for a physician, and information supplied pursuant to a REMS is of particular significance and import for a physician to rely upon in patient care. While an off-label REMS scenario likely would not arise for the majority of REMS drugs, it presents a challenging situation that is important for FDA to address. In a regime where product use and benefit information provided by a sponsor to a physician must be balanced by relevant risk and warning information, BIO believes that the reverse must also be the norm--that product risk information distributed by a Sponsor to meet a REMS requirement must also include necessary product use information, to serve as the basis for adequate information for the product's use.

II. THE MODIFICATION PROCESS SHOULD FACILITATE MINOR, EDITORIAL, AND NON-SUBSTANTIVE CHANGES TO REMS

BIO is pleased that the guidance addresses the important issue of how REMS programs should be modified in the post-market timeframe. However, BIO is concerned about the suggestion that all REMS modifications, regardless of whether they are substantive changes to the strategy or a minor editorial changes to an implementing tool, must be submitted through the prior approval supplements process. In the Draft Guidance, FDA states that “Any proposed modification to the approved REMS, including *any proposed changes to materials that are included as part of the REMS* (e.g. communication and education materials, enrollment forms, prescriber and patient agreements), must be submitted as a proposed modification to an approved REMS in a new prior-approval supplemental application . . . and must not be implemented until the modified REMS is approved by FDA.” (*Draft Guidance*, 945-949, emphasis added). We believe this process will create unnecessary delays in mitigating emerging safety issues and create an administrative burden for FDA and industry when minor changes are needed.

A. FDA Should Limit Review and Approval to Proposed REMS Document

It is important to differentiate between the approved “REMS document” that outlines the risk management strategy and the supporting “REMS Tools” that are used to administer that strategy. Under current practice, FDA requires review and approval of the proposed REMS document *and* the REMS “tools,” such as REMS introductory letters, attestation forms, enrollment forms, data collection forms, and websites, that effectively “touch upon” the REMS. The word-for-word pre-approval of the REMS “tools” (excluding Medication Guides which are regulated by 21 CFR 208) can be time consuming and burdensome for both FDA and Sponsor. In certain instances, this could significantly delay implementation of a REMS designed to mitigate a safety concern for a marketed product. Finally, this is unlikely to be sustainable as more and more REMS are required. Notably, since FDAAA went into effect about 18 months ago, 9 REMS with elements to

assure safe use have been approved; prior to that a total of 16 RiskMAPs with some element to assure safe use were approved over a 16 year period.

We recommend that FDA clarify in the Final Guidance that the “approved REMS” consist only of the concise REMS document and the ten elements outlined in FDAAA. In turn, the Agency should allow Sponsors the ability to develop REMS tools that are consistent with the approved REMS and statutory elements. We suggest that FDA should review and approve the REMS document governing the risk management strategy and that the Sponsor should be charged with ensuring that all supporting REMS tools are fully consistent and compliant with the approved REMS document, and FDA could then exercise general oversight as warranted.

We recognize that all requirements of an approved REMS must be clear enough to provide enforceable standards. However, this requirement must be balanced against the need for prompt and efficient communication of safety concerns and the practicality of operating a complex program that has implications for patient access to new medicines, and adds operational pressures to an already overburdened health care system.

B. A “Tiered Approach” to REMS Modifications to Facilitate Administrative Reporting of Minor Modifications to REMS Tools

If the FDA does not agree with the above recommendation, then we suggest alternatively that FDA allow Sponsors to make minor changes to approved REMS tools without obtaining prior approval from the agency through an administrative reporting process. Substantive modifications would continue to require prior approval supplements. Industry experience with administering risk management programs suggests that a level of flexibility must be built into a risk management program to accommodate changes.

First, no matter how carefully FDA and the Sponsor design a REMS, a Sponsor will inevitably need to improve the selected tools over time to allow for effective implementation and best meet the plan’s goals. But if prior review and approval of every change to a REMS tool is required, improvements can be delayed for weeks or months before FDA can review and approve the change.

Second, requiring prior review and approval of every change to a REMS tool, no matter how minor, is simply not sustainable or scalable as more REMS are approved by the FDA. Sponsors need to have flexibility to make timely adjustments to REMS tools and should not be required to invest the substantial resources needed to conduct a REMS assessment for every minor, non-substantive change. More importantly, FDA’s limited resources should not be devoted to reviewing supplements making only minor changes to an implementing tool. FDA’s resources should be devoted to reviewing substantive REMS changes or other activities that further the public health.

BIO recommends that in the Final Guidance, the Agency establish a more targeted, efficient, and scalable system, whereby Sponsors are permitted to make minor changes to the approved REMS tools in advance of FDA’s review and approval of the change. Changes falling under this procedure would be limited to technical, managerial,

administrative, and minor changes to approved REMS tools that do not alter the fundamental approved REMS document. These types of changes, such as improving enrollment processes through a web-based system or adding means to improve data collection (such as a phone call to prescribers), are often simple, ongoing program management improvements that are intended to provide better operation of a complex risk management program. These are not changes that would be expected to impact the safe use of the product or impact the risk mitigation strategy or goals of the REMS. FDA could require that all minor changes be submitted to FDA in some form, such as the next assessment report. BIO believes that such a system would be consistent with FDA's legal authority and would further the agency's public health mission. As REMS programs continue to proliferate and apply to additional products, the Agency should embrace a pragmatic approach to continual management and refinement of these programs.

i. FDAAA Permits Minor Changes to REMS Tools in Advance of FDA's Approval

BIO believes that this approach is consistent with FDAAA. Sections 505-1(g) and (h) of FDAAA set forth a procedure for making "modifications" to an approved REMS strategy. Section 505-1(g)(1), "Voluntary Assessments", provides that "[a]fter approval of a [REMS], the responsible person involved may ... submit to the Secretary an assessment of, and propose a modification to, the approved strategy for the drug involved at any time." (505-1(g)(1)). Following receipt of a proposed modification and assessment, the agency shall "promptly review ... each assessment of an approved [REMS] for a drug submitted under subsection (g)." (505-1(h)(1)). Until FDA acts, the "approved [REMS] strategy shall remain in effect." (505-1(h)(3)(B)). These provisions address "REMS strategy", but not REMS tools.

As reflected in the Draft Guidance, and consistent with the experience of BIO member companies, CDER officials have interpreted these provisions as requiring prior FDA review and approval for any change to a REMS including all the REMS tools, no matter how minor or insignificant. While this may have been a prudent strategy for FDA to adopt while the Agency and Sponsors gained initial experience with REMS, it is not required by the statute. Section 505-1(g) and (h) are triggered only when the Sponsor of a REMS proposes a "modification" to "the approved strategy" not a modification of the REMS tools. In circumstances where a Sponsor intends to make only minor or editorial changes to the approved REMS tools, the Sponsor has not proposed a modification to the "approved strategy" as that term is used in the statute.

