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October 13, 2009

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

Re: Docket No. FDA-2009-D-0283: Postmarketing Studies and Clinical Trials -- Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act

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Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the draft guidance on "*Postmarketing Studies and Clinical Trials -- Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act.*" BIO has long supported efforts to enhance the consistency, predictability, and transparency of the process for selecting appropriate post-marketing commitments (PMCs) and post-marketing requirements (PMRs), and we applaud FDA for issuing this guidance. In support of the guidance, we request additional clarification regarding the criteria for selecting postmarket studies or trials, the timeframe for interacting with sponsors when selecting appropriate PMC/PMRs, and the threshold for enforcement activities.

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

In light of the new FDA authority to require postmarket studies and trials under the *Food and Drug Administration Amendments Act of 2007* (P.L. 110-085, FDAAA), it is imperative that FDA and sponsors have a firm understanding of the statutory requirements and procedural considerations for deciding upon post-market studies/clinical trials. BIO was pleased to see FDA commission an outside consultant to study the PMC/PMR process and that the agency issued harmonized staff policies for selecting post-marketing studies. [1, 2, 3] Continued refinement of the processes for selecting PMCs and PMRs will help to ensure that FDA and sponsors can agree upon medically appropriate, ethical, scientifically sound, and operationally feasible studies that can be completed in the agreed upon timeframe and that will serve the interest of the public health. Ultimately, these studies will contribute to the body of knowledge around a product's benefit/risk profile and help to inform physician prescribing decisions and enhance patient care. BIO is pleased to offer the following general comments in support of the draft guidance.

I. Clarification of Study Purpose and Methodology that "Will not be Sufficient"

The draft guidance recognizes that under FDAAA, postmarket studies and clinical trials can be required if, based upon appropriate scientific data, a study or trial is warranted for one or more of the following purposes:

- To assess a known serious risk related to the use of the drug involved;
- To assess signals of serious risk related to the use of the drug;
- To identify an unexpected serious risk when available data indicate the potential for a serious risk.

BIO believes that it is important that FDA consider the potential need for a study, if any, and what the potential purpose of a study would be, prior to addressing the type of study or clinical trial that might be warranted. Clearly, Congress did not intend that all drug approvals would warrant a postmarket study or clinical trial, so it is important to first identify what the purpose of a study or trial might be, and whether a study or trial can address that purpose. Further, BIO believes that illustrations or examples of situations that fit the above three purposes would be useful to include in the guidance.

Under FDAAA, once a purpose of a study has been identified, there is a hierarchy for selecting postmarket studies and trials that would identify the most efficient and least burdensome means of investigating a pending safety question. Citing the FDAAA statute, the draft guidance document states:

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[1] Booz Allen Hamilton, *Postmarketing Commitments Study Final Report*, January 2008, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm071515.pdf

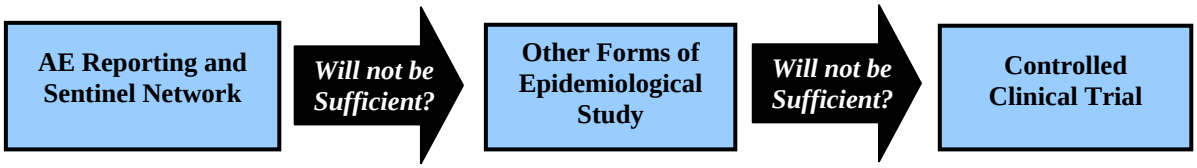
[2] Booz Allen Hamilton, *Final Report on the PMR/PMC Backlog*, April 10, 2009, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM181135.pdf

[3] CDER MAPP 6010.9 and CBER SOPP 8415

- "Under section 505(o)(3)(D)(i), before requiring a postmarketing study, FDA must find that adverse event reporting under section 505(k)(1) of the Act and the new pharmacovigilance system that will be established under section 505(k)(3) of the Act *will not be sufficient* to meet the purposes described in section 505(o)(3)(B)."
- "Under section 505(o)(3)(D)(ii), before requiring a postmarketing clinical trial, FDA must find that a postmarketing study *will not be sufficient* to meet the purposes described in section 505(o)(3)(B)." (Lines 152-158, *emphasis added*)

