

Alan Goldhammer, PhD

Associate Vice President,
US Regulatory Affairs



November 7, 2005

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

Re: Docket no. 2005D-0334; Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act; 70 Federal Register 53233

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) welcomes the opportunity to comment on the above referenced proposed draft guidance issued by the Food and Drug Administration (FDA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier, and more productive lives. Investing more than \$38 billion during 2004 in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

The guidance is well written and provides added description of the Pediatric Research Equity Act (PREA) and the expectations of the agency for compliance. PhRMA agrees that discussion of pediatric programs should take place as early as feasible. It is important, however, to recognize that programs discussed early in the drug development process are likely to change as information is acquired in later phase of development. Also, because Sponsors will be planning for one pediatric program to address both PREA and the options for exclusivity under the Best Pharmaceuticals for Children's Act (BPCA), the Agency needs to be prepared at an early stage to agree to a Written Request (WR), again with the expectation that such a WR may need to be amended as the program progresses.

There is a concern that PREA and the draft guidance may have the unintended consequence of substantially increasing the burden associated with an application or supplement to add a new indication, new dosage form, or new dosing regimen to labeling for a previously approved product. For such applications or supplements, the applicant must accept the potential triggering of a new requirement for pediatric clinical studies or development of an age-specific pediatric formulation. Under this draft guidance, it is noteworthy that even an NDA for a new pediatric formulation requires a pediatric assessment.

Our concern stems from recollection of the era in the 1970s through the early 1990s, when it was commonplace for sponsors to consider it overly burdensome to prepare and submit a supplement seeking FDA's approval for a new indication or new dosing regimen. It was not uncommon for off-label uses to remain off label, despite conduct of adequate and well-controlled trials, because of a perception of a substantial burden to prepare and defend an

Pharmaceutical Research and Manufacturers of America

1100 Fifteenth Street, NW, Washington, DC 20005 • Tel: 202-835-3533 • FAX: 202-835-3597 • E-Mail: agoldham@phrma.org

efficacy supplement. FDA addressed this historical consideration, explicitly, in May 1998 in the guidance for industry on evidence of effectiveness, which included the following statements:

"Another major goal of this guidance is to encourage the submission of supplemental applications to add new uses to the labeling of approved drugs. By articulating how it currently views the quantity and quality of evidence necessary to support approval of a new use of a drug, FDA hopes to illustrate that the submission of supplements for new uses need not be unduly burdensome." (Food and Drug Administration. *Guidance for Industry. Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*. May 1998.)

Since the intent of the PREA legislation is to ensure the timely conduct of pediatric clinical studies to ensure the availability of data for the safe use of medicines in children, PhRMA recommends including in the discussion on waivers FDA's willingness to entertain waiver requests for applications for new dosage forms or new dosing regimens when the applicant has already met (or is proceeding with due diligence to meet) the PREA requirements for the original product. New dosage forms and new dosage regimens may qualify for waiver under the provision that addresses meaningful therapeutic benefit over existing products and substantial use.

The following are some specific comments. In a separate section we have provided comments on the estimation of the Burden of the Proposed collection of information.

Section I. – Introduction

The definition of pediatric assessment found in footnote 3 is a key element for the understanding and compliance of PREA. We suggest that this footnote be brought up into the body of the text.

Section III (A) – PREA Statutory Requirements

There is potential conflict between the statement in Section III (A) ("*In general, PREA applies only to those drugs and biological products developed for diseases and/or conditions that occur in both the adult and pediatric populations*") and Section VI (Waivers and Deferrals), Subsection B. In Section VI (B), the "*disease-specific waiver*" is described and a list of "*adult-related conditions*" that may qualify a drug for such a waiver is provided in Attachment A.

PhRMA recommends deleting this paragraph from III (A). The statements imply that PREA applies only to certain drugs and applications for products with pediatric-specific indications. We are not aware of any basis in the statute for removing certain applications from the entire scope of the statute. The waiver provisions are available to applicants and should be used to exempt drugs for adult diseases for which no corresponding pediatric condition exists. In the case of an application for specific pediatric indications, if the application contains an "assessment" of all relevant pediatric age groups then PREA is satisfied by the initial development program. This does not mean that PREA did not apply to the application, but rather that the application, as submitted, met the requirements of PREA.

