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PhRMA

March 06, 2001

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

Re: Docket No. 00D-1595 - Draft Guidance for Industry, *Recommendations for Complying with the Pediatric Rule* (21 CFR 314.55(a) and 601.27(a)); 65 Federal Register 75720, December 4, 2000

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is submitting these comments on the Draft Guidance for Industry, *Recommendations for Complying with the Pediatric Rule* (21 CFR 314.55(a) and 601.27(a)). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members invested over $26 billion in 2000 for the discovery and development of new medicines. For this reason, PhRMA and its member companies are keenly interested in all aspects of the drug development process, including the development of medicines intended for use in the pediatric population.

PhRMA supports FDA in its efforts to provide consistent guidance to industry regarding compliance with the Pediatric Rule and member companies appreciate the opportunity to provide comments on the Draft Guidance. We believe that the Draft Guidance document is a good beginning, but there are a number of areas in the document that PhRMA thinks could be enhanced. Our general comments are below; we have inserted specific comments into the relevant sections of a copy of the Draft Guidance, which is attached. Underlying all of our comments is the general principle that PhRMA companies support development of pharmaceutical and biotechnology products intended for use in the pediatric population, as appropriate.

PhRMA continues to believe that the FDA exceeded its statutory authority in issuing the 1998 Mandatory Pediatric Rule to which this Draft Guidance applies. These comments are intended to assist the FDA in developing a Guidance that will enable manufacturers to understand how to comply with the Rule's requirements; they are not intended to imply that PhRMA concurs that FDA has the authority to issue or enforce the 1998 Rule.

The Draft Guidance raises concerns that we believe would benefit from further consideration by the Agency and should be addressed in a revised Guidance. These include:

- Labeling statements required as a result of "evidence" that a product would be ineffective or unsafe in pediatric populations should not be made on the basis of a lowered labeling standard (relative to the standard on which all other labeling statements are based under

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existing regulations). We believe that application of apparently inconsistent labeling standards would inevitably result in confusion and misunderstanding on the part of many, including health care providers;

- Current labeling restrictions prohibit comparative labeling statements without the support of adequate and well-controlled studies. In situations where safety and efficacy have yet to be shown in the pediatric population, it is not clear what labeling statements the Agency would expect regarding preferential use of other products that are already adequately labeled. Conceptually, recommending "preferential use" may imply usefulness of the unlabeled (new) product as second line therapy, or may imply that there are known risks when none have been identified;
- Performance of pediatric studies under the Rule may be required when the indication to be studied is the same disease in adults and children. However, the requirements under the Rule should be related to safety and pharmacokinetics in children. One might argue that where clinical studies of efficacy in the pediatric population are needed, the indication in children might be presumed to be different than that in adults, and therefore, not truly applicable under the Rule;
- The list of diseases for which disease-specific waivers may be granted should be designated as examples and should not be considered an exhaustive list. FDA should make clear that the list can be revised and other diseases not on the current list may qualify for disease-specific waivers. FDA should indicate how it intends to make such revisions to the list;
- The circumstances under which a request for a deferral may lead to an eventual request for a waiver are not clear. This requires elaboration. PhRMA suggests that specific examples be provided.

PhRMA supports the FDA's recommendation that sponsors submit their development plans for assessing pediatric safety and effectiveness as early as possible during the product development process. However, this intention seems to conflict with the Agency's position regarding the finalization of waiver decisions. According to the proposed guidance, the Agency could reconsider its previous decision to grant a waiver at any time prior to the issuance of the Approval Letter. Consequently, a pediatric plan based upon an early Agency decision could be found unacceptable during late-stage development or even regulatory review of the application. In such a situation, it is unlikely that a revised pediatric plan could be implemented without adversely impacting submission and review times based upon FDA's earlier decision. This is particularly likely if the sponsor/applicant finds itself obliged to collect new pediatric use data, develop new pediatric formulations or reconfigure product packaging. The proposed guidance does not detail what, if any, alternatives would be considered by the Agency in such circumstances. The guidance should make it explicit that submission and approval of an application not be delayed based upon a change in Agency position. PhRMA respectfully suggests that the Agency reconsider its position on this subject and amend the proposed guidance accordingly.

In addition, the Draft Guidance contains several important terms and phrases for which PhRMA requests definition, explanation, or further clarification by the Agency. The following are examples:

- The terms "pediatric assessment" and "pediatric study" should be used consistently throughout the document to avoid their potential misapplication;
- Further explanation should be provided, perhaps by example, of how the rule applies when "extrapolation from adult effectiveness data is inappropriate" (Section III.D. What Types of Studies ...) and, consequently, when efficacy studies in certain pediatric populations will be required.

Finally, we would like to point out two additional items related to the Final Rule that we believe should be reviewed for consistency. We request that the Agency address them:

- FDA has indicated in both the Final Rule and the proposed guidance that it will grant waivers if the sponsor/applicant demonstrates that it is not possible or practical to conduct pediatric studies because of difficulty in enrolling an appropriate number of pediatric patients in clinical studies. However, in actual practice, this policy is not always followed consistently by Agency reviewers when considering waiver requests, reviewing proposed protocols for pediatric studies, or issuing Written Requests. Therefore, PhRMA respectfully requests the Agency to remind its reviewers that, under the Rule, sponsors/applicants should not be obligated to conduct pediatric studies if the pediatric patient population is below the number specified in the Rule, or if such studies are not practical.
- There appears to be an inconsistency between the last sentence in Section II.A. of the Draft Guidance ("The Pediatric Rule does not require pediatric studies for the pediatric use of a drug for indications for which the sponsor has not obtained, or does not seek, approval.") and FDA's January 2001 Status Report to Congress on the Pediatric Exclusivity provision of FDAMA. In Section V.(D)(2)(b)(Ensuring that Certain Drugs of Importance are Studied) in the Report, it is stated that for drugs which are already marketed and which have no remaining patent protection or other exclusivity, or for very small market drugs, there is little incentive for manufacturers to do pediatric studies. To address this issue, FDA proposes that Congress should codify FDA's authority to require pediatric studies under the Pediatric Rule on drugs that are "of importance to children." In other words, the Report proposes to make the Pediatric Rule the law by means of express legislation. The Report then lists what factors FDA would use to determine which marketed drugs provide the greatest health benefit and would therefore be candidates for mandatory pediatric testing. One of the listed factors is as follows:

  > "... whether the drug is or would be used in a substantial number of pediatric patients either for treatment of a labeled indication, or off-label..."

Based on this factor, if the health benefit arises in an off-label indication, then it would appear that the required studies would have to be done for the off-label indication. Thus, the FDA

appears to be saying to Congress in the Report that the Agency should have the authority to require mandatory pediatric studies even in cases where the studies would involve off-label uses for which the sponsor never has, nor plans to seek approval. This contradicts the statement made by FDA in Section II.A. in the Draft Guidance document. Please clarify how the Agency will reconcile those two statements. In the event that Congress does not address this issue, what is FDA's intention going forward under the Final Rule?

The attached document contains specific comments on the Draft Guidance. PhRMA trusts that our comments will be useful to the Agency as this Draft Guidance is revised and would gladly meet to discuss any of our comments in more detail. Thank you for the opportunity to comment on this very important topic.

Sincerely,

Alan Goldhammer

Comments of the Pharmaceutical Research and Manufacturers of America (PhRMA) to Docket 00D-1595 on

FDA DRAFT GUIDANCE FOR INDUSTRY RECOMMENDATIONS FOR COMPLYING WITH THE PEDIATRIC RULE

(PhRMA comments indicated in boldface Arial font)

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Comment:
Although the intent is understood, please consider removing the first person language from the header sections and where it appears in the document text. Example: "When do I Submit My Pediatric Assessment?" A sponsor will be submitting an assessment, not an individual. It will be based on a complex team process of discussion and decision-making. Putting it into the first person singular inadvertently diminishes the extent of work and thought necessary for these decisions. PhRMA suggests, "When should a sponsor submit a Pediatric Assessment?" We feel this approach reads more professionally and note that it is consistent with other agency Q/A documents, e.g., Frequently Asked Questions on Pediatric Exclusivity (505A), The Pediatric "Rule," and Their Interaction (07/27/99).

Comment
Please adjust the numbering for "Introduction" and "Background" such that both are not numbered "I."

This draft guidance, when finalized, will represent the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This draft guidance provides recommendations for sponsors of new drug applications (NDAs) and biologics license applications (BLAs) on how to meet the requirements of the final Pediatric Rule[2]. Areas covered include pediatric assessments, pediatric plans, waivers and deferrals, compliance issues, pediatric exclusivity, and the role of the Pediatric Advisory Subcommittee.

I. BACKGROUND

Comment:
See comment in Table of Contents regarding paragraph numbering.

On December 2, 1998, the Food and Drug Administration published in the Federal Register the final Pediatric Rule. Under the Pediatric Rule, applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration must contain a pediatric assessment unless the sponsor has obtained a waiver or deferral of pediatric studies (21 CFR 314.55(a) and 601.27(a)).

Comment
The terms "pediatric assessments" and "pediatric studies" have different meanings; an assessment may be required for all relevant pediatric age groups (except if waivers or deferrals have been granted), but studies are not always required. However, beginning in the preceding paragraph, and continuing throughout this draft Guidance, there appears to be an interchangeable use of these two terms. Later in the Guidance, the term used to describe the requirement appears to switch to "studies." Indeed, Attachments A and B only mention "Studies" as the substrate for requesting a waiver or deferral. Please review the draft Guidance for consistency in the use of these terms so that the meaning is clear.

The rule became effective on April 1, 1999. Under the compliance dates in the final rule, pediatric assessments must be included in applications after December 2, 2000, for (1) NDAs, (2) BLAs, and (3) abbreviated new drug applications (ANDAs) that are based on suitability petitions for a change in active ingredient, dosage form, or route of administration[3].

II. OVERVIEW -What am I required to Do Under the Pediatric Rule?

A. General Requirements

The Pediatric Rule requires that every application (drug or biologic) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, contain a pediatric assessment or a deferral or waiver of the requirement for this assessment (see section IV.B). FDA can also require pediatric studies of marketed drugs and biological products (1) that are used in a substantial number[4] of pediatric patients for the claimed indications and where inadequate labeling could pose significant risks, or (2) that would provide a meaningful therapeutic benefit[5] over existing treatments for pediatric patients and where inadequate labeling could pose significant risks (21 CFR 201.23).

Comment
Please consider modifying the last sentence above as follows (added words underlined): "FDA can also require pediatric studies of marketed drugs and biological products (1) that are used in a substantial number of pediatric patients for the claimed indications and where inadequate labeling could pose significant risks, or (2) that would provide a meaningful therapeutic benefit over existing treatments for pediatric patients <u>for the claimed indications</u> and where inadequate labeling could pose significant risks..."

Comment
Please describe how FDA will triage the products that are deemed to contain inadequate labeling and proactively communicate with sponsors to enforce this aspect of the Rule.