In other words, a postmarket study, such as an epidemiological study, can be required only if spontaneous adverse event reporting or the Sentinel Network currently under development will not be sufficient to answer a pending drug safety question. Further, a post-market clinical trial could be required only if a post-market study will not be sufficient. (*See Table 1*)

Table 1: Statutory Post-Approval Study Decision Process



While BIO supports this tiered approach to selecting the appropriate post-market study/trial methodology, it is currently unclear how FDA defines the triggering phrase "will not be sufficient" when considering methods to study the drug safety question. We believe FDA should clarify the phrase "will not be sufficient" to help sponsors better understand and anticipate when PMRs may be required. We recommend that the draft guidance provide examples discussing when the adverse event reporting, the active pharmacosurveillance system, and epidemiological study methodologies "will not be sufficient" to assess known serious risks, assess signals of serious risk, and to identify unexpected serious risk. BIO had previously submitted comments related to pharmacoepidemiogical study selection that may be helpful to FDA when defining this phrase or providing examples of what constitutes insufficiency.[4]

An additional trigger for requiring a PMR is if the decision is based upon "scientific data deemed appropriate by FDA, including information regarding chemically-related or pharmacologically-related drugs." (lines 148-150). We encourage FDA to disclose what constitutes "scientific data deemed appropriate" to warrant a post-market study or trial. We believe that it is important that FDA be transparent in explaining the basis of its decisions and the data utilized in making decisions along this process. We request that the draft guidance make clear that FDA will disclose to the sponsor what data were used to determine the potential serious risk and how those data were used in the decision-

[4] Biotechnology Industry Organization (BIO), *Developing Guidance on Conducting Scientifically Sound Pharmacoepidemiologic Safety Studies Using Large Electronic Healthcare Data Sets*, June 6, 2008, http://bio.org/reg/20080606.pdf

making. Further, we request that discussion be held with the sponsor early enough in the process to allow the sponsor time to develop a response to FDA, either in the form of a proposed study or in the form of contrary data or analyses that might demonstrate a different perspective.

II. Timeframe and Processes for Sponsor Interaction

Best practices suggest that interactions between FDA and sponsors early in the review process and well in advance of the action date will encourage a selection of studies that will result in the most valuable and medically relevant information for patients, physicians, and regulators. Consistent with ongoing implementation of the Good Review Management Practices and Principles (GRMPs), FDA's commitment to notifying sponsors of target dates for key review milestones as part of the 74 day letter, including discussion of PMRs/PMCs, represents a significant enhancement in FDA's review process. However, there are additional considerations to maximize the value of this interaction for FDA and sponsors.

First, the draft guidance states that FDA plans to send a list of potential PMR/PMCs near the target date, giving the sponsor the opportunity to discuss design and timing with FDA. However, the draft guidance is not specific enough regarding when the applicant can expect to receive feedback from FDA. Of paramount concern for sponsors is that adequate time is included to have a dialogue with FDA on these important requirements. Sufficient time must be afforded for PMR discussions to enable adequate design and planning of the study or trial. BIO suggests that the guidance should discuss a process or timeline for this interaction as a standard provision. BIO believes that there should be at least 4-6 weeks to permit a dialog between sponsor and OSE/OND prior to issuance of PMR. And when PMRs are part of a REMS, the dialog should begin earlier (end-of phase 2 or preNDA).

