

§ 314.55(c)) and § 601.27(c) to authorize FDA to grant a waiver of the pediatric study requirement on its own initiative or at the request of the applicant unless the product represented a meaningful therapeutic benefit over existing treatments, or was likely to be used in a substantial number of pediatric patients. These provisions also require FDA to grant a waiver if necessary studies were impossible or highly impractical, because, e.g., the number of pediatric patients was very small or patients were geographically dispersed, or there was evidence strongly suggesting that the product would be ineffective or unsafe in some or all pediatric populations. If a waiver were granted because there was evidence that the product would be ineffective or unsafe in pediatric patients, this information would be included in the product's labeling.

An applicant could request a full waiver of all pediatric studies if one or more of the grounds for waiver applied to the pediatric population as a whole. A partial waiver permitting the applicant to avoid studies in particular pediatric age groups could be requested if one or more of the grounds for waiver applied to one or more pediatric age groups. In addition to the other grounds for waiver, the proposal would authorize FDA to grant a partial waiver for those age groups for which a pediatric formulation was required (see "Pediatric Formulations" in section III.I of this document), if reasonable attempts to produce a pediatric formulation had failed.

The proposal would require the applicant to include in the request for a waiver an adequate justification for not providing pediatric use information for one or more pediatric populations.

FDA would grant the waiver request if the agency found that there was a reasonable basis on which to conclude that any of the grounds for a waiver had been met. If a waiver were granted on the ground that it was not possible to develop a pediatric formulation, the waiver would cover only those pediatric age groups requiring a pediatric formulation.

The agency also proposed two possible methods of determining a "substantial number of patients." The first method would focus on the number of times the drug or biologic was expected to be used in pediatric patients, annually. Under this method, FDA tentatively concluded that 100,000 or more prescriptions or uses per year in all pediatric age groups would be considered a substantial number.

The second proposed method for establishing whether there was a substantial number of pediatric patients would focus on the number of pediatric patients affected by the disease or condition for which the product is intended. Under this method, FDA tentatively concluded that 100,000 pediatric patients affected by the disease or condition for which a product was indicated would be considered a "substantial number" of pediatric patients. FDA sought comment on the waiver criteria and on these methods of calculating a substantial number of pediatric patients. FDA also

sought comment on whether cost to the manufacturer should justify a waiver.

FDA received many comments on the waiver provisions of the proposal, and has made certain changes in response to the comments, as described below.

22. As proposed, new drugs and biologics are presumptively required to be studied in pediatric patients, unless a waiver is granted. The presumption in the proposal was supported by comments from pediatricians, a pharmacy organization, disease specific organizations, and medical societies, including the AAP. Several industry comments argued, however, that new drugs and biologics should presumptively not be covered by the rule, unless they were specifically identified by FDA as needing to be studied. One of these comments stated that companies should not have to waste the effort of applying for waiver for drugs of no potential benefit to pediatric patients, which the comment estimated as a majority of those developed.

FDA continues to believe that it is appropriate to presume that drugs and biologics should be studied in pediatric patients, and that this presumption should be overcome only if there are clear grounds for concluding that such studies are unnecessary. Pediatric patients are a significant subpopulation, affected by many of the same diseases as adults, and are foreseeable users of new drugs and biologics. The agency has stated, in the context of pediatric studies and other subpopulations, that an

application for marketing approval should contain data on a reasonable sample of the patients likely to be given a drug or biological product once it is marketed (59 FR 64240 at 64243; 58 FR 39406 at 39409, July 22, 1993). FDA does not believe that the cost of drafting a waiver request will be great, particularly where the basis for the waiver is that the product has no potential use in pediatric patients. To assist sponsors in preparing such waivers, FDA has included in this document a partial list of diseases that are unlikely to occur in pediatric patients and for which waiver requests need include only reference to this document.

23. FDA received many comments on the proposed criteria for waiving pediatric studies. A few comments supported the proposed criteria. Many comments from pediatricians, medical societies, and disease-specific organizations argued that the proposed grounds for waiver were too broad. Several of these stated that the rule should apply to drugs for all conditions that affect pediatric patients unless there is a special reason not to do so. One comment argued that waivers should be available only for drugs known to be extremely toxic in pediatric patients or to have no anticipated use in pediatric patients.

Other comments from the pharmaceutical industry argued that the waiver provisions were too narrow. One comment from a generic trade association urged that pediatric studies be required only when there is a significant public health concern

with respect to the safety of a drug product in pediatric patients or to the availability of adequate pharmacological intervention for pediatric patients for the indication. Another comment stated that the criteria in the proposal "do not begin to address the complexities associated with moving forward on a clinical development plan" and argued that additional criteria should include: (1) The lack of correlative safety evidence, (2) liability concerns, and (3) prohibitive cost (but the sponsor, not FDA, should be allowed to determine the importance of cost).