As used throughout Section 505-1, the term "strategy" is used to describe the specific elements of a REMS that are intended to address the risk of the particular drug or biologic. The minimum "strategy" that must be part of a REMS is a timetable for assessment of a REMS. (505-1(d)). If the agency makes specific findings, it may also require "Additional Potential Elements of Strategy," including a Medication Guide, patient package insert, or communication plan (505-1(e)). Finally, if the product were to be made available only if certain "elements to ensure safe use" were implemented, the "strategy" may incorporate such elements. (505-1(f)). The "strategy" described in Section 505-1, therefore, refers to the specific elements that address the risk of a

particular product. But where a Sponsor makes only minor or editorial improvements to the REMS tools, such as an enrollment form or communication materials, the “strategy” (which should be the approved REMS document) has not been modified.

The distinction between a REMS strategy and a REMS tool is significant and enables reasonable implementation of the FDAAA REMS Assessment and Modification provisions. If one were to interpret the statute as requiring that any changes to REMS tools -- including minor, non-substantive changes -- triggered Section 505-1(g), the Sponsor would uniformly need to conduct an “assessment” of the REMS and the proposed modification. In situations where the change is merely editorial in nature and could not reasonably be expected to impact the safe use of the product, such an assessment would be redundant to the periodic assessments already required under Section 505-1(d). For example, if a Sponsor seeks to change the toll free number on an enrollment form, clearly no “assessment” would be necessary to support that proposed “modification.” Conducting such assessments would be unnecessary and would result in both the Sponsor and FDA expending unnecessary resources.

ii. At Minimum, FDA has Authority to Exercise Enforcement Discretion

While BIO believes that FDA has ample statutory authority to permit Sponsors to make minor changes to REMS tools, at a minimum the Agency should reflect in the Final Guidance that it will exercise enforcement discretion to permit Sponsors to make minor changes to the approved REMS tools. In doing so, the Agency could describe, among other things, the specific types of changes that qualify for enforcement discretion (e.g., minor changes that could not reasonably be expected to impact the safe use of the product under the REMS) and the circumstances under which enforcement discretion would be exercised (e.g., only where the Sponsor has submitted information regarding a revised REMS tool prior to its adoption). Specifically, FDA should allow Sponsors to make technical, managerial, or administrative changes to REMS tools and submit the changes to FDA either as part of the next REMS assessment report, on a “first use” basis, or as an annual review submission. (See 21 CFR 314.81) This would empower Sponsors to manage REMS programs more effectively while allowing FDA the ability to oversee those changes in a timely fashion and not delay the implementation of these minor changes that don’t impact the approved REMS document.

C. REMS Tools Should be Updated via Administrative Reporting to Reflect the Current Labeling After a Safety Labeling Change

We also note that a similar administrative reporting process should be used to bring REMS tools into compliance with updated product labeling after a sponsor makes an FDA-approved safety labeling change or when FDA exercises its FDAAA safety labeling authority to request a labeling change under 505(o)(4). BIO understands that there have been instances in which a Sponsor with a product subject to a REMS made an FDA-approved safety change to the label, but FDA did not approve similar updated language on the REMS forms for more than six months after the label update. Such a delay could result in REMS forms that are out of date and inconsistent with the revised labeling.

We propose that Sponsors should also be able to update REMS tools according to a similar administrative reporting process in order to ensure that they are consistent with revised labeling and implemented in a timely manner.

III. ASSESSMENT OF THE EFFECTIVENESS OF REMS STRATEGIES

FDA and sponsors are just beginning to gain experience with assessing the effectiveness of REMS programs. While some unique assessment timetables call for assessments as often as every 6 months, most standard 18 month assessments are approaching or currently at hand for products that have been approved and/or marketed with a REMS since March 27, 2008. We believe that it is reasonable for the FDA guidance to provide initial instruction on how to conduct a REMS assessment and then provide expanded guidance to industry after gaining additional operational experience with REMS evaluations. BIO plans to provide FDA with additional comments and considerations around REMS assessments in the future and suggests that FDA carefully consider the feasibility of what is proposed as it formulates additional guidance on this topic in the future.

A. FDA Should Plan a Series of Public Workshops to Discuss REMS and REMS Assessments:

BIO recommends that FDA host a series of public workshops with public stakeholders to discuss the impact of REMS on the healthcare system and access to drugs. To date, many of the discussions around REMS implementation have involved FDA and drug manufacturers. However, the impact of REMS and efforts to improve the efficiency of REMS administration involve a wide range of stakeholders, including physicians, pharmacists, nurses, liability carriers, state licensing boards, and patients. REMS and important questions of benefit/risk management touch many diverse stakeholders and no single group will be able to resolve this issue alone.

For example, FDA expectation around the level of detail and information captured in a REMS assessment is extremely high. As suggested in the Draft Guidance, a Sponsor may be required to assess “each known occurrence of prescriptions written by a health care provider (HCP) who does not have required certification, etc...” Or the Sponsor may be required to ensure that each prescriber and patient is enrolled in the program. A compliance goal of one hundred percent is not feasible given the role of Sponsors, which is not that of HCPs who treat patients.

Making progress towards these lofty goals will not be possible without full engagement and cooperation from healthcare professionals and other healthcare delivery system stakeholders. A public workshop can initiate a productive dialogue and foster a spirit of cooperation for the common good. One area that would benefit from public discussion is survey methodology around patient/physician understanding of serious risks. This subject is extremely complex and multi-faceted and FDA and stakeholders would benefit from public discussion on this topic.

B. Pre-Determined “Targeted Values” and “Absolute Goals” are not Appropriate

The guidance suggests that a proposed REMS assessment plan in the REMS supporting document should include “Targeted values for each measure and the timeframe for achieving them. Include interpretations of expected results under best- and worst-case scenarios. In addition, this section should specify what values of measures at specific time points will trigger consideration of REMS modification” (Lines 795-798, emphasis added). We agree that it is appropriate to have well-defined, evidence-based, and objective performance measures tailored to those elements measuring the effectiveness of the REMS tool. However, we question whether it is appropriate or feasible to include predetermined “targeted values.” In many cases, Sponsors will not be able to predict what data will precipitate a REMS modification. Only when the data are gathered and analyzed could a Sponsor determine that a REMS might need modification. This provision inappropriately asks Sponsors to engage in and document speculation and also creates an unnecessary administrative burden.

Additionally, lines 371-373 suggest that REMS goals should be stated in “absolute terms.” We ask the agency to attempt to reconcile its view that the REMS goals be “ideal” outcomes that “might not be possible” to meet, with its view that the concise document in which the goals are contained are enforceable. Sponsors should not be set up for failure by having to commit to ideal goals that may not be achievable. We urge the agency to clarify how it intends to enforce goals that are stated in “absolute terms” or revise this approach. One way of reconciling these concepts is to rely, for enforcement purposes, on the objectives, which sponsors agree should be pragmatic, specific and measurable.