Secondly, the draft guidance should clearly state that prior to FDA sending a list of potential PMRs and PMCs to the applicant, there should be thorough discussions regarding each of the three conditions for a PMR (lines 145-165). Applicants should have adequate insight into FDA's process and rationale for determining that a PMR is required or a PMC is warranted so that there is opportunity for the applicant to develop alternate ways to further evaluate signals of serious risk. Transparency of this process is particularly important with regard to PMRs to assess signals of serious risk or unexpected potential risks. Conducting a postmarket clinical trial to identify an unexpected serious risk not discovered during the pivotal trial is challenging because it is built on hypothesis and may require a very large trial. A study designed to identify a potential risk should be limited to a "study" as defined in this draft guidance (eg, observational, animal, laboratory). As part of the discussion, FDA's assessment of the serious risk should take into consideration the patient population and the disease severity, and FDA should qualify the signal by qualitative and quantitative analysis.

Finally, after a sponsor has submitted the "timetable for completion of the study or clinical trial for the PMRs and a schedule for milestone submissions and final reports for

PMCs", FDA will decide "whether the proposed timetable will be realistic and provide for timely completion of the study or trial." (Lines 307-312) However, the draft guidance is silent regarding the timeframe for FDA feedback on the proposed timetable. We recommend that a reasonable time period be identified to acknowledge agreement with the proposed timetable and minimize the potential for misunderstandings regarding the expected deliverables. We suggest the guidance include language defining the duration that FDA would have to comment on a particular protocol. At a minimum, we encourage FDA to provide an acknowledgement within a reasonable time period that the submitted protocol will satisfy the intent of the PMR, or provide comments, if any.

III. Examples of PMCs and PMRs

In general, the use of examples in the draft guidance provides additional clarity and transparency around the criteria for PMRs and PMCs. However, BIO believes that the examples can be made more useful. First, the examples of categories of studies that would either be PMRs or PMCs are helpful, but there are few examples of PMCs. (Lines 187-294). It would be useful if the lists were better balanced with examples in each category and offered more relevant and realistic examples of the types of studies that could be considered a PMR. We have provided specific recommendations in the "Specific Comments" table below.

The draft guidance could also provide more illustration of the difference between the types of studies that are considered PMRs versus those that could be considered PMCs. Based on the examples provided, we can envision instances where some of the studies/trials discussed in the draft guidance could be interchanged as PMRs or PMCs, depending on the data from individual product programs. For example, a study conducted by one sponsor as a PMC could be a required study (i.e., PMR) for another program because of its safety profile.

Lastly, the examples should be presented in a manner that clearly distinguishes between studies and clinical trials. A simple notation next to each example such as (*Trial*) or (*Study*) would suffice.

IV. Definition of 'Good Cause" for Enforcement

The draft guidance states that "an applicant's failure to comply with the timetable, periodic report submissions, and other requirements of section 505(o)(3)(E)(ii) will be considered a violation unless the applicant demonstrates *good cause* for the noncompliance. Under section 505(o)(3)(E)(ii) of the Act, FDA will determine what constitutes *good cause*." (Lines 377-382, *emphasis added*) BIO encourages FDA to provide additional explanation and examples in the guidance of what the Agency considers "good cause" for failure to comply with planned milestones. This may include certain medical, ethical, and practical considerations that may constitute good cause for not completing a planned study or trial. For example:

- The trial is no longer feasible;

- Institutional Review Board (IRB) or ethics concerns preclude study start/completion;
- The standard of care has advanced making it difficult to enroll patients into a study with the older drug.
- Unforeseen difficulties with enrolling patients that meet the protocol-specified criteria

The draft guidance also states that "In determining the amount of a civil penalty, FDA will consider the applicant's efforts to correct the violation (see section 303(f)(4)(B) of the Act)." (Lines 402-403) BIO appreciates that the draft guidance takes into account a sponsor's good faith efforts to resolve a violation and we suggest that the guidance explicitly note that sponsors will be provided an opportunity to correct the issue before a civil monetary penalty (CMP) is imposed. We also recommend that the guidance further clarify when CMPs would be imposed. For example, the guidance should be clear that CMPs should only be imposed for egregious violations rather than minor infractions, unless those violations are numerous and repetitive.