FDA believes that the criteria for waiver in the final rule strike a careful balance. On the one hand, requiring studies for all new products would have potentially severe resource implications for manufacturers and the agency. On the other hand, obtaining studies only where the studies impose no burden on the sponsor would continue to expose millions of pediatric patients to unnecessary risks and ineffective treatment. Requiring pediatric studies only of those drugs or biologics that offer a meaningful therapeutic benefit or that are expected to be used in a substantial number of pediatric patients focuses limited resources on those products that are most critically needed for the care of pediatric patients.

24. Several comments addressed the definition of "meaningful therapeutic benefit." Some comments from the pharmaceutical industry stated that "meaningful therapeutic

benefit" should be defined as it is used in 21 CFR 314.500.

(That regulation applies to drugs "that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).") One of these comments suggested that analogous cases in the pediatric context would be: (1) Where the drug treats a pediatric disease for which no other treatments exist; (2) where the drug treats patients who are unresponsive to or intolerant of other drugs; or (3) where the drug produces a superior response over other treatments. One industry comment argued that the agency should consult with the sponsor, and the pediatric investigators involved to assess whether the drug will provide a "meaningful therapeutic benefit." According to the comment, the assessment should include the likely use of the product in a specific pediatric population, the likely benefit without increased risk to patients versus existing treatments, a "definitive need" for a new therapy in very serious or life-threatening illnesses, and the cost and feasibility of developing the necessary formulations and of conducting studies. Another comment from a disease-specific organization argued that "meaningful therapeutic benefit" should be a relative term, depending on the severity of the illness, the potential risk posed by the drug, and the availability of alternative treatments. One comment from a medical society devoted to the

product has the potential to offer a meaningful therapeutic benefit. FDA routinely estimates the therapeutic benefit of new drugs and biologics at the time applications are first submitted, in order to determine whether to assign "Priority" (expedited) status to the review of the application. In assigning Priority status to new drug applications, CDER determines whether the product, if approved, "would be a significant improvement compared to" marketed (or approved, if such is required) products, including nondrug products or therapies. "Improvement can be demonstrated by, for example: (1) Evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness in a new subpopulation" (Ref. 16). These criteria are similar to many of the criteria suggested in the comments. FDA notes that demonstration of an advantage over existing products may come from evidence other than head-to-head comparisons of the new product and existing products. For example, in some cases a new product could be shown to lack an adverse effect associated with an existing product, or to have an effect on a different outcome or on a different stage of disease than an existing product, without a direct comparison of the two products.

FDA has concluded that in determining whether a product offers a meaningful therapeutic benefit, it will use the Priority

definition, with some modifications. First, in determining whether a product is expected to be an improvement over other products, the comparison will be made only to other products that are already adequately labeled for use in the relevant pediatric population. Second, it is often therapeutically necessary to have two or more therapeutic options available, because some patients will be unresponsive to a given therapy. Because the Priority definition would not cover more than the first or second product for a given indication or in a given class (unless the product offered an advantage over others for the indication or in the class), a drug or biologic will also be considered to provide a meaningful therapeutic benefit if it is in a class of drugs and for an indication for which there is a need for additional therapeutic options. The specific number of products needed will depend upon such factors as the severity of the disease being treated, and the adverse reaction profile of existing therapies. FDA has added this definition of meaningful therapeutic benefit to §§ 314.55(c)(5) and 601.27(c)(5). This rule's definition of meaningful therapeutic benefit is intended to apply only in the pediatric study context and is not intended to alter the definition of a Priority drug.

25. Several comments addressed the definition of "a substantial number of pediatric patients." A few comments argued that it would be difficult to estimate product use until after marketing. Several comments argued that FDA should not base

waivers on the number of patients or prescriptions. Many other comments claimed that the proposed numerical cut-offs are arbitrary. These comments maintained that waivers should be decided on a case-by-case basis. Several comments urged that FDA consult with an expert panel in deciding whether pediatric use was substantial.

Comments from the pediatric community contended that the numerical cut-offs in the proposal were too high, and would preclude studies of many serious diseases affecting fewer than 100,000 pediatric patients. One comment, for example, voiced concern that pediatric patients with less common seizure types may not benefit from the regulations because the use is not sufficiently widespread. Another comment argued that numerical cut-offs should not apply to drugs for serious and life-threatening diseases, unless the number of pediatric patients was so low as to make clinical study impossible. Another comment suggested that studies be required not only for uses greater than 100,000 prescriptions, but for "drugs used chronically for a defined, though smaller group of pediatric patients, usually for organ-specific diseases, such as kidney failure or hypertension."

Comments from the pharmaceutical industry argued that the numerical cut-offs proposed by FDA were too low. Some of these comments argued that 100,000 prescriptions per year translates to fewer than 100,000 patients, and that the resulting population could be so small that it would be difficult to study. Several

of these comments urged that cut-off for substantial use be 200,000 patients with the disease, the threshold established by the Orphan Drug Act for identifying rare diseases.