Finally, there should be a distinction between section 501(e)(3) REMS that contain the more routine communication elements, versus section 501 (f)(3) REMS that include the types of risk minimization that are designed to directly impact “safe use” of the product. Specifically, we would like to see this distinction emphasized both at the point of defining the REMS objectives and also in relation to the REMS assessment. We recommend that a section (e) REMS almost by definition should have a goal that is defined as increasing awareness/knowledge. A section (e) REMS (communicative elements only) is not an “element to assure safe use” and is only one factor that influences patient/HCP behavior and impacts outcomes. There is statutory support for this point as well, in that the provision related to monitoring and evaluating third party behavior is limited to section (f) elements. Requiring REMS sponsors to set behavior/outcomes goals for communication elements would be inconsistent with FDA's own acknowledgement that little is known about how much these communication elements actually impact behavior. But we would agree that it is reasonable to set behavior/outcomes goals for the types of interventions contemplated by section (f) elements.

C. Sponsors Cannot “Audit” Third Parties to Ensure Compliance with REMS

We note that the guidance recommends that a proposed REMS assessment plan include “The type of data that will be collected, and the nature and timing of data collection, analyses, audits, or monitoring that will be used to assess the performance of each individual REMS element or tool in achieving the REMS’s objectives and goals.” (lines 799-803, emphasis added). In fact, the guidance states that the ETASU Implementation Plan may also require that “The applicant conducts periodic audits of pharmacies, practitioners, and health care settings to ensure compliance with ETASUs (e.g., documentation of safe-use conditions prior to dispensing drug)” and “If the ETASUs include limits on where and how a drug may be dispensed, the applicant conducts periodic audits of wholesale shipment or distribution systems to determine that the drug is only being distributed to authorized entities” (lines 615-620). BIO is concerned about the implication regarding Sponsor auditing of the activities of third parties. There are significant practical limitations in how sponsors may audit a third party, such as a pharmacy or physician’s office, that would not be a party to the REMS agreement or ETASU implementation system. While FDAAA provides that in certain instances sponsors may be required to “take reasonable steps” to monitor and evaluate third party implementation of REMS elements—and to “work to improve implementation of such elements by such persons”, (505-1(f)(F)(4)), sponsors should not be held responsible-- despite these “reasonable steps”-- for failures of third parties.

Every REMS - whether it contains subsection (e) communicative elements, subsection (f) elements to assure safe use, or both - imposes obligations on the Sponsor. An important component of every REMS assessment should therefore be a detailed description of the steps taken by the Sponsor to comply with its specific obligations under the REMS and an assessment of its compliance during the relevant period. For example, if the REMS includes a MedGuide, the assessment of that REMS should include a description of what steps the Sponsor takes in the area of manufacturing and packaging to affix the MedGuide to its product, as well as compliance metrics, data or information from its quality-control system or other measurements to establish compliance with the system as designed. If the REMS includes a plan for communication to healthcare providers, the assessment of that REMS should include a description of the intended recipients, the steps taken by the Sponsor to provide materials to those recipients, and the data or metrics collected by the Sponsor to verify that the materials were sent to recipients as designed. As another example, if the REMS includes the requirement that patients be enrolled in a registry, the assessment of that REMS should describe the steps the sponsor took to create the registry and enroll patients.

In addition to imposing explicit obligations on the sponsor, a REMS may implicitly embody the expectation that third parties make certain decisions or take certain steps with respect to the drug in question. For example, it may inherently rely on physicians reading Dear Doctor letters provided and adhering to the precautions described. A REMS may rely on pharmacists distributing MedGuides when they dispense the drug subject to that MedGuide and may rely on patients reading those MedGuides. And it may rely on actual prescribing and use patterns that adhere to the conditions described in the approved labeling.

Sponsors are not, however, legally responsible for the independent decisions or actions of third parties with respect to their drugs, even when those drugs are subject to REMS. FDA therefore should not, as part of the REMS assessment process, hold Sponsors accountable for these decisions and actions. There may, of course, be situations where a Sponsor has information about third party behavior. It is appropriate for REMS assessments to include whatever information is known to the Sponsor about third party decisions and behavior. FDAAA only authorizes FDA to require a Sponsor to monitor and assess a third party in cases where a REMS requires one or more of the following elements: that pharmacies and others dispensing a drug be specially certified; that a drug be dispensed to patients only in certain settings, such as hospitals; and that patients have evidence of “safe-use conditions” (e.g., laboratory test results).⁶ If a REMS contains any of these three elements, it may also include a system through which the Sponsor is able to monitor and evaluate implementation of the element by the relevant third parties.⁷

Even in these situations, the obligation to create a system to “monitor and evaluate” does not amount to an obligation to “audit.” Sponsors have no authority to require that the third parties cooperate with an audit to verify their compliance. In addition, monitoring third party behavior and decisions may be constrained by federal and state patient privacy laws, such as the *Health Insurance Portability and Accountability Act* (HIPAA).

Thus, for example, a REMS may require that a drug be dispensed only for inpatient use at a specially certified hospital. The sponsor could create a program through which it retains direct control over who purchases the drug. The sponsor could then specially certify hospitals and permit only these hospitals to use the program. To monitor and evaluate implementation, the sponsor could maintain a database of all specially certified hospitals and monitor distribution of the drug through regularly scheduled checks of the system to determine whether it is being shipped only to certified hospitals. The sponsor could not, however, be required to directly audit records of shipment that exist at third party locations, or to verify recommended administration of the drug by reviewing pharmacy or patient records.

As another example, a REMS could require patients to have evidence of certain laboratory test results before using a drug. To implement this element, a Sponsor could educate hospital staff, physicians, pharmacists, and other health care providers about the need for testing and support systems and practices within these institutions to ensure that the drug is dispensed only to patients with certain test results. To monitor and evaluate implementation, the Sponsor could survey these institutions and practices and inquire whether the system is being followed. The Sponsor could not, however, be required to audit actual dispensing patterns, for example by reviewing individual testing and dispensing records.

⁶ *Id.* § 355-1(f)(3)(B), (C), (D).

⁷ *Id.* § 355-1(f)(4).

D. Certification of Wholesalers and Distributors Exceeds “Reasonable Steps to Monitor and Evaluate Implementation”

We also ask FDA to please clarify how implementation of 505-1(f)(3)(B), (C), and (D), which pertain to certification of dispensers, dispensing in certain health care settings, and dispensing to patients with evidence of safe use, provides authority to require certification of wholesalers and/or distributors (lines 596-607). Certification of wholesalers and/or distributors seems to go beyond “reasonable steps to monitor and evaluate implementation” of certification of health care providers or pharmacies, dispensing in certain health care settings, and dispensing to patients with evidence of safe-use. In fact, interpreting “other parties in the health care system” who are responsible for implementing 505-1(f)(3)(B), (C), and (D) to mean wholesalers and/or distributors has difficulties. Wholesalers and/or distributors are not responsible for certification of health care providers, dispensers, dispensing in certain health care settings, nor dispensing to patients with specific evidence of safe-use conditions. The more conventional interpretation of “other parties” would be those who directly assist health care provider, dispensers, and patients, or who work in the specified health care setting, such as nurses and pharmacy technicians.