Comment
Clarify whether an "assessment" for a pediatric age group could be sufficient to make dosing recommendations in certain circumstances for a given age group. The guidance should include clarification about the use of traditional and population pharmacokinetics for determining the appropriate dosing in pediatric age groups.

In general, the Pediatric Rule pertains to those diseases and/or conditions that occur in both the adult and pediatric populations. Products intended for pediatric-specific indications will be subject to the requirements of the rule only if they are developed for a subset of the relevant pediatric population. The Pediatric Rule does not require pediatric studies for the pediatric use of a drug for indications for which the sponsor has not obtained, or does not seek, approval.

Comment
Please clarify the intended meaning of the term "relevant" in the second sentence above.

Comment
Please confirm that in order for the Pediatric Rule to be invoked, it should be agreed in advance that the indication under study is, in fact, the same disease in adults and children.

B.Postmarketing Requirements

The Pediatric Rule requires manufacturers to include in their annual postmarketing reports a summary of any new information pertaining to pediatrics. Specifically, the summary must list whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population

have been initiated (21 CFR 314.81 for NDAs, 601.27 for BLAs). Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, adolescents) must be provided, including dosage form (21 CFR 314.81 for NDAs and 601.27 for BLAs).

Comment

Please clarify whether studies reported under this clause should also be reported in annual reports to the IND (21 CFR 312.33). This may be of particular importance in cases where pediatric studies are conducted outside the US, and not under the IND.

1. Products to Which the Rule Does Not Apply

Orphan Drugs

If a product has been granted orphan designation for an indication or indications under section 526 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bb), submission of pediatric data is not required for applications to market the product for the orphan-designated indications and a waiver is not needed (21 CFR 314.55(d) for NDAs and 601.27(d) for BLAs).

Generic Drugs Under 505(j)

The rule does not impose any pediatric study requirements on applications for generic copies of approved drugs (see section 505(j) of the Act). Applications for drugs that are not duplicates of already approved products are required to comply with the rule. This includes applications submitted under 505(j)(2)(C) suitability petitions for changes in dosage form, active ingredient, or route of administration.

III. PEDIATRIC ASSESSMENTS

A. What is a Pediatric Assessment?

A pediatric assessment is the data set (results of studies) adequate to characterize the safety and effectiveness of a 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 is safe and effective (21 CFR 314.55(a) for NDAs, 601.27(a) for BLAs).

Comment

How is it to be decided whether a particular sub-population is relevant or not relevant? Is the "relevance" of a subpopulation determined using the "substantial number" assessment, as would be determined if a partial waiver were to be granted?

B. When Must My Application Contain Pediatric Assessments?

After December 2, 2000, all applications must contain a pediatric assessment to be in compliance with the rule, unless the applicant has obtained a waiver or a deferral of pediatric studies (21 CFR 314.55(a); 601.27(a)). In situations where the pediatric plan has been discussed during a meeting with the Agency, and a decision to defer or waive pediatric studies has been mutually agreed upon, the minutes of the meeting will serve to document the decision.

C. When Do I Submit My Pediatric Assessment?

A pediatric assessment must be submitted at the time an application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is submitted to the Agency, unless the requirement for the assessment has been deferred or waived (21 CFR 314.55; 601.27). If a deferral has been granted, the pediatric assessment will be due by the date specified by the Agency. If the studies submitted in response to the pediatric rule are also the studies for which you may be requesting

pediatric exclusivity, refer to the guidance for industry on Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act. As noted in that guidance, you should obtain your written request before submitting your studies.

D. What Types of Studies Should I Submit as Part of My Pediatric Assessment?

The pediatric data submitted in each case under the rule will depend on the nature of the application, what is known about the product in pediatric populations, and the underlying disease or condition being treated. In certain cases where the course of the disease and the drug's effects are expected to be similar in adults and pediatric patients, the Agency may find that pediatric effectiveness can be extrapolated from adult data, and, therefore, adequate and well-controlled trials of clinical effectiveness in the pediatric population will not be needed. However, additional information, such as dosing, pharmacokinetic, and safety data in pediatric patients may be important to support pediatric labeling. Further, if extrapolation from adult effectiveness data is inappropriate, adequate and well-controlled efficacy studies in the pediatric population will need to be conducted (see section 505 of the Act; 21 CFR 314.55; 601.27)). The rule does not require manufacturers to conduct separate studies in pediatric patients in every case. The Agency may determine that sufficient data can be obtained by including pediatric patients and adults in the original studies conducted on a product.

Comment
Please explain when "extrapolation from adult effectiveness data is inappropriate," and consequently, when "adequate and well-controlled efficacy studies in the pediatric population will need to be conducted." It appears that if consensus between a sponsor and the Agency is reached that the diseases are the same in adults and children, then there should not be any requirement to conduct efficacy studies in children. Rather, information on pharmacokinetics to establish the appropriate dosing regimen, relevant formulations and safety in children should be sufficient.

Comment
There needs to be clear and specific guidelines regarding how to relate data obtained from a pediatric population to data obtained from an adult population (and vice versa).

Pediatric studies in more than one age group may be necessary, depending on expected therapeutic benefit and use in each age group, and on whether safety and effectiveness data from one age group can be extrapolated to other age groups. FDA may conclude that it is not necessary to conduct studies in each age group if pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults or other pediatric age groups, and the extrapolation is supplemented with data to define dosing and safety for the relevant age groups. Although the complex medical state of neonates and infants make it critical to evaluate drugs that will be used for them, FDA recognizes that studies in these populations raise special ethical issues. Studies in these patients may be waived or may be deferred until additional experience with the drug or biological product has been gained. However, there will be cases in which the drug or biologic is an important advancement and it is anticipated that it will be used in these age groups. In such cases, studies will be required (21 CFR 314.55; 601.27), unless the applicant obtains a partial waiver (see section V.B.2).