FDA has decided to revise its proposed method of defining a substantial number of patients, in light of the comments. FDA agrees that Congress could be said to have considered more than 200,000 a substantial number of persons with a disease for purposes of developing a new indication. Recognizing that this rule does not require manufacturers to establish de novo the safety and effectiveness of a new indication, but to establish usefulness in a subpopulation, often without the need for new controlled effectiveness trials, FDA has taken the percentage of the population under 16 years of age (approximately 23 percent, according to 1998 U.S. Census data) (Ref. 3) and multiplied it by 200,000 to determine the number of pediatric patients with the disease or condition that will be considered a substantial number. Thus, more than 46,000 pediatric patients affected by a disease or condition will be considered a substantial number. To determine what would constitute a substantial number of patients in a pediatric subgroup, FDA will use the percentage of the population in that subgroup and multiply it by 200,000. (For example, using 1998 U.S. Census data, 2.8 percent of the population is under 2 years of age, 14.6 percent of the population is 2 to 12 years of age, and 5.7 percent of the population is 12 to 16 years of age.) FDA will use recent

available U.S. Census data in determining what constitutes a substantial number of pediatric patients. This definition of "a substantial number of pediatric patients" has not been codified, however, and FDA may modify it, after consulting with the pediatric panel discussed in section III.M of this document ("Pediatric Committee"). Any modification will be issued as a guidance document.

In response to those comments that voiced concern that this definition would exclude a number of serious diseases, FDA emphasizes that the definition of "meaningful therapeutic benefit" assures that drugs and biologics will be covered by the rule if they are medically needed as therapeutic options because there are insufficient products adequately labeled for pediatric patients for that indication or in that drug class. Until there are enough adequately labeled products available, many new drugs and biologics for serious and life-threatening diseases will be considered to offer a meaningful therapeutic benefit and thus will be required to be studied, even if the products are not also used in a substantial number of pediatric patients. This will be particularly true during the first few years after implementation of this rule when few drugs and biologics will yet be adequately labeled for use in pediatric patients, and a larger proportion of new entrants into the marketplace will be considered to be medically necessary therapeutic options.

In response to the comments arguing that FDA's proposed numerical cut-off is too low and will result in too many pediatric studies, FDA expects to defer until after approval many of the studies of products that will be used in a substantial number of pediatric patients but that do not offer a meaningful therapeutic benefit. As described previously in response to comments on the deferral provisions, studies of new drugs and biologics that do not offer a meaningful therapeutic benefit and are members of a class that is already adequately labeled for pediatric patients are likely to be deferred until well after approval of the product for adults.

FDA notes that the definition of a substantial number of pediatric patients chosen by the agency is similar but not identical to one of the criteria employed by the agency in determining which marketed drugs on the list published by the agency under section 111(b) of FDAMA, 21 U.S.C. 355A(b) (the list), are considered a priority for conducting pediatric studies under FDAMA. Drugs on the list were designated as a priority if, among other things, they were widely used in the pediatric population, as measured by more than 50,000 prescription mentions per year, based on IMS, Ltd. data. As noted in the comments, prescription mentions per year may exceed the number of patients with the disease because many patients will receive more than one prescription per year. Thus, this criterion used in designating priority drugs on the list will probably cover more drugs than

the definition of substantial number of pediatric patients used in the rule. FDA believes that it is appropriate to be more inclusive in its designations of priority drugs under FDAMA, which imposes no requirement on the manufacturer to conduct a study, than for refusing to grant a waiver under this rule, which does result in a requirement imposed on the manufacturer.

26. A few comments addressed the provisions that would permit waiver if pediatric trials were impossible or impractical. One comment argued that the provision authorizing waiver if the proposed population was "too small or geographically dispersed" was too broad. This comment urged that tests should be waived only if "significant efforts to recruit patients fail." The comment also argued that the unsupported suggestion that tests are "impractical" should not be accepted, and that evidence of due diligence should be required. Another comment argued that waivers should never be granted because the population is too small or dispersed. According to this comment, many safety and pharmacokinetic studies are already performed in dispersed populations, and the comment maintained that no experimental drug should be administered to a child with a serious or life-threatening disease without requiring that some safety data and pharmacokinetics data be obtained. Another comment observed that although only 600 renal transplants are performed each year in pediatric patients, pediatric academic centers have been creative in forming collaborative efforts to study these small groups.

One comment from an organization devoted to children with HIV stated that the "impossible or highly impractical" standard must be narrowly interpreted, and that a manufacturer should show that all reasonable efforts to recruit patients have failed. According to this comment HIV/AIDS drugs should be a benchmark of when a waiver should not be granted: Any group as big or bigger than the pediatric AIDS population should be considered big enough to study.

Another comment argued that because of special difficulties encountered in recruiting pediatric patients into studies of blood products, such as parental fear of disease transmission, the inability to obtain a sufficient number of test subjects should be added to the criteria for waiver or to the definition of "highly impractical."