Section IV (B), VI (B) and VI (D) – When to Submit the Pediatric Assessment in Compliance with PREA

A pediatric assessment is due at the time of the application for an NDA or sNDA (for new indication, new dosing regimen or new route of administration) unless a deferral or waiver has been granted.

1. We recommend that paragraph 4 under Section V (A) found on page 7 of the guidance be placed in this section (Section IV B) with the comments as noted below.

Paragraph 4 currently under Section V (A) *“When a decision to waive or defer pediatric studies is made at key meetings, the minutes from those meetings reflecting the decision **generally** will be provided to applicants for their records. Alternatively, a separate letter **may be** sent to the applicant conveying FDA’s decision to either waive or defer the pediatric assessment. If a deferral of studies is granted at the time of the meeting, a due date for submission **generally** will also be included in the meeting minutes or a separate letter.”* (Emphasis added)

While perhaps not the intent, the terms “generally” in the first and third sentences, and “may be” in the second, leave open the possibility for confirmation of the decision not to be conveyed to the applicant in any written form. We suggest that a clear statement be made to indicate that the decision will be conveyed to the applicant, either in the minutes of the meeting or in a separate letter. It would also be helpful to state the time frame in which FDA will provide confirmatory documentation.

2. The draft guidance provides recommendations for consultation and discussion of the pediatric plan for studies of serious and life-threatening conditions as well as for other conditions. Such discussions are described only in relation to standard meetings such as the pre-IND or End-of-phase 1 meeting (for serious or life-threatening diseases) or the end-of-phase 2 meeting for other conditions. In general, such meetings are considered “Type B” meetings. Occasionally, however, it becomes necessary for sponsors to meet with the agency on issues with a pediatric program outside of these standard meetings. We recommend that reference to such meetings be included in the guidance and that such pediatric development meetings be generally characterized as Type B meetings unless they are necessary for an otherwise stalled development program, in which case they would qualify as Type A meetings.

Useful language pertaining to the timing for discussion of waivers or deferrals is found on pages 10 and 11 of the draft November 2000 Guidance for Industry: Recommendations for Complying With the Pediatric Rule (21 CFR 314.55(a) and 601.27(a))

For waivers:

“Ordinarily, a discussion on waiving pediatric studies should take place at the End-of-phase 2 or pre-NDA/pre-BLA meeting, and this discussion should be reflected in the minutes of the meeting. If this did not occur, and a sponsor wishes to obtain a waiver, the waiver request should be submitted to the Agency at least 60 days prior to the application submission.”

For deferrals:

Ordinarily, a discussion of deferral of pediatric studies should take place at the End-of-phase 2 or pre-NDA/pre-BLA meetings, and this discussion should be reflected in the minutes of the meeting. If this did not occur, and a sponsor wishes to obtain a deferral, the deferral request should be submitted to the Agency at least 60 days prior to the application submission.

We recommend including this language in the final guidance.

Section IV(C) – What Types of Data Are Submitted as Part of the Pediatric Assessment?

PhRMA suggests that the guidance also describe the types of study that would be expected in addition to those that may not be needed.

The second paragraph in this section states: *“If extrapolation from adult effectiveness data is inappropriate, adequate and well-controlled efficacy studies in the pediatric population may nevertheless be required. Additional information, such as dosing and safety data, could also be important to support pediatric labeling decisions.”*

Reference to “well-controlled efficacy studies” (plural) implies the need for more than one such study. This may not always be necessary. We recommend rewording this paragraph to allow for situations in which, for example, a single efficacy study and a PK study are considered by the review division to be appropriate to extend labeling to the pediatric population.