You should contact the appropriate review division to discuss the type of pediatric studies needed to complete your pediatric assessment.

E. When Should I Initiate Pediatric Studies?

The Agency expects that most sponsors will initiate pediatric studies of drugs and biologics for life-threatening diseases for which adequate treatment is not available earlier in development than would be appropriate for less serious diseases. In some cases, pediatric studies of a drug or biological product for life-threatening diseases may begin as early as phase 1 or phase 2 when the initial safety data in adults

become available. The medical need for these products may justify early pediatric trials despite a paucity of safety and effectiveness data.

Comment

In a manner similar to the first sentence in section III.D, please consider modifying the first sentence above as follows (added wording underlined): "The timing of initiating pediatric studies will depend on the nature of the application, what is known about the product in pediatric populations and the underlying disease or condition being treated. Generally, however, the Agency expects that most sponsor will initiate pediatric studies for drugs and biologics . . ."

In general, products with a narrow therapeutic index that do not fulfill an urgent need should be studied in pediatric patients later in drug development.

In certain cases, the Agency recognizes that scientific and ethical considerations will determine that pediatric studies should not begin until after approval of the drug or biological product for use by adults. For example, where a product has not shown any benefit over other adequately labeled products in the class, the therapeutic need is likely to be low, and 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 after initial marketing. To encourage use of properly labeled drugs in pediatric patients, the Agency may require that products carry labeling statements recommending preferential use in pediatric patients of products that are already adequately labeled.

Comment

Please clarify the preceding sentence. Labeling restrictions in the current Regulations prevent direct comparisons between products without adequate and well-controlled studies. It may be inferred that, if a sponsor has conducted pediatric studies and the product is labeled for pediatric use, that product has somehow been labeled as a reduced risk in children without the benefit of comparative studies.

Comment

If this last clause were to remain in the final Guidance, at what time point would this requirement be enforced? If a sponsor is conducting, or has agreed to conduct pediatric studies, will it be required to add this statement until these studies have been completed and submitted for review?

Comment

Please specify if labeling statements are to be specific or general. If such language is to be specific about other medications, then please comment about the updating of such labels as newer and effective products are brought to market. What provisions are in place at FDA for monitoring and determining what is the most effective therapy and specific product for a given indication?

IV. THE PEDIATRIC PLAN

A. When Should I Develop a Pediatric Plan?

Sponsors are encouraged to submit to the Agency their development plans for assessing pediatric safety and effectiveness as early as possible. Sponsors should be prepared to discuss their plans for pediatric studies with the Agency at critical points in the drug development process for a particular product.

1.Products Intended for Life-Threatening or Severely Debilitating Illnesses

Pre-investigational new drug application meetings should include plans for studying the drug product in pediatric populations.

Comment

Please clarify whether the reference to "plans" is a general discussion or a discussion about a specific written pediatric plan.

End-of-phase 1 meetings consist of reviewing and reaching agreement on the design of phase 2 controlled clinical trials. For these products a possible goal of phase 2 testing is to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing (21 CFR 312.82). The need for, as well as the design and time of, studies of the drug in pediatric patients should also be discussed at end-of-phase 1 meetings for these products. For drugs for life-threatening diseases, the Agency will provide its best judgment at the end-of-phase 1 meetings whether pediatric studies will be required and whether the submission will be deferred until after approval. The minutes of the meetings should reflect whether pediatric studies are likely to be required, waived, or deferred. If deferral of studies is granted at the time of the meeting, a projected date for submission should be included.

Comment

Please clarify whether the Agency's best judgement will include age-group specific requirements for the pediatric rule or whether it will be a more general determination that studies will need to be conducted.

2.Other Products

End-of-phase 2 meetings should be used to determine whether it is safe to proceed to phase 3, to evaluate the phase 3 plan, protocols, the adequacy of current studies, and plans to assess pediatric safety and effectiveness. At least 1 month prior to an end-of-phase 2 meeting, the sponsor should submit background information for the meeting. The background package should include plans for pediatric studies, including a time line for protocol finalization, enrollment, completion, and data analysis. Alternatively, information to support any planned request for waiver or deferral of pediatric studies should be submitted. The review division will provide its best judgment of the pediatric assessment that will be required for the drug product, and whether its submission can be deferred. In addition, there should be a discussion of the applicant's intent to qualify for and studies needed for pediatric exclusivity.

The minutes of the meeting should indicate whether pediatric studies are likely to be required, waived, or deferred. If a deferral of studies is granted at the time of the meeting, a projected date for submission should be included.

Pre-NDA or pre-BLA meetings should include a discussion of any major unresolved problems and whether ongoing or recommended studies are adequate to assess pediatric safety and effectiveness.

B. What Ages Should I Cover in My Pediatric Plan?

In general, the age range of the pediatric population is considered to be birth to 16 years. The Pediatric Rule requires the assessment of safety in each age group in which the drug or biological product will provide a meaningful therapeutic benefit or will be used in a substantial number of pediatric patients for the indications claimed. Age groups should be defined flexibly, depending on the pharmacology of the drug or biological product, the manifestations of the disease in various age groups, and the ability to measure the response to therapy.

Comment

Please consider modifying the last sentence above as follows (added wording underlined): "Age groups should be defined flexibly, depending on the pharmacology of the drug or biological product, the ability to produce necessary

formulation(s), the manifestations of the disease in various age groups, and the ability to measure the response to therapy."