FDAAA does not state other entities that may be certified. Rather, it permits a system to monitor and evaluate implementation of entities responsible for certification of pharmacies, practitioners, health care settings, dispensing in certain health care settings, and dispensing to patients with evidence of safe-use conditions. We also note that in the example in lines 618-620, the wholesaler is not responsible for pharmacy certification, nor implementation of their certification training and evaluation of their compliance with certification requirements.

E. 60-Day Data Lock May Not Be Feasible for Non-Standard Assessment Timetables

The draft guidance also suggests that “To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment” (lines 646-648). Although this recommendation may be reasonable for products on a standard 18 month, 3 year, 7 year assessment timetable, it may be difficult for Sponsors to comply with for products with non-standard assessment timetables, such as those with drugs that are assessed every six months. This may prevent the Sponsor from collecting adequate data and not allow adequate time for analysis. For example, longitudinal patient-level data can be very detailed and analysis of these data is necessary to address elements of the REMS plan. Claims data can take the form of either Pharmacy Prescription Claims or Medical Claims Data. Pharmacy data are available about 10 weeks after the data cutoff. Medical data are sometimes not available for 6 months or more. Of significant note, several states drafted new legislation to restrict pharmaceutical industry access to individual prescriber-level data. Currently, the data are still captured by other states and can be reliably projected nationally. However, a significant move by other states to limit this information would severely limit Sponsors’ ability to evaluate and report REMS activities.

For these reasons, we ask that FDA provide flexibility with respect to the time of the data lock depending on the assessment timetable and types of data used. In general, we suggest that the 60 day cutoff for data be revised to 90 days to collect, analyze and respond depending on the data set used in the REMS assessment. We also suggest the Guidance include the following timing caveat for utilizing certain data sources, such as Claims data, in line 649: “Secondary data collections must reflect the most recent time point consistent with usual and customary data collection from recognized sources.” This approach allows for flexibility in the way data are captured, but still meets the intent of the Guidance, i.e. the evaluation of the drug use by indication or concomitant use with other products.

CONCLUSION:

BIO appreciates this opportunity to comment on the Draft Guidance for Industry on “*Format and Content of Proposed Risk Evaluation and Mitigation Strategies, REMS Assessments, and Proposed REMS Modifications.*” We have included specific comments in the chart below and additional information in the appendix. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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

SPECIFIC COMMENTS

<u>SECTION</u>	<u>ISSUE</u>	<u>PROPOSED CHANGE</u>
I. & II. INTRODUCTION AND BACKGROUND		
<i>A. FDAAA and REMS: Initial Approval and Postmarket Requirements (lines 49-94)</i>		
<p>Lines 53-54:</p>	<p>This statute “authorizes FDA to require persons submitting certain applications (applicants) to submit a proposed REMS as part of such an application if the FDA determines that REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug.”</p> <p>As discussed in our general comments, in the absence of adequate FDA-Sponsor communication during clinical development and application review, FDA can only conclude that a REMS is required after review of such an application. Thus it is unreasonable to expect the applicant to include the proposed REMS with the application.</p>	<p>We request clarification of this provision and greater incorporation of REMS discussions into the GRMPS.</p>
<p>Lines 63-65:</p>	<p>What is the nature and standard for “new safety information” that changes the benefit/risk relationship such that “the benefits of the drug are no longer considered to outweigh the risks of the drug”?</p> <p>It would be valuable for FDA to share the “new safety information,” including any analysis and the importance that the FDA attaches to it with the Sponsor before the final determination is made that a REMS is necessary.</p> <p>The time from notification of such a determination to the preparation of the REMS is 120 days, which is quite short.</p>	<p>Please include a mechanism by which FDA would inform the Applicant that a REMS is being considered by adding on Line 64: “If on the basis of new safety information, FDA is considering that a REMS would be necessary, FDA will share that risk information and its concerns with the Applicant.”</p> <p>Additionally, please explain how “New Safety Information” is defined, what quality standards and review standards it must meet, and how, where and to whom it is communicated.</p>
<p>Lines 66-68:</p>	<p>What is FDA's target time line for responding to a new REMS submission? As REMS are currently not bound by PDUFA timelines, what timelines does FDA propose for its own</p>	<p>Please clarify FDA’s internal performance goals for reviewing REMS in order to create clarity for Sponsors, increase FDA performance, and ensure</p>

	<p>performance in evaluating REMS and REMS elements? Currently, Sponsors have no expectation of when their submissions will be reviewed. The current experience indicates that it takes at least 12 months to review and approve the proposed REMS along with the REMS tools for a marketed product (even for those only requiring a medication guide and communication plan). The importance of the safety risk that led to the requirement of REMS seems to be minimized by such lengthy delay. As discussed in our general comments, we urge that FDA consider the broad interpretation of what constitutes a REMS document, as described by the FDAAA legislation, to allow Sponsors the ability to develop REMS tools that are consistent with the regulatory requirements but fit within the existing healthcare practice framework. The Sponsor should be charged with ensuring that the implementation of REMS tools including educational, communication and promotional materials, are fully consistent and compliant with the approved REMS. FDA could then exercise oversight using current enforcement discretionary powers. Requiring all REMS tools and documents to be pre-approved word for word is excessively burdensome for both FDA and the Sponsor, and in certain instances, could impact the goal of the REMS.</p>	<p>timely implementation of measures to mitigate risks.</p>
<p>Lines 75-81:</p>	<p>While we appreciate that FDA allows Sponsors to submit a REMS on the Sponsor's own initiative, we note that to date, FDA has been generally unwilling to engage in substantive REMS discussions until the very end of the review process. In fact, FDA has refused to engage in meaningful REMS discussions until labeling is finalized or near-finalized. This refusal on the part of the FDA to engage in REMS discussions makes the prospect of companies voluntarily submitting REMS exceedingly unlikely. If FDA wants Sponsors to submit REMS voluntarily, we suggest that FDA must be willing to engage in collaborative, substantive dialogue with Sponsors throughout the review process. In addition, the Sponsors also need a better understanding of what the FDA considers when determining that a product requires a REMS and each of the REMS elements especially ETASU.</p>	<p>We request that FDA be more open to dialogue with Sponsors regarding risk management throughout the drug development process.</p>