We suggest the following *“If extrapolation from adult data is inappropriate, studies in the pediatric population may be required. Additional information, such as dosing and safety data, could also be important to support pediatric labeling decisions.”*

Section V (A) – When to Develop a Pediatric Plan (Paragraph 4) – Page 7

We suggest that this paragraph be moved to section IV (B) – When to Submit the Pediatric Assessment in Compliance with PREA

Section V (B) – “What Ages to Cover in a Pediatric Plan”

1. Footnote 7 refers to the meaning of “substantial number” of pediatric patients. It notes that PREA does not define “substantial number” and that *“in the past”* FDA generally considered 50,000 patients to be a substantial number. The footnote continues, *“The 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.”*

This description of the way the determination of “substantial number” will be made provides no guidance to applicants or to the Agency review staff. It appears to dismiss the previously generally accepted benchmark of 50,000 patients with the disease or condition. Under this policy, determinations will be open to the discretion of each review division on a case-by-case basis. Because the estimate of use in a “substantial number” of patients is an important determinant of whether a pediatric assessment is required, we recommend that FDA continue to use the 50,000 patient cutoff, and reference the logic for the 50,000 patient number originally

described in the Preamble to the Pediatric Final Rule, 63FR 66632 (Dec 2, 1998) at 66636. We further recommend that this information be placed in the guidance rather than a footnote.

2. (Paragraph 2, Page 7): The draft guidance quotes the PREA definition of “*meaningful therapeutic benefit*” which includes estimation by FDA that, “...if approved, the drug or biological product would represent a significant improvement...compared with marketed products adequately labeled for that use in the relevant pediatric population.” It continues with the statement, “Improvement over marketed products **might be demonstrated by...**” (Emphasis added)

The latter statement creates some confusion by implying a requirement to demonstrate “improvement over marketed products.” Under the statute, FDA may waive a pediatric assessment if it finds, among other things, “...that the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients,” and it may require a pediatric assessment of a marketed product if “there is reason to believe” that the product would represent a meaningful therapeutic benefit. It does not appear that the FDA requires a demonstration of improvement over marketed products, as is suggested by the language in the draft guidance, before making these judgments. Nor does there seem to be a requirement, if a pediatric assessment is required, that the studies must be designed to demonstrate superiority over approved and adequately labeled products.

It may be preferable, therefore, to revise the above statement to, “Improvement over marketed products might be suggested by...”

3. (Paragraph 3, Page 8): “*The BPCA defines “pediatric studies” or “studies” to include studies in all ‘pediatric age groups (including neonates in appropriate cases)’ in which a drug is anticipated to be used (section 505A(a) of the Act)*”

We recommend deleting this sentence. Reference to the BPCA for the purposes of describing the age ranges that should be included in studies required under the PREA is both unnecessary and potentially confusing. For example, it is possible for a given drug that the age ranges to be studied under the PREA, which is generally confined to the same indications as approved in adults, may be different from those included in a Written Request under the BPCA that may be intended to investigate safety and effectiveness in a unique pediatric conditions. Besides, the age ranges covered under PREA can be adequately described without reference to a different statutory provision.

4. (Paragraph 4): “*The complex medical state of neonates and infants makes it critical to evaluate drugs specifically for their use. The Agency is also aware that trials in neonates and infants pose special ethical issues. FDA generally will require studies in neonates and infants under PREA **if the drug represents an important advancement** and its use in these age groups for the **approved indication** is anticipated. However it is possible that partial waivers for these specific age groups might be appropriate under certain circumstances when “necessary studies are impossible or highly impracticable,” or when “**there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group**” (section 505B(a)(4)(B)(i) and (ii) of the Act).*” (Emphasis added)

There are several issues in this paragraph that should be clarified to provide more consistency with the plain language of the statute. First, biological products should be included in the first and third sentences in addition to drugs; second, it is unclear whether the important advancement referred to is an advancement in the indication in the adult population or a presumed advancement in the treatment of neonates and infants; and third, reference to the “approved indication” suggests that required assessments of new drugs in neonates and infants would always be deferred until after approval.

Thus we recommend that the text be modified as follows:

*“The complex medical state of neonates and infants makes it critical to evaluate drug and biological products specifically for their use. The Agency is also aware that trials in neonates and infants pose special ethical issues. FDA generally will require studies in neonates and infants under PREA **if the drug or biological product represents an important advancement for pediatric patients in that age group and its use in these age groups for the adult indication is anticipated.**”*

It has been the experience of some PhRMA-member companies that it is very difficult to obtain a partial waiver for a specific age group. We recommend that the FDA consider inclusion of further information in this section of the draft guidance. Suggested text is noted below.