Comment
Please clarify the Agency's position with respect to the ICH E-11 guideline and premature babies (ICH E-11, 2.5.1): "the study of medicinal products in preterm newborn infants presents special challenges because of the unique pathophysiology and responses to therapy in this population. The complexity of and ethical considerations involved in studying preterm newborn infants suggest the need for careful protocol development with expert input from neonatologists and neonatal pharmacologists. Only rarely will it be possible to extrapolate efficacy from studies in adults or even in older pediatric patients to the preterm newborn infant." Perhaps this could be accomplished by reference to the ICH document.

C. Do I Have to Develop a Pediatric Formulation?

Under the Pediatric Rule you may be required to produce a pediatric formulation if one is necessary, particularly in cases where a new drug or biological product provides a meaningful therapeutic benefit over existing treatments and the required pediatric studies are to be conducted in the age groups needing the pediatric formulation. You must use appropriate formulations for each age group for which the assessment is required (21 CFR 314.55(a); 601.27(a)). It is usually prudent to begin the development of a pediatric formulation before initiation of pediatric clinical trials.

FDA can waive the requirement for pediatric studies in age groups requiring a pediatric formulation if the manufacturer provides sufficient evidence that reasonable attempts to produce a pediatric formulation have failed. The manufacturer should provide evidence that unusually difficult technological problems prevented the development of a pediatric formulation. FDA will consider the potential importance of the product for pediatric patients when determining whether those problems were severe enough to warrant a waiver of pediatric studies. In certain cases the Agency may also take to an appropriate advisory committee or other external expert body questions about whether a waiver should be granted in light of the technical difficulties in producing pediatric formulations. For additional information on waivers, see section V.

Comment
Please consider modifying the second sentence in the paragraph above as follows (added wording underlined): "The manufacturer should provide evidence that unusually difficult technological or other problems prevented the development of a pediatric formulation." Please provide clarification regarding the term "appropriate" formulation. Perhaps this can be stated here as well as referencing other guidance documents from the FDA on this matter.

V. WAIVERS AND DEFERRALS

A. What is a waiver?

A waiver removes the requirements for conducting a pediatric assessment for part or all of the pediatric population for a particular application. The Pediatric Rule allows FDA to waive the pediatric study requirement, based on established criteria, for some or all pediatric age groups. FDA can grant a full or partial waiver of the pediatric study requirements on its own initiative or at the request of a sponsor. If a sponsor requests a waiver, it is the sponsor's responsibility to provide adequate justification in writing for the waiver.

B. How Do I Get a Waiver?

Discussions with FDA should occur early in the drug development process, as described in section VA. A sponsor can request a full waiver of all pediatric studies if one or more of the following criteria for a waiver apply to the pediatric population as a whole.

Comment

As discussed previously, please choose a single defining term between "assessment" and "study" as used here and elsewhere in the discussion below.

1.Full Waiver

A full waiver may be granted if the applicant provides evidence that:

The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients; or

Necessary studies are impossible or highly impractical because the number of patients is so small or geographically dispersed; or

There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

Disease-Specific Waivers

FDA has developed a list of diseases that have extremely limited applicability to pediatric patients in that the signs and symptoms of these diseases occur for the most part in the adult population. Thus, products being developed for the treatment of these conditions in adults are likely to be granted a waiver. These include the following:

Comment

To clarify that the list below is not meant to be exhaustive, please modify the last sentence above as follows (added words underlined): "These include, but are not limited to, the following:" and/or include a statement that FDA may revise the list in the future (as indicated in the preamble to the rule) and describe some of the criteria for making such revisions.

Alzheimer's disease
Age-related macular degeneration
Prostate cancer
Breast cancer
Non-germ cell ovarian cancer
Renal cell cancer
Hairy cell leukemia
Uterine cancer
Small cell and non-small cell lung cancer
Squamous cell cancers of the oropharynx
Pancreatic cancer
Basal cell and squamous cell cancer
Endometrial cancer
Osteoarthritis
Parkinson's disease
Amyotrophic lateral sclerosis
Arteriosclerosis
Infertility
Symptoms of menopause

2. Partial Waiver

A partial waiver excusing the sponsor from carrying out studies in particular age groups can be requested if one or more of the grounds for waiver apply to one or more pediatric age groups. In addition, FDA can grant a partial waiver for those age groups for which a pediatric formulation is essential to the conduct of studies if reasonable attempts to produce a pediatric formulation have failed. However, if a waiver were granted on the grounds that it was not possible to develop a pediatric formulation, the waiver would cover only those pediatric age groups needing a pediatric formulation. A partial waiver can be granted for a specific age group
if the applicant provides evidence that:

The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group; or

Necessary studies are impossible or highly impractical because the number of patients in that age group is so small or geographically dispersed; or

There is evidence strongly suggesting that the drug product would be ineffective or unsafe in that age group; or

The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

Comment
Accompanying the publication of the Final Rule on December 2, 1998 was a comment referring to 15,000 patients in a particular age group as the basis for granting a partial waiver for that specific age group. Since age groups are to be defined flexibly according to the Final Rule, please clarify that the reference to 15,000 patients is a guideline and not a standard; reference to this number should be addressed in a flexible manner.

3.Information in a Waiver Request

FDA has developed a sample waiver request and included it in this guidance as Attachment A. To request a waiver, a sponsor should provide:

Product name and indication
Age groups included in waiver request
Reason for waiving pediatric studies
Justification for waiving pediatric studies

4. Waiver Decision

FDA will grant a waiver request if there is a reasonable basis on which to conclude that any of the grounds a waiver have been met. If a full or partial waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information must be included in the product's labeling (21 CFR 314.55(c); 601.27(c)).