FDA agrees with those comments urging that this ground for waiver be interpreted narrowly and that unsupported assertions be rejected as a basis for waiver. Although the number of patients necessary to permit a study must be decided on a case-by-case basis, FDA agrees that there are methods available to conduct adequate studies in very small populations. Moreover, where only safety or pharmacokinetic studies are required to support pediatric labeling, the size of the population or geographic dispersion would only rarely be a sufficient basis to consider trials impossible or highly impractical. Because of the speed and efficiency of modern communications tools, geographic

dispersion will justify a waiver only in extraordinary circumstances and will generally have to be coupled with very small population size. FDA is not persuaded that inability to recruit patients because of parental fears associated with administration of the drug is an adequate basis to conclude that studies are impractical where there is also evidence that similar products are regularly prescribed to pediatric patients outside of clinical trials.

27. Several comments responded to the request for comment on whether cost should justify a waiver. Comments from the pediatric community argued that cost to the manufacturer should never or rarely justify a waiver. Two of these comments stated that the cost of failure to study is always higher than the cost of research. Another comment stated that cost may be a factor, but FDA must be careful not to allow studies to be waived automatically because they "cost too much." Two comments from a pharmaceutical company and a pharmaceutical trade association argued that FDA should not have responsibility for assessing the costs of a study.

In light of the comments, FDA has concluded that it does not have an appropriate basis to evaluate and weigh cost in granting or declining to grant a waiver. Therefore, cost will not ordinarily be a factor in determining whether a waiver should be granted.

28. One comment claimed that the proposal lacks adequate regulatory procedures for timely processing of waiver requests and will result in a new layer of bureaucracy.

As described previously in response to comments on the deferral provisions, preliminary decisions on whether to grant waivers will be provided to the sponsor at the end of phase 1 for drugs and biologics for life-threatening diseases and at the end of phase 2 for other products. FDA does not agree that processing of waiver requests will result in a new layer of bureaucracy. The decisions will be made by the division responsible for reviewing the NDA or BLA. FDA intends to ensure that the process is timely and fair. To reduce the burden on manufacturers in applying for waivers and deferrals, FDA intends to issue a guidance document providing a format for a request for waiver or deferral.

29. One comment asked that the rule clarify that the onus is on the manufacturer to justify waivers. Another comment argued that the proposed standard for granting a waiver ("reasonable basis") places an inadequate burden of proof on manufacturers. According to this comment, manufacturers should be required to present "persuasive proof," and FDA should have to find that the grounds for waiver have "in fact" been met.

FDA agrees that the burden is on the manufacturer to justify waivers, but believes that the rule already adequately imposes that burden. The rule requires both a certification from the

manufacturer that the grounds for waiver have been met and an adequate justification for the waiver request. FDA believes that it would be inappropriate to require "proof" that the grounds for waiver have "in fact" been met because each ground requires a degree of speculation about the safety and effectiveness of, or the ability to test, a product, in a population in which it has not yet been tested.

30. Many comments from pediatricians, disease-specific organizations, a pharmacists' organization, a medical society, several companies, a pharmaceutical trade association, and the AAP urged that the decision to require pediatric studies be reviewed by a panel of outside pediatric experts. Some of the comments recommended that the panel include industry representatives. The comments were divided on whether the panel would review only waiver requests or would be responsible for identifying, in the first instance, those drugs that need study. Some of these comments believed that the rule should include no criteria for granting waivers and that the decision should be made on a case-by-case basis in consultation with the expert panel.

As described later in this document, FDA intends to convene a panel of pediatric experts, which will include one or more industry representatives, to assist the agency in implementing this rule. FDA will bring before that panel some issues related to waivers. FDA does not believe, however, that it is reasonable

to bring every product undergoing clinical studies before the panel for a decision on whether pediatric studies are required. Because many dozens of drugs and biologics reach the end of phase 1 and phase 2 each year, and the panel could not realistically meet more than once every few months, insisting that each product be brought before the panel would introduce substantial delay into the development and review of drugs and biologics. Moreover, many waiver decisions will be straightforward and noncontroversial.

FDA does, however, agree that it would be beneficial to have the advice of pediatric experts on its administration of the waiver provisions of the rule. FDA will therefore ask the panel, at least on an annual basis for the first several years, to review the agency's waiver decisions and provide advice on whether it believes that the criteria used in making those decisions were appropriate. FDA will use the advice it receives to modify future waiver decisions. FDA also expects to consult with individual members of the panel on difficult waiver decisions in their fields of expertise.

31. One comment suggested that FDA identify diseases that are not likely to occur in pediatric patients, such as prostate cancer, and classes of drugs not likely to be used in pediatric patients, and grant blanket waivers. Another comment listed the following product classes as having no applicability to pediatric patients: Alcohol abuse agents, Alzheimer's agents, Amyotrophic

lateral sclerosis agents, antifibrosis therapy, antiparkinsonian agents, fertility agents, gout preparations, multiple sclerosis drugs, oral hypoglycemics, osteoporosis agents, oxytocics, tremor preparations, uterine relaxants, and vasodilators (including cerebral vasodilators).

FDA agrees that there are some disease and drug classes that have extremely limited applicability to pediatric patients and that waiver is appropriate for these. The decision to grant a waiver in such cases would be based on a conclusion that a disease does not have sufficient significance in the pediatric population (either because of frequency or severity) to constitute a meaningful therapeutic benefit for pediatric patients or to be used in a substantial number of pediatric patients. FDA emphasizes that this decision would not be intended to prevent or impede studies of these diseases or drug classes in the pediatric population, should a sponsor wish to conduct them.