- Studies may be impossible or highly impractical, for example, because (a) the limited number of affected patients in the age subgroup in the United States does not permit a prospective clinical trial to be conducted or (b) an age-appropriate formulation could not be developed for the product.
- The product may be expected to be ineffective or unsafe in the age subgroup, for example, because (a) previous human studies in adults or other age subgroup do not support a reasonable likelihood of effectiveness in the age subgroup in question, (b) previous human studies in adults or older pediatric patients demonstrate serious adverse events or deaths associated with the drug that preclude further clinical investigation in younger age subgroups or, (c) juvenile toxicology studies demonstrate toxicities relevant to the age subgroup.

Section V(C) – “Must the Sponsor Develop a Pediatric Formulation?”

Paragraph 1, page 8

1. The language in PREA consistently refers to “drug and biological products.” However, it also requires pediatric assessments, *“gathered using appropriate formulations for each age group for which the assessment is required that are adequate to assess the safety and effectiveness of the drug or biological product for the claimed indications in all relevant pediatric subpopulations; and to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective.”* This language creates confusion with respect to the correct interpretation of a number of terms in the statute, including, “drug or biological product,” “formulation,” “appropriate formulation,” “relevant pediatric subpopulations,” “age group for which the assessment is required,” and “pediatric subpopulation for which the drug or biological product is safe and effective.” Because reference to a “product” (as in “drug product”) is generally understood to be specific as to manufacturer, dosage form, strength, release

characteristics, route of administration, and includes, among other things, formulation, the terms of the statute appear to be in conflict. An assessment using a different formulation would not also be an assessment of the safety and effectiveness of the “drug or biological product” that triggered the required assessment, but of another product, albeit one containing the same active substance.

If, for example, a modified release dosage form is developed for the adult population, the formulation itself, with its unique release characteristics, may make the product inappropriate for use in pediatric patients below a certain age, even if the active ingredient may have potential use in younger patients if delivered by a different dosage form. We believe that the “age group for which the assessment is required” in this situation should be viewed as the age group for whom the modified release dosage form is appropriate. This may extend to development of a different strength of the modified release dosage form but not necessarily to the study and development of an immediate release product containing the same active ingredient or even a parenteral dosage form. Studies to address the safety and effectiveness of the active ingredient in alternative dosage forms should be pursued under the voluntary provisions of the BPCA instead.

Similarly, if more than one sponsor holds an approved application for a product containing the same active ingredient, one of which is a modified release formulation appropriate only for adults while the other is an immediate release liquid but lacking labeling in all “relevant” pediatric age groups, would the applicant holding the modified release product approval be required to develop a competing immediate release liquid dosage form if it introduced a new adult dosing regimen for its modified release product?

We recommend including a discussion of and rationale for the Agency’s interpretation of the PREA with respect to this issue and suggest that a narrow interpretation of the term “appropriate formulations” is appropriate in view of the clear and abundant reference to “products” in the statute.

2. The draft guidance states, “*FDA interprets the language “request for approval of a pediatric formulation” to mean that applicants must submit an application or supplemental application for **any not previously approved formulation(s) used to conduct their pediatric studies.** Where appropriate, applicants may need to begin the development of a pediatric formulation before initiation of pediatric clinical trials.*”

This interpretation creates a number of potential issues, including:

- It would require sponsors who use more than one formulation during the course of pediatric studies to submit marketing applications for each formulation used.
- It suggests that applicants should develop a marketable formulation or formulations before initiating clinical trials (to avoid having to submit multiple applications for each variation in formulation), thereby delaying the clinical program and eventual availability of a product designed and labeled for pediatric use.
- It discourages efforts to improve upon an initial formulation as the clinical program progresses.

In reality, an applicant may normally make formulation changes as a development program progresses and more than one formulation may be used in the course of conducting the pediatric studies. Furthermore, the possibility exists that an applicant may choose to develop an improved formulation for commercial marketing during the pediatric drug development program – a formulation that is bioequivalent to, but different from, the formulation(s) used to conduct the pediatric studies. Such commercial formulations could extend to different dosage forms from those used in the clinical program. Therefore, while a literal reading of the language in PREA suggests that applications be submitted for any formulation used to conduct pediatric trials (and only for those formulations), we recommend that the Agency adopt a less restrictive, reasonable interpretation to facilitate pediatric product development.