Comment
Please clarify how the rationale for obtaining a waiver based on safety will be translated into product labeling.

For waivers agreed to at the end-of-phase 2 or pre-NDA/pre-BLA meetings, the meeting minutes will document the waiver of pediatric studies. Full or partial waiver documentation should be

submitted in an NDA or BLA in the Pediatric Use part of item 8, the Clinical Data Section of the application (Form FDA-356h), and also under item 20, Other. In the latter item, the sponsor should identify the location (volume and page number) of the waiver in the NDA or BLA submission. Decisions to waive the requirement for pediatric studies that are made early in the pre-approval development period (e.g., end-of-phase 1 or end-of-phase 2 meetings) reflect the Agency's best judgment at that time. If, 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 NDA or supplemental NDA approval letter.

Comment

PhRMA supports the FDA's recommendation that sponsors submit their development plans for assessing pediatric safety and effectiveness as early as possible during the product development process. However, this intention seems to conflict with the Agency's position regarding the finalization of waiver decisions. According to the proposed guidance, the Agency could reconsider its previous decision to grant a waiver at any time prior to the issuance of the Approval Letter. Consequently, a pediatric plan based upon an early Agency decision could be found unacceptable during late-stage development or even regulatory review of the application. In such a situation, it is unlikely that a revised pediatric plan could be implemented without adversely impacting submission and review times, which were based upon FDA's earlier decision. This is particularly likely if the sponsor/applicant finds itself obliged to collect new pediatric use data, develop new pediatric formulations or reconfigure product packaging. The draft guidance does not detail what, if any, alternatives would be considered by the Agency in such circumstances. The guidance should make it explicit that submission and approval of an application will not ordinarily be delayed based upon a change in Agency position. PhRMA respectfully requests that the Agency review its position on this subject and amend the guidance as suggested.

The FDA has indicated in both the rule and the draft guidance that it will grant waivers if the sponsor/applicant demonstrates that it is not possible or practical to conduct pediatric studies because of difficulty in enrolling an appropriate number of pediatric patients in clinical studies. However, this policy is not always followed in actual practice by certain Agency reviewers when they consider waiver requests, review proposed protocols for pediatric studies, or issue Written Requests. PhRMA requests that the Agency remind its reviewers that under the rule, sponsors/applicants should not be obligated to conduct pediatric studies if the pediatric patient population is below the number specified in the Rule, or if such studies are not practical.

Comment

With respect to reference to "volume and page number," please confirm that an electronic submission reference may be otherwise referred to, such as file name, or Item number in the submission.

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.

Comment

Please clarify what the implications are for not having submitted the request for the waiver at least 60 days before the application. We would recommend that the Agency

specify in the Guidance a time-frame for acting on such requests and to state the form in which it intends to convey its decision to the sponsor.

C. What is a Deferral?

A deferral permits the sponsor to submit the pediatric assessment after the submission of an NDA, BLA, or supplemental NDA or BLA. FDA has the authority, on its own initiative or at the request of the applicant, to defer the submission of some or all of the required pediatric data until after approval of the product for adult use (21 CFR 314.55(b); 601.27(b)).

Comment
If a deferral has been granted and then subsequent information comes to light during the conduct of pediatric trials that prompts a request for a waiver, will FDA consider such a request? What will be the timing of and process for such a request?

D. How Do I Get a Deferral?

1.Information in a Deferral Request

FDA has developed a sample deferral request and included it in this guidance as Attachment B. To request a deferral, a sponsor should provide:

- Product name and indication
- Age groups included in deferral request
- Reason for not including entire pediatric population
- Reason for deferring the studies
- Description of planned or ongoing studies
- Evidence that planned or ongoing studies are proceeding
- Projected date until which submission of studies would be deferred (deferral date)

Comment
Please reword the third bullet. The second bullet already requests specification of the age groups to be considered for deferral. Consider the following alternative: "Reason for requesting deferral of pediatric assessment in specified age group(s)." In addition, the 4th bullet, "Reason for deferring the studies" should be revised to read, "Reason for deferring the pediatric assessment." As pointed out in the introduction under "What is a deferral," the term refers specifically to the submission of the pediatric assessment, not the conduct of studies. Sponsors may, in fact, not be deferring studies, but, due to the length of time expected for completion, it may be reasonable not to require the results of the studies to be submitted concurrently with the adult application.

Comment
Please reword the next-to-last bullet. By definition, planned studies can't be proceeding. Consider wording such as "Evidence that studies are either planned or ongoing."

2.Deferral Decision

The decision to defer and the date when pediatric data are to be submitted will be determined on a case-by-case basis. FDA can grant a deferral if, among other reasons, the drug is ready for approval in adults before studies in pediatric patients are complete (21 CFR 314.55(b)(1); 601.27(b)(1)). Additional factors that will be considered are the need for the drug or biologic in pediatric patients, the availability of sufficient safety data to initiate pediatric trials, the nature and

extent of pediatric data needed to support pediatric labeling, the existence of substantiated difficulties in enrolling patients, and evidence of technical problems in developing pediatric formulations.

If the FDA agrees to defer the submission of pediatric studies and the application is otherwise approvable, the Agency would approve the product if the applicant agrees to submit the pediatric studies within a specific time period (i.e., deferral date) after approval. The deferral date should specify the date on which pediatric data should be submitted in an application, not the date when the studies are to be initiated. For a deferral granted during the pre-approval development period, the Agency can reevaluate the length of the deferral, taking into account any new information on other drugs in the class approved for use in the pediatric population during the time the product was in development and information reviewed in the NDA or BLA. FDA will review the development of pediatric studies and information as required in the annual reports to determine whether pediatric assessments are being conducted with due diligence.