The agency has identified the diseases following for which waivers will be likely to be granted. Some of the diseases listed in the comment are included in FDA's list. Others, such as osteoporosis, gout, multiple sclerosis, and tremors can develop in children, and are not included in FDA's list. Waiver decisions on products for the listed diseases are expected to be straightforward and noncontroversial. FDA may add to or revise this list in the future by issuing guidance documents. An

applicant who wishes to obtain a waiver because the product is indicated for a disease on the list may refer in the waiver request to this FEDERAL REGISTER notice, or to any guidance document modifying this notice. FDA's list follows:

1. Alzheimer's disease.
2. Age-related macular degeneration.
3. Prostate cancer.
4. Breast cancer.
5. Non-germ cell ovarian cancer.
6. Renal cell cancer.
7. Hairy cell Leukemia.
8. Uterine cancer.
9. Lung cancer.
10. Squamous cell cancers of the oropharynx.
11. Pancreatic cancer.
12. Colorectal cancer.
13. Basal cell and squamous cell cancer.
14. Endometrial cancer.
15. Osteoarthritis.
16. Parkinson's disease.
17. Amyotrophic lateral sclerosis.
18. Arteriosclerosis.
19. Infertility.
20. Symptoms of the menopause.

F. Pediatric Use Section of Application

FDA proposed to add § 314.50(d)(7), under which applicants would be required to include in their applications a section summarizing and analyzing the data supporting pediatric use information for the indications being sought. FDA received no comments on this provision. The new pediatric use section will be required to contain only brief summaries of the studies together with a reference to the full description of each provided elsewhere in the application.

G. Planning and Tracking Pediatric Studies

1. Sections 312.23(a)(3)(v), 312.47(b)(1)(i), (b)(1)(iv) and (b)(2), and 312.82--Early Discussion of Plans for Pediatric Studies

In the proposal, FDA identified several critical points in the drug development process, before submission of an NDA or BLA, during which the sponsor and FDA should focus on the sponsor's plans to assess pediatric safety and effectiveness. These time points include: Any pre-IND meeting or "end-of-phase 1" meeting for a drug designated under subpart E of part 312 (21 CFR part 312), the IND submission, the IND annual report, any "end-of-phase 2" meeting, the presentation of the IND to an FDA drug advisory committee, and any pre-NDA or pre-BLA meeting. Of these, the pre-IND meeting, the "end-of-phase 1" meeting, the IND submission, the IND annual report, the "end-of-phase 2" meeting,

and the pre-NDA/pre-BLA meeting are codified in part 312, FDA's regulations governing IND's.

In a separate rulemaking, FDA has already amended the IND annual report requirement to include discussion of pediatric patients entered in trials (63 FR 6854, February 11, 1998). In the proposal, FDA proposed to amend §§ 312.23(a)(3)(v), 312.47(b)(1)(i) and (b)(2), and 312.82(a) and (b) to specify that these meetings and reports should include discussion of the assessment of pediatric safety and effectiveness. To assist manufacturers in planning for studies that may be required under this proposal, FDA also proposed to inform manufacturers, at the "end-of-phase 2" meeting, of the agency's best judgment, at that time, of whether pediatric studies would be required for the product and when any such studies should be submitted. The proposal also stated that, in addition to the discussions of pediatric testing codified in the proposal, FDA would assist manufacturers by providing early consultations on chemistry and formulation issues raised by requirements under this rule.

Because, as described previously, studies of drugs and biologics for life-threatening diseases may begin as early as the end of phase 1, FDA will, at the end-of-phase 1 meeting, provide the sponsor of such a product the agency's best judgment, at that time, whether pediatric studies will be waived or deferred. Section 312.82(b) has been revised to include this requirement. Because studies of other products may begin as early as the end

of phase 2, FDA will, at the end-of-phase 2 meeting, provide the agency's best judgment, at that time, whether waiver or deferral is appropriate. Although a formal request for deferral or waiver is not required until submission of the NDA or BLA, FDA has revised § 312.47(b)(1)(iv) to state that a manufacturer who plans to seek a waiver or deferral should provide information related to the waiver or deferral in the advance submission required before the end-of-phase 1 or end-of-phase 2 meeting, as appropriate.

As described earlier, a pediatric study required under this rule may be eligible for exclusivity under FDAMA, if such study "meets the completeness, timeliness, and other requirements of [section 505A]." (See 21 U.S.C. 355A(i).) Among other requirements, a pediatric study must, to be eligible for exclusivity, be responsive to a written request for the study from FDA. To obtain a written request, a manufacturer may submit a proposed written request to FDA that contains the information described in a guidance document issued by FDA entitled, "Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act." A manufacturer who has been told in the end-of-phase 1 or end-of-phase 2 meeting that it is FDA's best judgment at that time that it does not intend to waive the study requirement may submit a proposed written request at any time thereafter. FDA will issue a written request for a study required under this rule promptly after an adequate proposed written request is submitted.