<p>Lines 75-79, 87-90:</p>	<p>The guidance states that “If an applicant voluntarily submits a proposed REMS, it will not be approved as a REMS unless and until the FDA determines that it is required to ensure that the benefits of the drug outweigh the risks and that it meets the FDAAA criteria.” (lines 87-90) A Sponsor may wish to pursue risk mitigation strategies even if such strategies are not necessary to ensure the benefits of the drug outweigh the risks. These programs would be designed to optimize the product’s benefit/risk profile. We suggest that a Sponsor should be allowed to suggest a RiskMAP program that could be upgraded to a REMS program if necessary.</p>	<p>Please add the following at lines 75-76 (additions in bold underline):</p> <p>“An applicant may voluntarily submit a proposed REMS <u>or RiskMAP</u> without having been required to do so by FDA.” <u>FDA may determine that a proposed RiskMAP should be deemed a REMS and vice versa.</u></p>
<p><i>B. Relationship Between a REMS and RiskMAPs (lines 96-141)</i></p>		
<p>Line 142:</p>	<p>Lines 99-102 states that “A RiskMAP is a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits.”</p> <p>As discussed above with regard to Lines 75-79, 87-90, it would be helpful to make explicit that a Sponsor may elect to undertake a RiskMAP as a tool to optimize the benefit-risk profile even if the overall benefit-risk relationship does not require a REMS.</p> <p>The draft guidance is silent with regard to the path forward for products with RiskMAPs pending review at the Agency.</p>	<p>Please add a statement that makes explicit the option that a RiskMAP can be used as a tool to optimize the benefit-risk even if the overall benefit risk profile when such mitigation activities are not necessary to ensure that the benefits of the drug outweigh the risk.</p>
<p>Line 128:</p>	<p>With respect to the two bullets that pertain to ANDAs, we recommend that the Draft Guidance track more closely to the statutory requirements, as opposed to using the terms “comparable” and “applicable.” Understanding that FDA will address in a future guidance the provisions in FDAAA that only apply to ANDAs, we recommend that if the agency touches on those types of REMS here, that it be specific about what the statute requires.</p>	<p>The guidance should utilize the statutory language for REMS requirements for ANDAs.</p>

<i>C. Products Deemed to Have in Effect an Approved REMS (lines 143-177)</i>		
Lines 143-177:	<p>Please clarify for drugs deemed to have an approved REMS with elements under subsections 505-1(e) and (f) in effect for the drug on March 27, 2008 whether those elements listed under (e) and (f) are, in fact, inclusive of all elements necessary to assure safe use authorized by the statute. If so, please state the Agency's expectation that the content of proposed REMS for drugs should not include an element of promotional review 30-days prior to dissemination because this element is not part of (e) or (f). Some of the RiskMAPs for products with deemed REMS contain provisions for additional risk mitigation measures, e.g., review of promotional pieces 30 days prior to dissemination. Please state the Agency's expectation with regard to these additional measures vis-a-vis the REMS.</p> <p>In addition, please clarify that approval under 505-1 for deemed drugs supersedes approval under 21 CFR Subpart H 314.520 and 21 CFR Subpart E 601.42. In this manner, future REMS of non-deemed products either with same risks or in the same drug class as deemed drugs will have REMS with similar requirements.</p>	Please clarify.
<i>D. Assessments and Modifications of Approved REMS (lines 227-260)</i>		
Line 245:	<p>The requirement to submit an assessment at the time of submission of a supplemental filing (for new indication for use) should be qualified; it is an unreasonable burden to make a new assessment if the last assessment was within 6 months. We request that FDA exercise its discretion in interpreting these statutory provisions, to allow a copy of the last assessment report to satisfy this requirement if the most recent assessment report was produced within the last 6 months.</p>	Sponsors should be allowed to include a copy of the last assessment report if the most recent assessment report was produced within the last 6 months.
Line 249:	<p>The statute and draft guidance provide for the possibility that a REMS might include only a timetable for submission of assessments. Please provide the Agency's perspective on whether this could reasonably be expected to happen in a real-life setting.</p>	Please clarify or delete

Lines 253-258:	The concept of "new effectiveness information" is introduced for the first time. This information could be used to make modifications to the content of a REMS, yet this concept has not been previously defined in the statute or draft guidance.	Please consider removing the phrase "new effectiveness information." If not, please clarify the Agency's thinking on how new effectiveness information can alter a product's benefit-risk profile and lead to amended REMS assessment timetables and/or risk management strategies. "When required by the FDA, within a time period to be determined by the FDA, if the FDA determines that new safety or effectiveness information indicates that the timetable for submission of assessments should be modified"
<i>E. REMS are Enforceable (lines 262-277)</i>		
Line 274:	The guidance states that "a person may not introduce or deliver for introduction into interstate commerce an approved drug...if the person fails to maintain compliance with the requirements of the approved REMS..." How does this apply to exporting a product? What about exporting a drug to an area that does not require a REMS or similar risk mitigation/minimization plan? If there were a problem with the US REMS could material be exported to the EU which does not require the same ETASU?	Please clarify.
Lines 282-284, 294-296, and 339-342:	The Draft Guidance states that the "proposed REMS," which it describes as the "concise document," "will be the basis for enforcement." (282-284). It also states that any proposed materials "should be appended to the proposed REMS." FDA should clarify whether it considers these materials to also be enforceable under its Title IX powers of FDAAA. Such a reading appears to be broader than the "elements" of an approved REMS, which the statute clearly contemplates as being enforceable. FDA should reconcile the multiple statements in this section and clearly articulate what it considers to be enforceable under FDAAA.	The Final Guidance should be more specific regarding enforceability. Specifically, the guidance is not precise as to what is considered part of the proposed REMS and therefore, enforceable.

III. CONTENT OF A PROPOSED REMS

A. *Content of the Proposed REMS (lines 290-656)*

Line 299:	The Draft Guidance states the proposed REMS should include the date by which each of the REMS elements will be implemented. In our dynamic business environment, it is extremely difficult to choose a specific date for implementation. Flexibility should be incorporated into the selection of implementation timeframes.	The Draft Guidance should be revised to state the proposed REMS should include a timeframe within which implementation should occur, preferably based on a specific activity (e.g., at product launch or within 30 days of product launch).
Line 310-316:	Given the importance of review and approval of REMS in a timely manner, it is important for Sponsors to understand FDA’s internal performance goals for responding to REMS submissions. Current experience indicates that review and approval of REMS for both pre-approval and post approval products are delayed even when there are no elements to assure safe use. This delay has been more than 12 months for post-approval products from the time the sponsors were required to have a REMS when a new safety issue was identified (in one instance, even for a product with only a MedGuide and communication plan). This results in substantial delay in the communication of new safety information. Recognizing that the REMS provisions of FDAAA have no formal performance goals, we suggest that FDA needs to determine and communicate how it intends to track its own performance in evaluating REMS submissions.	The guidance states that “prior to approval, FDA may require applicants to revise the proposed REMS....” The guidance should clarify whether this includes the REMS tools and the timing for review and approval of the proposed REMS. FDA should also consider developing performance goals for REMS and integrating REMS milestones into the GRMPs.
Line 317:	Details regarding which components of the REMS documentation will be publicly posted are unclear. Will only the REMS document be posted, or also the REMS Supporting Documents and other details? Additionally, the Draft Guidance is silent on the nature of the Sponsor’s ability to review this posting for proprietary information.	Please clarify.
Line 342:	FDA should follow consistent timeframes for review of a proposed modification to a REMS. As discussed in our general comments, we suggest that FDA either limit review and approval	Please include.