Comment
Obtaining data for some pediatric age groups may be considerably more challenging than for other age groups (i.e. neonates and infants). Will there be a provision for extension of a deferral if data, after due diligence, can not be obtained for a particular age group by the deferral date. If due diligence is met, please specify that either a deferral will be extended or that a waiver will be granted. Any such waiver or deferral based on additional experience should be specified in writing (i.e. signed minutes to a meeting).

Comment
Please clarify how the time frame for the deferral will be established if the reason for the request for deferral is for problems developing a pediatric formulation. The guidance should return to the language in the rule which requires that a specified time frame, not a distinct date, be established. The guidance should stipulate the Agency's intention to work with the applicant in setting this time frame.

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.

Comment
Please see comments above regarding the waiver for issues around the 60-day time period.

VI. COMPLIANCE WITH THE PEDIATRIC RULE - WHAT HAPPENS IF I DON'T DO A PEDIATRIC ASSESSMENT?

If pediatric studies to evaluate safety and effectiveness are not submitted by a manufacturer in the time allowed, the drug product may be considered misbranded or an unapproved new drug or unlicensed biologic (21 CFR 201.23(d)). When a product is misbranded or an unapproved new drug, sections 302, 303, and 304 of the Act (21 U.S.C. 332, 333, 334) authorize injunction, prosecution, or seizure. The Agency can also seek an injunction or bring prosecution under the Public Health Service Act. FDA can bring an enforcement action for injunctive relief for failure to submit a required assessment of pediatric safety or effectiveness. Violation of the injunction could result in a contempt proceeding or such other penalties as a court orders (e.g., fines). However, FDA does not intend to deny or withdraw approval of a product for failure to conduct pediatric studies except in rare cases, because removal of a product from the marketplace could deprive other patients of the benefits of a useful medical product.

To determine whether pediatric assessments are needed or are being carried out with due diligence, FDA amended 21 CFR 314.81(b)(2) for NDAs and 601.27 for BLAs (annual postmarketing reports) to require that the annual reports filed by the manufacturer contain information on labeling changes that have been initiated in response to new pediatric data, analysis of clinical data that have been gathered on pediatric use, assessment of data needed to ensure appropriate labeling for the pediatric population, and information on the status of ongoing pediatric studies. The annual report also must contain an estimate of patient exposure to the drug product, with special reference to the pediatric population if possible (21 CFR 314.81(b)(2)(i); 601.27(a)). If a manufacturer fails to conduct required pediatric studies, FDA can bring issues related to progress of the pediatric studies before a panel of experts, and can use other forms of publicity to provide the public with information about the status of required pediatric studies, in addition to the enforcement actions discussed above.

Comment
Please clarify what would constitute relevant information on labeling changes that have been initiated in response to new pediatric data.

Comment
Based on the wording in the last sentence, PhRMA is concerned that publicly disclosing a sponsor's progress towards compliance with the Rule without its permission would jeopardize the confidential and proprietary nature of a sponsor's ongoing research. Given that the Agency has always protected the confidentiality of sponsors' proprietary research information, please comment on what "other forms of publicity" the Agency contemplates using "to provide the public with information about the status of required pediatric studies," and how FDA will continue to protect proprietary information from public disclosure.

VII. EXCLUSIVITY AND THE PEDIATRIC RULE

A. How will the Rule and Exclusivity Interact?

Under the Pediatric Rule, and as described in section III of this guidance, FDA has the authority to require a pediatric assessment of safety and effectiveness of certain drugs or biological products. In contrast, the pediatric exclusivity provisions of the Modernization Act provide incentives to conduct studies, but do not require them (see the guidance for industry on Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act).

1.Already Marketed Drugs

FDA believes that with respect to already marketed drugs eligible for exclusivity under the Modernization Act, the availability of pediatric exclusivity may decrease the Agency's need to exercise its authority to require studies. The Agency will allow manufacturers of marketed products ample opportunity to voluntarily obtain a Written Request and submit studies identified in the Written Request for already marketed drugs and biologics. If the Agency finds that after such an opportunity there still remains a need for studies on certain drugs or biologics, the Agency can exercise its authority under the rule to require studies. In addition, FDA can exercise its authority to require studies on marketed drugs and biologics that are not eligible for exclusivity under the Modernization Act. The Agency will restrict its authority to require studies of marketed drugs and biologics to the compelling circumstances described in 21 CFR 201.23.

Comment
Clarification of the "compelling circumstances" described in 21 CFR 201.23 should be provided.

2.New Drugs

New drugs for which the sponsor is required to conduct a pediatric assessment of safety and effectiveness under the rule may also qualify for exclusivity. To qualify for pediatric exclusivity, the sponsor must obtain a Written Request from the FDA and satisfy the other requirements of section 111 of the Modernization Act (see the guidance for industry on Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act).

B. If I Satisfy the Requirements of the Rule, Will I Qualify for Exclusivity?

To qualify for pediatric exclusivity, studies conducted to satisfy the requirements of the Pediatric Rule must also satisfy the requirements for pediatric exclusivity (see section 505A(i) of the Act). For pediatric exclusivity, FDA issues a Written Request for studies on the use of an active moiety for all indications that occur in pediatric populations. Under the Pediatric Rule, FDA requires studies only on those indications included in the application subject to the Rule. To ensure eligibility for pediatric exclusivity, sponsors should follow the procedures outlined in the guidance for industry on Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act.