CONCLUSION:

BIO appreciates this opportunity to comment on *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act."* We have included specific technical comments in the table below. 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

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 42:	We suggest insertion of a footnote clarifying that unless specified otherwise, the term drug refers to both a new drug and a biological product. Although the text in this section is taken directly from the Act, and 505(o) as stated applies to drugs (505b) and biologics (Section 351 of PHSA), clarification of this point will be useful.	Please add footnote clarifying that the term drug refers to both a new drug and a biological product.
II. BACKGROUND		
B. New FDAAA Authority and Requirements		
Line 99:	The definition of clinical trials should be the same as "Clinical Investigation" defined under 21.CFR 312 3 (b). The CFR definition for clinical investigation excludes the use of a marketed drug in the course of medical practice. It is not clear whether the draft guidance definition of clinical trial excludes such use.	Please revise the definition to be harmonized with the definition of "Clinical Investigation" defined under 21.CFR 312 3 (b).
Lines 99:	It is unclear if a Registry, where investigators determine the method of assigning treatment or an intervention, would be classified as a clinical study or clinical trial.	Please clarify.

III. IMPLEMENTATION OF POSTMARKETING STUDY AND CLINICAL TRIAL REQUIREMENTS UNDER FDAAA		
Line 175:	The guidance should state that postmarketing commitments with a primary safety endpoint that meet the definition of study or clinical trial under the draft guidance but were agreed upon between FDA and the applicant prior to the effective date section 505(o)(3) of the Act will not be considered PMRs.	Please clarify.
A. Postmarketing Requirements (PMRs)		
Line 187:	The title of this section could be misleading to a reader as it suggests that it includes information about postmarketing requirements when in fact it merely lists some examples of the types of studies or clinical trials to be considered a PMR.	We believe the subsection should be titled: "Examples of Postmarketing Requirements (PMRs)" to better reflect what is portrayed in this subsection of the draft guidance.
Line 189:	The guidance should provide examples of studies that will be considered PMRs that are not required under FDAAA, i.e. those required under subpart H of 21 CFR part 314, subpart E of 21 CFR part 601, the Pediatric Research Equity Act, and the Animal Efficacy Rule. These studies will usually have a primary efficacy endpoint.	Please include relevant examples.
Lines 191-198:	The requested study design for observational pharmacoepidemiologic studies should take into consideration that many safety studies may not be able to test pre-specified hypothesis, e.g., for very rare events, and may not have an appropriate available control group for comparison. In addition, confounding by indication may result in section bias or inability to conduct a fair comparison.	Please note the inherent limitations of this methodology.

Lines 202, 287:	The example provided for a PMR (line 202) and PMC (line 287) are similar and the guidance document needs clarity on when an epidemiological study designed to evaluate the background rate and incidence of a serious adverse event should be a PMR or PMC.	Please clarify.
Lines 211-212:	We note that PMRs should be primarily used to investigate serious safety issues.	We recommend revising the sentence to read, "While efficacy may be evaluated, the primary goal of the PMR would be to evaluate **a serious** safety **concern**." This provides clarity that this is for a serious safety issue rather than any identified safety event.
Line 214-215:	Some of the examples provided in this subsection require additional clarity. For example, an evaluation of asthma exacerbations would likely be considered an efficacy study depending on the overall purpose of the trial (Lines 214-215).	Please clarify how this example qualifies as a PMR.
Lines 232-238:	Additionally, it is unclear why carcinogenicity study data and reproductive study data are listed under Post-marketing requirements (Lines 232-238). From our perspective, these types of studies generally would be conducted prior to marketing.	Please clarify if these studies are listed to cover rare instances of additional studies getting performed after marketing or if this is referring to long-term safety studies to evaluate latent safety concerns.
Lines 240-252:	Most of the examples in section III.A. of studies that would meet the criteria for a PMR seem appropriate but there are some that appear questionable. In the examples of in vitro laboratory studies, for example (lines 240-252), studies to define the mechanism of drug resistance and to validate an immunogenicity assay could be safety related, but would not	Please clarify or move the examples to the list in section III.B. of studies that would typically be considered PMCs.