Paragraph 2, Page 8:

FDA can waive the requirement for pediatric studies when FDA finds that "reasonable attempts" to produce a pediatric formulation have failed. It has been the experience of some PhRMA-member companies that it is difficult to obtain such a waiver. We recommend that further information be included in the guidance so that FDA and sponsors can have a clear understanding of acceptable bases for such a waiver. Specifically, please consider incorporating the following text into this section of the draft guidance:

"FDA will usually expect that 'reasonable attempts' to produce a pediatric formulation will consist of a pharmaceutical development report documenting efforts to produce at least 2 different products (e.g., suspension, syrup, solution, or chewable tablet) through work encompassing a total of at least 4 different formulations. This report must include documentation of specific tests and results to show the failure of these products and formulations to yield the desired strength, quality, purity, and identity for the proposed pediatric formulation."

Section V (D): "When to Initiate Pediatric Studies"

The following comments apply to the discussion of situations when studies should not begin until after approval and initial marketing of a product. The draft guidance states, "*...for example, where a product has not shown any benefit over other adequately labeled products in the class, the therapeutic benefit is likely to be low, or the risks of exposing pediatric patients to the new product may not be justified until after the product's safety profile is well established in adults....*"

1. Except in the case of serious or life-threatening conditions, it is commonly considered prudent to postpone clinical trials of new drugs in pediatric patients until a certain amount of post-marketing experience is obtained in a larger population than that exposed in clinical trials. A product may not have shown benefit over other "adequately labeled products in the class" because of such limited exposure or it may not have been compared to other such products in clinical trials. In addition, there may not be other products in the class that are adequately labeled for pediatric use. The example in the draft guidance should be revised so as not to suggest that a decision to defer pediatric trials indicates that a product has a low therapeutic benefit or that it is associated with unusual risks. It is more commonly a matter of prudence in the face of a lack of broad human exposure to the drug.

2. It is unclear whether “adequately labeled products in the class” refers to a broad therapeutic class (such as antihypertensives), or a more specific pharmacological class (such as in ACE Inhibitors).

Section VI – Waivers and Deferrals

1. Subsection B (4) – Waiver Decision

In the third paragraph in this section, the draft guidance states that the Agency may reconsider its earlier decision on a waiver if it becomes aware of new or additional scientific information that affects the criteria on which the waiver decision was based. We recommend that, in the event a waiver is rescinded, the applicant should automatically qualify for deferral without having to apply for deferral through the process described in Section VI(D) as allowed by PREA Section 505B(a)(3)(A)(iii) – “there is another appropriate reason for deferral.”

2. Subsection D (1) Criteria for Deferral (Section 505B(a)(3) of the Act)

There appears to be some conflict between the text of the draft guidance and the Attachment B (Sample Deferral Request) that will benefit by clarity of the guidance intent. The text states, *“In addition, the applicant must submit certification of the reason(s) for deferring the assessments, a description of the planned or ongoing studies, and evidence that the studies are or will be conducted with due diligence and at the earliest possible time.”* The Sample Deferral Request, however, asks, *“Has a pediatric plan been submitted to the Agency? If so, provide date submitted; If not, provide projected date pediatric plan is to be submitted.”*

The text of the draft guidance suggests that not only the plan but also evidence of due diligence to conduct proposed studies is needed before a deferral decision can be made. On the other hand, the deferral request appears only to seek information on whether the plan has been submitted or when the sponsor plans to do so. We recommend incorporating the same language into the text as appears in Attachment B to resolve this conflict.

Subsection D (2) – Information in a Deferral Request

The seventh bullet in the list calls for, *“evidence that planned or ongoing studies are proceeding.”* We recommend that this sentence be revised as it is unclear what manner of evidence would show that a planned, but not yet initiated, study is “proceeding.”

We recommend the following language:

- Evidence that studies are being developed or ongoing studies are proceeding.

For consistency we recommend that the text in this section conform to the language appearing in Attachment B.

Subsection D (3) – Deferral Decision

The draft guidance provides for the possibility that FDA may reevaluate the length of the deferral “closer to the time of approval,” based on new information. .