	to the REMS document rather than the REMS implementing tools or adopt a process of administrative reporting for minor changes to REMS tools that are not substantive (e.g., changing from paper to on-line forms with no change in content, changing contact phone numbers, adding email to fax notifications, etc.). FDA should adhere to 180-day regulatory timeframes for review of substantive modifications of REMS.	
Line 352:	The inclusion of named personnel in the REMS is not consistent with how FDA recognizes/manages other compliance positions in the company (i.e. Quality, Compliance) and is inappropriate to post publicly. This information could be considered to be proprietary; therefore, the Final Guidance should provide for protection of personal privacy and proprietary information. Furthermore, we request that FDA provide more clarity on its expectations with regard to the identified contact person.	Please clarify. Contact information should be consistent with how FDA recognizes/manages other compliance positions in the company.
Line 386-421:	<p>The draft guidance discusses the criteria for imposing a Medication Guide and a patient package insert. Medication Guides focus on narrow but important safety concerns, but good patient package inserts provide a more comprehensive education to the patient about the risks and benefits of the drug. We ask the Agency to address how to make Medication Guides more broadly useful education tools, especially considering that approximately 75% of REMS contain only Medication Guides.</p> <p>Additionally, FDA states that it might require both a Medication Guide and patient package insert for the same drug, yet no explanation is given describing when and why such a situation would occur.</p> <p>In Part III, Section A 3. "Additional Potential REMS Elements," the draft guidance specifies the types of changes to a Patient Package Insert (PPI) that would not typically trigger the need to convert a PPI to a Medication Guide. These changes include editorial changes and changes related to how to use the product, unless the changes have the potential to mitigate a serious risk</p>	<p>As FDA develops its guidance and processes for REMS implementation, it should address enhancing the utility of Medication Guides.</p> <p>Please clarify, including hypothetical examples.</p> <p>We recommend that the FDA provide examples of situations that would trigger the need to convert a PPI to Medication Guide, as the draft guidance only specifies changes that would not trigger such a conversion. Additionally, we also ask the Agency to state if there would be any</p>

	(lines 412-418).	exceptions to the changes listed that would not trigger the conversion of a PPI to a Medication Guide.
Line 435-438:	We request that FDA provide more clarity regarding ANDA communication plans. The section states that “If an NDA has been approved with a REMS with a communication plan, and subsequently an abbreviated new drug application (ANDA) is approved with that NDA product as the reference listed drug, then FDA must undertake the communication plan.” It is unclear how FDA will conduct the communication plan, especially if the communication materials are copyrighted or trademarked. Furthermore, we ask the Agency to explain how the communication plans it undertakes will be evaluated.	Please clarify in this or future guidance.
Lines 435-444:	One interpretation of this section is that FDA may consider “reclassifying” certain REMS elements, specifically, converting communication plans into ETASUs, based on the fact that an ANDA is approved for a reference product that has a communication plan. Such a “reclassification” based on that criteria would be inappropriate and disruptive to both the sponsor and the healthcare system, especially where there have been no new safety findings for the reference product and the approved REMS program for the reference product has met its goals by conducting the required assessments.	In the context of describing the obligations of the reference product sponsor, ANDA sponsor, and FDA, the Draft Guidance states that tools that have “previously been considered part of a communication plan...may fit under one or more elements to assure safe use (ETASU) if specified criteria are met.” The guidance should elaborate on what this means, and what those “specified criteria” are.
Lines 450-457:	There should be transparency in how FDA makes the determination for the requirement of ETASU. Understanding the Agency’s rationale and criteria is critical for sponsors to be able to develop, implement, and execute a suitable REMS program.	As discussed in our general comments, the guidance should clarify the objective measures used to determine the suitability of ETASU.
Line 487:	Additional recertification or re-enrollment without additional criteria such as new safety information or changes in the REMS requirement will add additional burdens on the health care providers, hospitals and clinics.	The guidance should outline criteria for when recertification or reenrollment is required (e.g. if there has been new safety risks were identified since the implementation of the REMS program).

Lines 531-533:	This section states that the Applicant may be required to “Ensure that the drug is dispensed only to physicians’ offices equipped to treat the potential risks associated with the drug following administration of the drug.” It is not reasonable for the Applicant to determine whether the physician’s office has suitable equipment. The applicant may be required to have physicians confirm that they are equipped suitably when they are certified but the Applicant cannot reasonably be expected to determine ongoing compliance.	Please clarify or remove this provision.
Line 556-569:	This states that “Elements under 505-1(f)(3)(E) might require that patients be monitored or that specific follow-up should occur at specific time points.” We have concerns regarding sponsors ability to comply with this as a REMS element. Patient privacy laws, such as HIPAA, may make this impossible without other elements.	We suggest that this activity either be removed or needs to be a subset of sections D. or F. and not a stand-alone element.
Lines 571, 589-592:	Some institutions consider REMS registries to be experimentation on human subjects, thus requiring IRB and/or ethics panel approval. There are examples of institutions that have declined to use a product because of inability to reconcile REMS registry with IRB requirements.	The guidance should clarify FDA’s position on whether or not registries require IRB approval.
Lines 637-641:	The draft guidance states the required timeframes for assessment described in the statute can be met through assessments submitted according to different timeframes described in the approved REMS. The draft guidance is silent with regard to the impact on these timeframes of voluntary sponsor assessments submitted earlier than those specified in the approved REMS.	The guidance should be revised to include the following statement after the sentence ending on line 641 (addition in bold underline), <u>“Furthermore, voluntary sponsor assessments at dates earlier than those specified in the approved REMS may meet the required assessment dates required in the approved REMS and section 505-1(d).”</u>
Lines 637-641:	Timeframes for assessment are generally negotiated, but FDA is the final decision maker with regard to the requirement. Because Sponsors have global obligations for risk management activities, including risk mitigation, REMS assessment timelines should be developed with consideration to global risk management	Please include in the guidance reference to assessment timelines should be developed with consideration to global risk management timelines and obligations.

