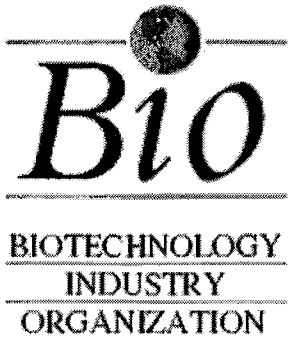


November 7, 2005

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 2005D-0334, Federal Register: September 7, 2005 (Volume 70, Pages 53233-53235)

Dear Sir/Madam:

The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. BIO appreciates the opportunity to comment on the Food and Drug Administration's (FDA's, the Agency's) draft guidance, "How to Comply with the Pediatric Research Equity Act."

BIO wishes to commend FDA for preparing this draft guidance, which will assist BIO member companies with the interpretation and understanding of the Pediatric Research Equity Act (PREA). BIO has reviewed the draft guidance and has the following comments and requests for clarification.

**1) Compliance Dates in the Draft Guidance are Not Consistent with PREA for Certain Applications Granted Deferrals (PREA, Section 4(b))**

The information concerning compliance dates for applications subject to PREA (see Attachment C of the guidance) does not appear to be consistent with PREA. A copy of the table of compliance dates from Attachment C of the draft guidance is included below.

| Categories of Applications | Expected Date of Compliance |
|---|---|
| Application or supplement submitted between 4/1/99 and 12/3/03, no waiver or deferral was granted and no studies were submitted | Immediate unless FDA specified later date |
| Application or supplement submitted between 4/1/99 and 10/17/02, studies were deferred to a date after 4/1/99, but no studies were submitted | Deferral date + 411 days |
| Application or supplement submitted between 10/17/02 and 12/3/03 and approved after 12/3/03, studies were deferred | Immediate unless later date is specified in deferral letter |
| Application submitted after 12/3/03, studies were deferred | Date specified in deferral letter |

| | |
|---|---|
| 4/1/99 | Date Ped Rule became effective |
| 10/17/02 | Date Ped Rule suspended |
| 12/3/03 | Date PREA enacted |

PREA does not provide for the distinctions made in rows 2 and 3 of the table listed above, which deny certain applications the 411-day extension. Under PREA, all submissions submitted between 4/1/99 and 12/3/03 for which sponsors were granted deferrals receive a 411-day extension (stated in PREA as the number of days equal to the number of days between 10/17/02 and 12/3/03) to the date specified in the deferral letter.

We request that the Agency revise the implementation dates in the Final Guidance to be consistent with PREA. We recommend that the table containing the implementation dates be revised as follows:

| Categories of Applications | Expected Date of Compliance |
|---|---|
| Application or supplement submitted between 4/1/99 and 12/3/03, no waiver or deferral granted | Immediate unless FDA specified later date |
| Application or supplement submitted between 4/1/99 and 12/3/03, studies were deferred | Deferral date + 411 days |
| Application submitted after 12/3/03, studies were deferred | Date specified in deferral letter |

| | |
|---|---|
| 4/1/99 | Date Ped Rule became effective |
| 10/17/02 | Date Ped Rule suspended |
| 12/3/03 | Date PREA enacted |

**2) Request for Clarification of Statement that FDA May Reconsider Waiver Decisions Until Time of Approval**

The draft guidance indicates that prior to approval, the Agency may reconsider its earlier decision to waive a pediatric assessment, and that a waiver decision does not become final until an approval letter is issued. The draft guidance states, "[i]f, prior to approval, the Agency becomes aware of new or additional scientific information that affects the criteria on which the waiver decision was based, the Agency may reconsider its earlier decision. A waiver decision becomes

final once issued in the approval letter for an NDA, BLA, or supplement." (See page 12 of the draft guidance).

We request that the Agency clarify this statement to describe how the Agency will handle the reversal of an earlier decision to waive a pediatric assessment. We are concerned that the reversal of a decision to waive a pediatric assessment during the development phase, or during the review of a pending application, may cause a delay in the submission of the application and/or the approval of the application. PREA specifically states, with respect to the latter, that the requirement of a pediatric assessment should not delay approval of applications for use of the product in adults—(Section 2(a)(3)). Additionally, an application may contain information on pediatric subpopulations for which approval also would be delayed if application approval were slowed.