	typically directly "assess a known serious risk", "assess signals of serious risk", or "identify an unexpected serious risk".	
Lines 263-265, 268, 272:	In addition, the PMR examples included for drug interactions or bioavailability studies, including food interaction PK studies, (lines 263-265, 268, 272) could cause confusion since in many cases when such studies are requested, scientific data indicating potential for a serious risk are not available.	It is therefore recommended that the text starting on line 263 be reworded to clarify that **"most postmarketing drug interaction and bioavailability studies would not meet the criteria for a PMR unless scientific data are available indicating potential for a serious safety risk."**
A. Post-Marketing Commitments (PMCs)		
Line 274	As discussed above regarding the subsection on PMRs, the title of this section could be misleading to a reader as it suggests that it includes information about postmarketing commitments when it lists examples of the types of studies or clinical trials to be considered a PMC.	We believe the subsection should be titled: "Examples of Postmarketing Requirements (PMCs)" to more accurately characterize what is portrayed in this subsection.
Lines 293-294:	We recommend that Section III.B. be expanded to include additional examples of types of studies that would not meet the criteria for PMRs, but might be considered agreed-upon PMCs.	For instance, the examples on lines 293-294 should be expanded to include clinical trials designed to further evaluate the effective dose range, including the efficacy of lower or higher doses. We also recommend that an additional bullet point be added to include most postmarketing drug interaction and bioavailability/food effect studies (cross reference comment above on section III.A.)

IV. PROCEDURES		
Lines 299-317:	The guidance should clearly state that if any PMR study or clinical trial does not demonstrate an increased risk then these study results are sufficient and no additional PMR studies/trials are to be conducted (absent a compelling reason for further study).	Please clarify and incorporate where necessary.
Lines 302-303:	The draft guidance states that "FDA plans to inform the applicant of the planned target date for communication of feedback from the review division to the applicant regarding PMRs and PMCs. FDA plans to communicate the planned target date in a letter sent within 14 days of the 60-day filing date." However it is unclear how the target dates are determined.	Please clarify that the PMC/PMR target dates in the 74 day letter are determined based upon the PDUFA IV commitment to providing a planned review timeline that is "consistent with the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products (GRMPs), taking into consideration the specific circumstances surrounding the individual application." (PDUFA IV Commitment letter, p. 10)
Lines 305-317:	The processes described in the draft guidance should be fully harmonized with internal CDER and CBER MAPPs on the procedure for selecting PMR/PMCs.	Section IV, the paragraphs describing procedures (lines 305-317) should contain a cross-reference or footnote referring to the CDER MAPP 6010.9 and CBER SOPP 8415 that describe FDA's procedures for identifying and communicating PMRs/PMCs to applicants.
Line 316	The guidance should clarify that that the action letter will contain the agreed upon timetable for each PMC or PMR, rather than just the list of PMR/PMCs.	We suggest that line 316 be revised to read: "**The agreed timetable and schedule of milestone submissions and final reports for** each PMR and PMC will be included in the action letter issued at the completion of the application review.'
Line 314-317:	We believe a protocol does not need to be fully agreed upon prior to an action as this could lead to an unnecessary delay in receiving an action letter. However, we support that the trial concept, as outlined in current approval letters,	Clarify that the agreed upon trial concept, as outlined in current approval letters, continues to be appropriate.