FDA also sought comment on the types of evidence that FDA should examine to ensure that deferred pediatric studies are carried out in a timely fashion. In response to comments, FDA has revised §§ 312.47(b)(1)(iv) and (b)(2) to require submission of information about planned and ongoing pediatric studies.

32. One comment supported the proposed provisions and the need for early consultation with sponsors, stating that discussions should take place as early as possible in drug development. The comment urged that proposed § 312.47(b)(1) be revised to acknowledge the possibility that studies could already be underway.

FDA agrees with this comment and has revised § 312.47(b)(1) as suggested in the comment.

33. Several comments provided suggestions on how to assure that deferred studies are carried out expeditiously. One comment urged that the criteria to ensure deferred studies are carried out in a timely fashion be modeled on the AIDS Clinical Trials Group (ACTG) system of National Institute of Allergy and Infectious Diseases (NIAID). Another comment recommended that evidence demonstrating that the required studies were underway be submitted to FDA within 6 months of approval. This comment suggested that the evidence should include: (1) A finalized protocol, (2) evidence of sufficient entry of patients to address the objective of the protocol, and (3) a time line for data analysis and submission to FDA. Another comment argued that

the burden should be on manufacturers to provide evidence that studies are being conducted with due diligence through submission of protocols, progress reports and certifications by researchers. To hold manufacturers accountable, this comment suggested that nonproprietary information related to deferrals be made available to the public, including deferral requests, FDA action, postmarketing status reports, and the time line for deferred studies. One comment argued that FDA's current procedures are adequate to track the timeliness of pediatric studies. A pharmaceutical trade association argued that FDA should institute an adequate tracking system and meet periodically with the sponsor to discuss the progress of the studies, but that no new rules are needed.

FDA agrees that an adequate system for ensuring that studies, both deferred and nondeferred, are carried out in a timely manner requires the submission of plans and progress reports from the sponsor at defined intervals. As described previously, FDA will provide sponsors with a preliminary decision on whether pediatric studies will be required and their timing at the end-of-phase 1 meeting, for drugs and biologics for life-threatening diseases, and at the end-of-phase 2 meeting, for other products. FDA has revised § 312.47(b)(1)(iv) to state that sponsors should submit, in the advance submission for the end-of-Phase 2 meeting, a proposed time line for protocol finalization, enrollment, completion, data analysis, and submission of

pediatric studies, or, in the alternative, information to support a planned request for waiver or deferral. For drugs and biologics for life-threatening diseases, the submission should be made in advance of the end-of-Phase 1 meeting. FDA has also revised § 312.47(b)(2)(iii) to state that sponsors should submit, in the submission in advance of the pre-NDA or pre-BLA meeting, information on the status of needed and ongoing pediatric studies. The proposed language of § 312.47 has been slightly modified to seek information on "needed" and ongoing studies rather than "planned" and ongoing studies. This change has been made because not every sponsor elects to have an end-of-phase 1 or end-of-phase 2 meeting. In those cases, the need for a pediatric study may be discussed for the first time at the pre-NDA or pre-BLA meeting. FDA has also revised the title of § 312.47(b)(2) from "'Pre-NDA' meetings" to "'Pre-NDA' and 'pre-BLA' meetings. This is merely a clarification, because part 312 is expressly applicable to products subject to the licensing provisions of the Public Health Service Act, as well to products subject to section 505 of the act and 21 CFR 312.2(a).

2. Sections 314.81(b)(2) and 601.37--Postmarketing Reports

To permit FDA to monitor the conduct of postapproval studies to ensure that they are carried out with due diligence, FDA proposed to amend § 314.81(b)(2) of the postmarketing report requirements to require applicants to include in their annual reports: (1) A summary briefly stating whether labeling

supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated; (2) where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population; (3) an analysis of available safety and efficacy data in the pediatric population and changes proposed in the label based on this information; (4) an assessment of data needed to ensure appropriate labeling for the pediatric population; and (5) whether the sponsor has been required to conduct postmarket pediatric studies and, if so, a report on the status of those studies. (Additional postmarketing reporting requirements are described under "Remedies" in section III.L of this document.) Although the proposal was intended to cover both drugs and biological products, the proposal inadvertently omitted a postmarketing reports requirement specifically applicable to biological products. In the final rule, FDA has corrected this oversight and included an identical postmarketing reports requirement in § 601.37.

FDA notes that FDAMA includes a provision requiring reports of postmarketing studies in a form prescribed by the Secretary of Health and Human Services (the Secretary) in regulations. (Section 506 of the act (21 U.S.C. 356B).) At such time as regulations implementing this provision are issued, FDA may

modify or withdraw §§ 314.81(b)(2) and 601.37 for consistency with the implementing regulations.

34. Three comments from the pharmaceutical industry agreed that it was appropriate to require postmarketing reports on the progress of postapproval pediatric studies. One comment argued, however, that collection of this information along with an adequate system to track pediatric studies could preclude the need to finalize the rule. Another comment argued that the required analyses of pediatric data "may lead to exposure of a larger number of children to an unapproved product." This comment also contended that estimates of patient exposure are difficult to obtain and unreliable.