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VIII.THE PEDIATRIC ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE - WHAT IS ITS ROLE?

The Pediatric Advisory Subcommittee was formed as part of the Anti-Infective Advisory Committee to provide advice and expertise on the implementation of the Pediatric Rule for all drugs and indications. Specifically, the subcommittee may:

Provide annual assessment of the implementation of the rule

Review the Agency's record of granting waivers and deferrals

Discuss ethical issues raised by clinical trials in pediatric patients

Review the need for additional therapeutic options

Recommend specific marketed drugs and biological products that should be studied in pediatric patients

Monitor the timeliness or progress of studies

Review trials design and data analysis (often in conjunction with other advisory committees or with specific disease experts from those committees as part of the pediatric subcommittee)

IX.ADDITIONAL INFORMATION

A.Where Can I Get More Information About Complying With the Pediatric Rule?

You can get general information about complying with the pediatric rule from the Pediatric Implementation Team (PdIT), 301-594-7337, e-mail pdit@cder.fda.gov. Additional pediatric information is available at http://www.fda.gov/cder/pediatrics.

You can get specific information about the types of pediatric studies that should be conducted for your drug product from the appropriate review division. You can also refer to the pediatric rule (21 CFR 314.55) and the preamble to the pediatric rule (63 FR 66632; December 2, 1998).

B. Where Can I Get More Information on Pediatric Exclusivity?

You can get general information and the latest statistical information regarding pediatric exclusivity at http://www.fda.gov/cder/pediatrics. You can also refer to the guidance for industry on Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act.

Attachment A - Request for Waiver of Pediatric Studies

IND/NDA/BLA number (as applicable) _____
Sponsor: _____
Indications(s): _____

1. What age ranges are included in your waiver request?_____

2. Reasons for waiving pediatric studies:

(a) No meaningful therapeutic benefit over existing treatments and is unlikely to be used in a substantial number of pediatric patients
(b) Studies are impossible or highly impractical because the number of patients is so small or geographically dispersed
(c) The product would be ineffective or unsafe in all pediatric age groups
(d) Attempts to develop a pediatric formulation for a specific age group have failed
(e) Disease-specific waiver indicated for the treatment of the condition in adults (please check)

____Alzheimer's disease
____Age-related macular degeneration
____Prostate Cancer
____Breast cancer
____Renal cell cancer
____Non-germ cell ovarian cancer
____Hairy cell cancer
____Pancreatic cancer, colorectal cancer
____Osteoarthritis
____Squamous cell cancers of the oropharynx
____Uterine cancer
____Basal cell and squamous cell cancer
____Endometrial cancer
____Small cell and non-small cell lung cancer
____Parkinson's disease
____Amyotrophic lateral sclerosis
____Arteriosclerosis
____Symptoms of menopause
____Infertility
____Other (please state and justify)

3. Justification for waiver (not necessary if category 2(e) is checked):

Attachment B - Request for Deferral of Pediatric Studies

IND/NDA/BLA number (as applicable) _____
Sponsor: _____
Indications(s): _____

(NOTE: If more than one indication, address the following for each indication.)

(a) Is the indication for a life-threatening condition that occurs in the pediatric population? Yes___ No___

(b) If yes, are there approved therapies labeled for use in the pediatric population? Yes___ No___

(c) If yes, list the approved therapies and labeled pediatric age groups(s) of approval.

1.What ages are included in your deferral request?_____

Reason for not including the entire pediatric population in the studies or in the deferral request:

(a) Adequate pediatric labeling___
(b) Studies Completed in Ages___
(c) Requesting a waiver___
(d) Other___
(e) Currently conducting pediatric studies that will be submitted with application

2.Reason(s) for deferring pediatric studies:

(a) Adult studies completed and ready for approval___
(b) Additional postmarketing safety data needed___
(c) Technological problems with development of a pediatric formulation (provide documentation)___
(d) Difficulty in enrolling pediatric patients (provide documentation)___
(e) Other (specify)_____

3.Have pediatric drug development plans been submitted to the Agency?
Yes___ No___

If yes, date submitted_____

If no, projected date pediatric plan is to be submitted_____

4.Suggested deferred date for submission of studies

FOOTNOTES

[1] This guidance has been prepared by the Pediatric Implementation Team in the Center for Drug Evaluation and Research (CDER) in consultation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.
[2] "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients," 63 FR 66632, December 2, 1998.

[3] On November 4, 1999, FDA received a citizen petition raising issues associated with the relationship between the Pediatric Rule and abbreviated new drug application suitability petitions. The issues raised in the petition are still under consideration by the Agency. Therefore, this guidance does not address pediatric studies associated with suitability petitions.

[4]FDA considers the term substantial number of patients to mean 50,000 pediatric patients in the U.S. with the disease or condition for which the drug or biological product is indicated.

Comment
Please provide additional clarification that the 50,000-patient estimate should be obtained from sources considered reliable for a particular population or condition.

Comment
Please include reference to the criteria for granting a waiver for a given age subgroup in children.
The following language from the preamble should be included in the footnote regarding "substantial numbers": "[A] partial waiver for a particular pediatric age group would be available...if 15,000 patients in that age group were affected by the disease or condition."

[5]The term meaningful therapeutic benefit is defined as a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population. Examples of how improvement might be demonstrated include evidence of increased effectiveness in treatment, prevention, or diagnosis of disease, elimination or substantial reduction of a treatment-limiting drug reaction; documented enhancement of compliance; or evidence of safety and effectiveness in a new sub-population; or the drug or biological product is in a class of products or for an indication or indications for which there is a need for additional therapeutic options.