	should be agreed upon.	
V. REPORTING		
Line 320-364	The guidance should allow for the ability to negotiate frequency and/or timing of reporting on PMRs. PMC/PMR periodic reporting will be on an annual basis, generally based on the anniversary of the NDA/BLA approval date. On the other hand, the minimum required REMS assessments are at 18 months, 3 and 7 years, but several REMS have been approved with assessments every 6 months for at least the first 2 years, and annually thereafter. A product REMS will have its own anniversary date. Therefore, the timing of PMC/PMR annual reports and REMS assessments, as well as other reports that may include PMC/PMR information such as IND annual reports and PSURs, could lead to reporting every few months on this information. The value of such frequent reporting may be limited.	Please note that the Agency is willing to discuss the frequency and/or timing of reporting on PMRs in order to streamline reporting requirements. Additionally, we recommend that lines 332-334 be revised to read: **"**For each PMR required under FDAAA, the applicant must submit a timetable for completion of the study or clinical trial and must ~~periodically~~ report on the status of the study or clinical trial **on a periodic basis agreed upon by FDA and the sponsor** (see section 505(o)(3)(E)(ii))."
A. PMR Reports		
Lines 337-339:	Section V.A., regarding the last sentence in this paragraph (lines 337-339) indicating that status reports must include "documentation" that the PMR is registered.	It is recommended this be revised to clarify that providing the CTN number would be sufficient
C. Other Section 505(o) Studies and Clinical Trials		
Lines 348-352:	The guidance should clarify what types of studies or clinical trials in addition to CMC commitments and stability studies are considered to be "otherwise undertaken" under Section	Please clarify

	505(o)3(E)(ii) of the Act and 21 CFR 314.81(b)(2)(viii). For example, types of clinical trials that should not be included are: ISS studies since they are not conducted by or on behalf of the applicant; clinical trials exempt from IND requirements under 21 CFR 312.2(b) or where IND requirements are not applicable under 21 CFR 320.31; and non-interventional studies.	
D. Status in REMS Assessments		
Lines 354-364:	We also would like to suggest that additional clarification be provided regarding the link/relationship between Risk Management Plans (RMP)/REMS and the "list of PMRs and PMCs". For example, are PMRs usually also included in a RMP or REMS?	Please clarify.
Lines 359-362:	Section V.D., the sentence in lines 359-362 indicates applicants can satisfy the requirement for reporting on the status of post-approval studies and clinical trials in REMS assessments by referring to the most recent annual report, but then adds: "and including any updates to the status information since the annual report was prepared." This would be cumbersome as in many instances there would be changes in enrollment figures that would require multiple updates at multiple reporting intervals (annual report plus REMS assessment report).	We recommend that this be modified to clarify that the requirement to report on the status of post-approval studies and clinical trials in REMS assessment reports could be satisfied by referring to the most recently submitted annual report.
Line 362	Please add <u>"material or significant"</u> in front of the word update and delete the word "any". Otherwise any small update (such as one additional patient enrolled in the clinical trial) could eliminate the ability to reference the annual	Revise to read: "Applicants can satisfy these requirements in their REMS assessments by referring to relevant information included in the most recent annual report required under section 506B of the Act and 21 CFR 314.81(b)(2)(vii) or 21 CFR 601.70 and including

	report. The suggested language adds reasonable flexibility.	~~any~~ **material or significant** updates to the status information since the annual report was prepared."
VI. DISPUTE RESOLUTION		
Lines 367-371:	This section states that "The applicant may appeal a requirement to conduct a postmarketing study or clinical trial using the usual dispute resolution procedures (Guidance for Industry, *Formal Dispute Resolution: Appeals Above the Division Level*)[15] (see section 505(o)(3)(F) of the Act)." The *appeal* process under dispute resolution described in "Guidance for Industry, *Formal Dispute Resolution: Appeals Above the Division Level"* can take more than 30 days, however, if the violation continues more than 30 days after FDA notifies the applicant of the violation, the penalties double for the following 30-day period and continue to double for subsequent 30-day periods, up to $1 million per period and $10 million for all violations adjudicated in a single proceeding.	BIO proposes that there should be a "clock stop" during the appeal process to allow the FDA and the sponsor time to resolve the dispute without the monetary leverage tilting the scale in favor of discouraging appeals and true scientific debate.
VII. ENFORCEMENT OF REQUIREMENTS FOR POST-MARKETING STUDIES AND CLINICAL TRIALS		
Lines 374-404:	Please see the comments in section IV of the "General comments" section of this document.	