FDA disagrees that postmarket reports and a tracking system are an adequate means of assuring that drugs and biologics are appropriately labeled for pediatric use. As shown above, even postmarket commitments to conduct pediatric studies have infrequently resulted in pediatric labeling submissions. FDA also disagrees that the analyses required under § 314.81(b)(2) require exposure of any new patients. The analyses referred to in the provision are of already collected data. Finally, the rule requires estimates of patient exposure "where possible." If there are no data on which to make such estimates, the estimates are not required. FDA notes, however, that there are commercial data bases designed to estimate use of marketed drugs.

35. One comment argued that FDA should require postmarket surveillance of approved drugs that do not have pediatric labeling, to generate helpful comparative information and provide additional information useful for analysis of adverse event profiles.

The provisions of the final rule require manufacturers of approved drugs without pediatric labeling to conduct postmarket surveillance on their products and provide an analysis of available safety and efficacy data in the pediatric population.

H. Studies in Different Pediatric Age Groups

Because the pharmacokinetics and pharmacodynamics of a drug or biological product may be different in different pediatric age groups or stages of development, FDA proposed to require an assessment of safety and effectiveness in each pediatric age group for which a waiver was not granted. The following age categories for the pediatric population were distinguished in the proposal: (1) Neonates (birth to 1 month); (2) infants (1 month to 2 years); (3) children (2 years to 12 years), and (4) adolescents (12 years to 16 years). The proposal stated that the need for studies in more than one age group would depend on whether the drug or biological product was likely to be used or offered meaningful therapeutic benefit in each age group (see "Waivers" section III.E of this document), the metabolism and elimination of the drug, and whether safety and effectiveness in one age group could be extrapolated to other age groups. The

proposal further stated that it would not ordinarily be necessary to establish effectiveness in each age group, but there would generally need to be pharmacokinetic data in each group to allow dosing adjustments. The proposal recognized that studies in neonates and young infants present special problems, and sought comment on whether it is appropriate to require the assessment of safety and effectiveness in this age group.

36. Several comments addressed the requirement that all relevant age groups be studied. Some comments opposed studies in more than one age group. One comment contended that requiring safety data in each pediatric group may place an unnecessary burden on the sponsor, and that FDA should require safety data only in one group, presumably that with the highest potential use. Another comment claimed that requiring studies in all four age groups would almost never be justified. In most cases, according to this comment, it should be possible to study a single subgroup and extrapolate. Other comments argued that studies in more than one age group could be necessary depending on the pharmacokinetics of the drug, the disease, and expected use of the drug. Most of these comments stated that the type and extent of studies in different age groups must be decided on a case-by-case basis. Several comments contended that drugs should be studied in each age group in which they are expected to be used. One comment stated that studies in toddlers are especially needed. A comment from an organization devoted to pediatric AIDS

argued that all age groups should be studied unless the manufacturer provides compelling evidence that it would be impossible or virtually impossible to study that group.

FDA continues to believe that studies in more than one age group may be necessary, depending on expected therapeutic benefit and use in each age group, and on whether data from one age group can be extrapolated to other age groups.

37. Many comments argued that the pediatric subgroups identified in the proposal were arbitrary and that FDA should be flexible in determining which age ranges or stages of development need to be studied. A comment from a pharmaceutical trade association contended that rigid age divisions for required studies were inappropriate, and that the method by which the compound is cleared from the body must be considered in light of what is known about physical development. The AAP stated that the groups identified in the proposal provide acceptable guidelines, but should not be adhered to rigidly. One comment argued that the definition of pediatric patients should include all subgroups of growth and development from 0 to 21 years.

FDA agrees that the age ranges identified in the proposal may be inappropriate in some instances and that it will be

reasonable in some cases to define subgroups for study using other methods, such as stage of development. FDA has deleted the references in the rule to specific age ranges.

38. Several comments addressed inclusion of neonates in studies. One comment maintained that because neonates are a special challenge, they should not ordinarily be included in studies under this rule. Another comment described the difficulties in conducting studies in infants and neonates and recommended that before studies in this group there be an assessment of "the expected extent of use and potential benefit in this patient population" and an evaluation of safety data in adults and older pediatric patients. One comment contended that there are not many instances in which the benefit will outweigh the risk of exposing neonates and young infants to drugs. This and another comment also argued that it is not always possible to extrapolate from data in older pediatric patients. A pharmaceutical trade association maintained that validated end-points and ability to assess these by age should determine which age groups to include, and that it may not be possible to study certain end-points in very young pediatric patients. One comment argued that early research on neonates raises special ethical issues. Citing the 1977 FDA guideline, this comment asserted that testing in neonates should occur only when substantial evidence of benefit or superiority over accepted agents has been demonstrated in older pediatric patients and adults.