We request that the Agency clarify how a reversal on a waiver decision will be handled so that it does not adversely affect either the planned submission of an application with a development program well underway, or the approval of a pending application. We would like to see the Agency state, at a minimum, that if a previously granted waiver is rescinded, deferral will be granted automatically, so as not to delay approval of the application.

Additionally, we believe that sponsors should have an opportunity to discuss with FDA any decision to rescind a previously granted waiver, prior to the Agency taking such an action. Such consultation is particularly important where a waiver was granted because a sponsor certified that the product would be ineffective or unsafe in the pediatric population. We urge that FDA specifically include a requirement and process for this consultation in the Final Guidance.

**3) Request for Clarification of Statement that FDA May Reevaluate the Length of the Deferral Closer to the Time of Approval**

The draft guidance states that "[f]or a deferral granted during the pre-approval development period, it is possible that FDA may reevaluate the length of the deferral closer to the time of approval..." (See page 13 of the draft guidance). We request that the Agency clarify that it will discuss with the sponsor any reevaluation of the length of deferral to agree upon a feasible timeframe for completion of the pediatric assessment.

**4) Request 60-Day Timeframe for FDA Decision on Requests for Waivers or Deferrals**

In the current draft guidance, FDA does not provide a timeframe for its decisions regarding requests for waivers or deferrals. Because of the amount of time and effort required to plan for and initiate clinical studies, we believe it is essential for the Agency to adopt such a timeframe. This will prevent unexpected delays during the pre-submission development program that ultimately could translate to delays in approvals.

We request that the Agency adopt a 60-day timeframe for reaching a decision on a "complete" request for a deferral or waiver submitted to the Agency. A complete waiver or deferral request could be defined as one that contains all the elements outlined in the sample requests found in Attachments A and B of the draft guidance.

**5) Request Information Concerning Meetings to Discuss Pediatric Plans, Deferrals, and Waivers**

Under PREA, provisions are made for meetings between FDA and sponsors to discuss issues such as timelines for the submission of pediatric assessments, and requests for waivers and deferrals. *Section 2(e) Meetings* of PREA states, "[b]efore and during the investigational process for a new drug or biological product, the Secretary shall meet at appropriate times with the sponsor of the new drug or biological product to discuss- 1) information that the sponsor submits on plans and timelines for pediatric studies; or 2) any planned request by the sponsor for waiver or deferral of pediatric studies."

The draft guidance is silent with respect to meetings that sponsor companies may request with FDA on PREA issues. We recommend that FDA include in the Final Guidance a section on meetings to discuss issues concerning PREA requirements such as pediatric assessments, timelines for submission of information, and waivers and deferrals. We request that the guidance provide details of how such meetings should be requested and who should be included in the discussions. We recommend that the meetings include representatives from both the Division of Pediatric Drug Development (DPDD) and the reviewing division. Clarification of the roles of the divisions also would be useful.

**6) Request Clarification with Respect to the Definition of "Substantial Number"**

*Section B. What Ages to Cover in a Pediatric Plan* of the draft guidance includes a brief discussion of the meaning of "substantial number" of pediatric patients (footnote 7, page 7). While noting that PREA does not define "substantial number," the footnote states that "[i]n the past, FDA generally has considered 50,000 patients to be a substantial number." The guidance further states that "[t]he Agency, however, will take into consideration the nature and severity of the condition in determining whether a drug or biological product will be used in a substantial number of patients." It appears that FDA is replacing a previously generally accepted number with a subjective approach, but without clarifying how decisions on patient numbers will be made. Since use in a "substantial number" of patients is an important determinant of whether a pediatric assessment is required, we urge that explicit guidance be provided as to how determinations of "substantial number" of patients will be made.

Please do not hesitate to contact me for further information on any of the topics we address above.

Sincerely,

/s/

Sara Radcliffe
Managing Director
Science and Regulatory Affairs