PhRMA strongly recommends including language in the guidance that makes clear the importance of involving the applicant at the earliest possible time whenever reevaluation of the length of a deferral is being considered to assure that any new date is mutually agreeable and reasonably achievable.

Under the current draft guidance, FDA does not provide a timeframe for which it will reach decisions with respect to requests by sponsors for waivers or deferrals. Due to the amount of time and effort required to plan for and initiate clinical studies, we believe that it is essential for the Agency to adopt a timeframe for decisions on deferrals and waivers.

A specified timeframe for Agency decisions will prevent unexpected delays during the pre-submission development program caused by late decisions on deferrals and waivers. Such delays in the development program may ultimately 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 which contains all of the elements outlined in the sample requests found in Attachments A and B of the guidance.

Section VIII – PREA and Pediatric Exclusivity

We commend the agency for its desire to meet the goal of generating pediatric data in a manner that minimizes duplication of studies though its encouragement of meeting both PREA and exclusivity commitments through one development program. It is recognized that the planning for studies to meet both PREA and pediatric exclusivity will need to be addressed by the Sponsor and the reviewing Division on a case-by-case basis.

Attachment B – Sample Deferral Request

Consistency of language between Attachment B and section VI.D.2 is suggested.

Attachment C

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 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 specifies 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

II. Comments on the Accuracy of FDA's Estimate of the Burden of the Proposed Collection of Information, Including the Validity of the Methodology and Assumptions Used.

We consider the burden estimates published in the September 7, 2005 Federal Register to be substantially below the actual amount of time sponsors must spend to in preparing and submitting the types of information described. Estimates are provided for four categories of activity. They are (1) the time to prepare each assessment [505B(a)(1)] and [(a)(2)]; (2) the time to prepare a deferral request [505B(a)(3)]; (3) the time to prepare a full or partial waiver request [(505B(a)(4)]; and the time to prepare for meetings [505B(e)]. No information was provided regarding the assumptions on which the estimates were based, nor was the methodology described. Without knowing the scope of activity FDA included in its estimate, it is impossible to judge whether the estimates are reasonable or to offer estimates that we believe more closely represent the burden imposed.

For example, FDA estimates:

a) 50 hours to prepare each pediatric assessment. A pediatric assessment is *"...required to contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in the relevant pediatric subpopulations and to support dosing and administration for each subpopulation for which the product is safe and effective."*

As noted, the Federal Register notice does not describe what elements of a pediatric assessment FDA considered in making its estimate. Considering that a pediatric assessment requires, among other things, development of a pediatric plan, drafting and finalization of protocols, conduct of studies, data collection, validation and auditing, analysis of collected data, preparation of one or more study reports, and preparation of an application or supplemental application, it is clear that only the smallest fraction of these activities could have been included in order to conclude that a resource expenditure of 50 hours (little more than 1 person for 1 week) would, on average, be sufficient to satisfy this requirement.

b) 24 hours to prepare a deferral request and 8 hours to prepare a waiver request.

As is clear from the sample request forms (Attachments A and B for waiver and deferral respectively), considerable review of available information regarding the drug and the disease or condition, including the prevalence and presentation of the disease in children must be completed in order to prepare the justification for waiver or deferral in accordance with the procedures outlined in the draft guidance. As with the estimate for submission of pediatric assessments, there is no discussion of the elements of a waiver or deferral request that were considered in reaching the estimates provided. Both appear significantly below the amount of time actually required to prepare and submit such requests.

c) 16 hours per meeting submission:

Sponsors take preparation for meeting with FDA very seriously to maximize the benefit they receive from discussions with Agency staff. It is common practice for a product team to

convene weekly meetings to define the specific questions they need to ask and to prepare an appropriate background package. Obviously, additional time is needed between such discussions to draft the necessary sections of the meeting package and, later, to make any revisions agreed upon by the team. Sixteen hours, even as an average appears to significantly underestimate the typical time spent by sponsors in preparing for an FDA meeting on pediatric issues. As with the other two estimates, no details are provided regarding the elements of meeting preparation that were considered by FDA in arriving at its estimate.

PhRMA trusts these comments are useful to the Agency as it moves forward to finalize this guidance.

Sincerely,

A handwritten signature in cursive script, appearing to read "Alan Helleman".