	assessment timelines.	
<i>B. Content of the REMS Supporting Document (lines 658-904)</i>		
Lines 683-703:	These factors are similar to the Safety Specification of the European Union Risk Management Plan (EU-RMP) and we view this as an opportunity to coordinate with the EU-RMP and the ICH E2E definition of the Safety specification for the specific safety concerns that the REMS addresses.	Please consider or discuss opportunities for international harmonization or risk minimization requirements.
Lines 683-694, 697-703, 733-746:	As discussed in our general comments, oftentimes Sponsors and FDA disagree as to the necessity of a REMS or the REMS elements. It might be helpful to advance the dialogue between Sponsors and the FDA if the FDA was required to list this information and defend its rationale for various REMS elements. This would facilitate mutual understanding and communication of FDA's rationale for requiring a REMS.	As discussed in our general comments, more transparency in FDA decision making with regard to REMS should be built into FDA processes and guidance.
Line 697-703:	The international regulatory history of the risk management of the product could become very burdensome for Sponsors and may be extremely misleading to FDA when one considers the differences in practice of medicine and regulatory structures outside of the US. We support efforts to harmonize regulatory requirements, but it should be noted that at the present, regulatory structures and requirements are very diverse worldwide. Asking sponsors to submit all of its international filings is overly burdensome to the Sponsor and to FDA.	The suggested contents of the supporting document are overly burdensome and may be confusing. We suggest that risk management plans being submitted to other regulators which conform to ICH guidances can be substituted in place of background. This will enable simplification and take work out of the system.
Line 746:	To date, FDA has placed the burden for soliciting feedback on REMS feasibility solely upon the Sponsor except for class REMS. Additionally, the FDA has often been reluctant to consider the feedback Sponsors have provided to justify various aspects of the feasibility of REMS within the current healthcare system. In the interest of transparency and effective public communication, the FDA should share the responsibility for listening to health care providers and patient groups. FDA should conduct public workshops with interested parties and listen to stakeholders as to	The FDA and Sponsors should both solicit feedback from patients and the healthcare community as to the feasibility of a REMS. The Agency should add language to the guidance that would establish expectations that FDA dialogue directly with stakeholders in the healthcare community with regard to REMS.

	the feasibility of REMS. Sponsors, of course, should share their feedback, but this burden cannot rest upon the backs of Sponsors alone.	
Line 757:	The guidance should reconcile its requirement for sponsors to verify that proposed elements are not unduly burdensome with the reality that it is the agency that has determined that certain REMS elements are necessary.	We ask FDA to affirmatively state through some type of certification process that it has determined after careful consideration and stakeholder input that the elements are not unduly burdensome.
Lines 761-762:	The guidance requirement for extensive rationale regarding “how the proposed ETASU conform to those required for other drugs with similar risk” seems unrealistic for a sponsor to judge another products REMS. Although the sponsor can review the REMS proposed document on the FDA website but not the REMS supporting document, it is unrealistic to have expectation that a sponsor to provide a summary of this information to the FDA. The FDA has this information and not the Sponsor.	Please remove this provision.
Line 798:	As discussed in our general comments, only when the data are gathered and analyzed could a Sponsor determine that a REMS might need modification. This section asks Sponsors to engage in speculation and conjecture. It is also tremendously burdensome.	Please remove or re-phrase.
Line 839:	In Part III, Section B 4. “REMS Assessment Plan,” the draft guidance discusses information to be included in a REMS assessment plan to assess whether the REMS elements are meeting the REMS goals and objectives. This section provides general information on REMS assessments; however, we recommend that more guidance be provided for developing and conducting REMS assessments. For example, if a REMS includes a Medication Guide, the guidance states that a survey of patients’ understanding of serious risks of the drug should be included in the REMS assessment (line 839). However, the guidance does not describe elements of the assessment protocol that would be needed to develop an adequate survey. Similarly, detailed guidance is not provided for developing assessment protocols for Communication	We realize that FDA intends to release future guidance on REMS assessments, but we would like to emphasize the importance of the Agency providing such guidance.

	Plans or Elements to Assure Safe Use that may be part of a REMS.	
C. Foreign Language REMS (lines 907-916)		
Lines 906-916:	<p>The guidance clearly states that translations are not part of REMS and BIO agrees that excluding translations from Prior Approval Supplements is logical and consistent with labeling requirements.</p> <p>Moreover, we note that with respect to foreign language REMS, the agency has drawn comparisons to its labeling jurisprudence (“[c]onsistent with CDER’s approach to foreign-language labeling...”). BIO applauds the agency’s proposed approach to foreign-language versions of REMS, and urges FDA similarly to entrust Sponsors with responsibility for REMS materials being “complete and accurate,” even if the agency has not preapproved every technical or non-substantive change.</p>	No changes necessary.
IV. REMS ASSESSMENT AND PROPOSED REMS MODIFICATION SUBMISSIONS TO FDA		
Line 945:	"Any" is burdensome especially given FDA's current extended review times. Requiring all improvements to a REMS, including administrative changes, to obtain prior approval is overly burdensome to the FDA and Sponsors and does not advance a legitimate public health interest.	Please note BIO’s general comments on this section and allow for modification of REMS tools through an administrative reporting process rather than prior approval.
V. COMMUNICATING WITH FDA REGARDING REMS		
A. Submission Type (lines 968-1006)		
Lines 966-1006:	<p>Page 23, Section V. Communicating with FDA Regarding REMS: This section does not include information on how to request a meeting with FDA over possible REMS or if such a topic may be included in the usual types of meetings FDA and industry hold, such as EOP2, pre-NDA, and Type A,B, and C meetings. It is important that industry and FDA be able to discuss proposals and concerns prior to actual submissions to make negotiations on the REMS submissions as efficient as possible, given the required timeframes.</p>	Please see BIO’s recommendations in the above general comments regarding timing of meetings to discuss REMS and incorporating REMS discussion into the GRMPs. Also please clarify that REMS meetings can be requested through the PDUFA meeting request process.

Lines 976-977:	FDA should clearly indicate that a proposed REMS submitted after approval and not associated with an existing supplement be classified as a labeling supplement.	The guidance should clearly state that a proposed REMS submitted after approval and not associated with an existing supplement be categorized as a labeling supplement.
Lines 981-986:	In Part V, Section A. "Submission Type," the draft guidance states that a REMS assessment that includes a proposed modification should be submitted as a supplemental application, but a REMS assessment alone is not considered a supplemental application (lines 981–986). We recommend that the Agency provide additional clarification on how REMS assessments that do not include a proposed modification be submitted. For example, would there be any cases in which it would be acceptable to submit a REMS assessment as part of a product’s Annual Report? We feel that additional information on the submission of REMS assessments would help to streamline the REMS process.	Please clarify.
Lines 984-987	<p>The guidance states that REMS assessments that include a proposed modification to the approved REMS be submitted either as a new supplemental application or included in a related supplemental application. Please include FDA review times for such supplements, as discussed above in our comments on line 342.</p> <p>Additionally, please clarify if REMS assessments are viewed by FDA as “clinical data” and thus triggering user fees.</p>	Please clarify.
Lines 1004-1005:	FDA should tell the Sponsors the exact eCTD location instead of referring the Sponsor to another division within the FDA.	Please specify preferred eCTD location for REMS documents in final guidance.

APPENDIX A: Lifecycle opportunities to discuss risk management with FDA

**RISK MANAGEMENT PLAN DISCUSSIONS IN THE
PRE-NDA/BLA PERIOD:**

- Pre-IND Meeting
 - Discuss expectations for class REMS requirements versus possibility of next in class to have a REMS and what data would be needed to obviate needs of REMS.
 - If new safety information has arisen and triggers possible need for risk mitigation during development and postmarketing, discuss need for additional information and process and procedures to mitigate risk.
- IND Submission:
 - Discuss patient inclusion and exclusion criteria relating to risk assessment.
 - Discuss issues of informed consent as risk communication.
 - Discuss other steps needed to ensure safety (potential ETASU processes and procedures).
 - Discuss investigator qualifications and training.
- EOP2 Meeting
 - Discuss and formally agree on the methodology to evaluate potential or identified safety risks during the Phase III studies such as frequency of laboratory tests, adjudication of adverse events, the high level design of post-marketing studies and any additional risk mitigation strategies including REMS. This commitment by both FDA and Sponsors would be analogous to agreement on efficacy endpoints between FDA and Sponsor resulting from a Special Protocol Assessment (SPA) process, but would address a safety signal and would not be binding.
 - Possible pilot testing of Medication Guide.
 - Same items as pre-IND and IND submission
- Guidance/Advice Meeting
 - If new data and new safety information suggest different approaches for risk mitigation processes and procedures than agreed to in the protocol or, for a marketed product, suggest a need for a REMS or changes to an approved REMS, the new data and new safety information, along with proposals for mitigation, may be discussed during a guidance meeting with the Agency. This meeting would be a Type A meeting as it deals with a serious unexpected safety issue or information relating to the assessment of the REMS.
- Advisory Committee/ Public Meetings/Workshops (also see 505-1(h)(7): Process for Addressing Class Effects)
 - Either during development of a new drug or for products on the market, if new safety information arises necessitating public advisory committee input on the interpretation of new safety information, the need for a

REMS, or the need for changes to REMS, FDA and Sponsor should have timely exchanges of scientific information and ensure productive public discussion during the Advisory Committee.

- 505-1(h)(7) relates to when a serious risk may be related to the pharmacological class of drug, FDA may defer assessments of the approved REMS for such drugs until the FDA has convened 1 or more public meetings to consider possible responses to such concern
 - Deferral notice must be provided in 5 days and published in the Federal Register, and provide public notice of meetings that include the description of the deferral. 505-1(h)(7)(D) describe the actions which may follow after such public meetings.
 - SOPs and guidances should be developed to ensure matters are brought to completion for public safety.
- Pre-(s)NDA/(s)BLA Meeting
 - Discuss potential REMS submission including which, if any ETASU would be expected, and what would be needed in the REMS assessment.
 - Plan for 60 day (or 30 day) mandatory initiation of discussions of REMS and REMS assessment with sponsor per 505-1(h).
 - Discuss results of pilot testing of risk materials and mitigation processes that impact REMS submission.
 - Clarify what will be inspected of the proposed REMS or approved REMS.

**RISK MANAGEMENT PLAN DISCUSSIONS IN THE
FDA REVIEW PERIOD:**

- NDA/BLA Filing meeting, 60-day Filing, and REMS Review
 - 45-days post-submission is the recommended time for FDA to have an internal filing meeting. FDA then should communicate if the REMS inclusion is adequate for review, or if inadequate, what the deficiencies are. FDA should ensure that initiation of discussions of REMS/REMS assessment with Sponsor is scheduled, per 505-1(h).
 - 505-1(h) requires prompt review of submitted proposed REMS and REMS Assessments.
 - Not later than 60 days after submission, negotiations are to begin (or, if under an order under 505-1(g)(2)(D), not later than 30 days).
 - 60 days after submission starts the mandatory initiation of discussions with Sponsor and OND/OSE.
- 74-day Letter
 - Identify deficiencies in the REMS from filing review.
 - PDUFA IV requirement for identifying when negotiations for labeling and PMR/PMCs will begin, phased in through FY12—include REMS negotiations as REMS will impact labeling and safety studies.

- Mid-Cycle Review
 - Identify and communicate new safety information that may necessitate a REMS or alter the proposed REMS.
 - Provide advice on revisions needed for REMS elements or content.
 - Provide status of REMS review.
- IR and DR letters from Review Team Meetings
 - Provide sponsor with information needed for adequate REMS review.
- Administrative Rounds and Internal Processes
 - FDA management should have regular internal discussions with team leaders on safety issues, need for a REMS, criteria for REMS being met, and status of REMS review.
 - SOPs for communication with the Sponsor, inclusion of REMS decision criteria per (505-1(a)(1) (A-F)) in review templates, quality assurance processes such as SWAT review should be written.
 - Training of staff on REMS requirements and SOPs should be routine for new hires.
- NDA/sNDA/BLA Pre- and Advisory Committee Discussion
 - Provide Sponsor with comments about REMS to ensure productive, transparent public discussion on safety issue and risk mitigation in briefing book and public presentation.
 - Discuss expectations of health outcomes desired from REMS.
 - Discuss considerations of medical practice and access to ensure REMS processes and procedures are appropriate.
 - Ensure patient and medical practice/nursing/pharmacy/other relevant stakeholders are part of the public discussion.
- Regulatory Briefings
 - FDA staff and management discuss REMS issues needing advice.
 - Provide Sponsor with feedback on status and comments on REMS after considering advice from briefing.
- Pre-Approval Safety Conference
 - OND staff to discuss pre-market safety database with OSE staff.
 - Review expected health outcomes with REMS that have been vetted and shared with sponsor.
- Labeling Negotiations
 - Include discussion of Medication Guide and patient package insert.
- Postmarketing Studies Requirements Discussions
 - Discuss expectations of REMS programs and PMRs, such as registry studies, confirmatory studies, etc.
 - Discuss any concerns regarding pediatric studies and REMS.

- Action Letter
 - CR letters should contain clear information of deficiencies to address regarding REMS; opportunity for a meeting should be provided if clarification is needed.
 - Define Class 2 Resubmissions to include REMS Medication Guide and patient package inserts.
- If an After Action Review takes place REMS should be included in the agenda.
- Postmarketing Safety Discussions (*See Guidance/Advice Meeting*)
 - Sponsor and FDA discuss safety concerns arising with REMS or new safety information as soon as possible in on-going manner.