Other comments argued that neonates should not be excluded from studies. According to one comment, study designs will be appropriate and necessary ethical issues will be addressed if neonatologists are included in the review of studies. Another comment stated that neonates represent the greatest disparity in drug disposition compared to adults, and that, on a scientific and ethical basis, they must therefore be included in drug studies. The AAP stated that premature infants, newborns, and infants are more difficult to study, but that the difficulties do not outweigh the importance of studying them. According to this comment, inadequate study of neonates has led to frequent and severe toxicity. This comment agreed that it is inappropriate to extrapolate from older pediatric patients to the youngest age group.

FDA agrees that the benefits and risks to premature infants, neonates, and infants must be carefully weighed before these pediatric patients are included in pediatric studies. Although the agency believes that studies in these groups may be frequently waived or deferred until adequate safety data have been collected, there will be cases in which the drug or biologic is important and expected to be used in these groups. In such cases, it will be appropriate to require studies in these groups. To exclude them from study would be to subject the most vulnerable patients to the risks of the drugs in clinical use without adequate information about safety or dosing. FDA agrees

that studies in neonates and young infants raise special ethical issues, but once these issues are addressed in each case, the studies should proceed.

I. Pediatric Formulations

As described in the proposal, testing of a product in pediatric patients could require the development of a pediatric formulation. Many young children are unable to swallow pills and may require a liquid, chewable or injectable form of the product. A standardized pediatric formulation also ensures bioavailability and consistency of dosing, compared to alternatives such as mixing ground-up tablets with food, and permits meaningful testing of safety and effectiveness. FDA proposed in §§ 201.23, 314.50(g)(1) (now 314.55(a)) and 601.27(a) to require a manufacturer to produce a pediatric formulation, if one were necessary, only in those cases where a new drug or new biological product provided a meaningful therapeutic benefit over existing treatments, and where the study requirement had not been waived in the age group requiring the pediatric formulation. The proposal recognized that the difficulty and cost of producing a pediatric formulation may vary greatly depending upon such factors as solubility of the compound and taste. FDA proposed to waive the requirement for pediatric studies (see "Waivers" in section III.E of this document) in age groups requiring a pediatric formulation, if the manufacturer provided evidence that

reasonable attempts to produce a pediatric formulation had failed.

FDA sought comment on whether it is appropriate to require a manufacturer to develop a pediatric formulation, on whether the cost of developing a pediatric formulation should ever justify a waiver of the pediatric study requirement, and on how to define "reasonable attempts" to develop a pediatric formulation.

39. Many comments from the pediatric community argued that it is appropriate to require manufacturers to produce pediatric formulations. Several comments from pediatricians and parents described the difficulties and uncertainties in attempting to administer adult formulations to pediatric patients, and argued that pediatric formulations are essential to assure bioavailability, accurate dosing, and patient compliance, and to avoid wasting medications. The AAP argued that FDA should require development of an appropriate formulation for each age group for which the drug will be used, taking into account ease of administration and ability to dose accurately.

Comments from the pharmaceutical industry described technical problems in producing pediatric formulations, including stability, taste and palatability, and claimed that FDA underestimated these difficulties. Some of these comments maintained that requiring development of pediatric formulations during the investigational phase will necessitate diversion of resources, increase the cost of the adult formulation, and create

a disincentive to produce drugs with pediatric uses. One comment argued that it would be wasteful to require development of a pediatric formulation before some evidence of effectiveness has been collected and dose selection has been achieved, because before that time the drug could be abandoned because of lack of safety or effectiveness. A pharmaceutical trade association opposed a pediatric formulation requirement, arguing that the government has no right to tell manufacturers what products to market. This comment stated that only if FDA successfully demonstrated that "all attempts to develop a voluntary solution have failed" might the industry consider other options. One comment stated that a single drug could require more than one pediatric formulation for different pediatric age group, such as a chewable tablet, a nonalcohol containing liquid, and sprinkles. Counting failed attempts, this comment claimed that producing a pediatric formulations may cost millions of dollars.

FDA believes that for drugs and biologics that offer a meaningful therapeutic benefit to pediatric patients, it is essential to provide pediatric formulations that ensure bioavailability and accurate dosing. FDA disagrees that it is inappropriate for the government to require manufacturers to produce pediatric formulations. As many comments demonstrated, adult formulations of these drugs are frequently used in pediatric patients because there is no other choice. Drug manufacturers profit from these uses, but do not take

responsibility for them. Where a product is commonly being used in a subpopulation for an indication recommended by the manufacturer, it is appropriate to require the manufacturer to take steps to ensure that the use is safe and effective.

FDA agrees that producing a pediatric formulation can be difficult or, rarely, impossible and has attempted to account for this problem by permitting waiver of the pediatric study requirement where reasonable attempts to produce a pediatric formulation have failed. FDA notes that the pharmaceutical industry did not respond to FDA's request to help define what should constitute such "reasonable attempts."

To permit pediatric studies that may begin, for products for life-threatening diseases, at the end of phase 1, or, for other products, at the end of phase 2, it may be necessary to begin development of a pediatric formulation before initiation of clinical trials. FDA does not agree that it is wasteful to begin development of a pediatric formulation at this stage. This rule is premised on the view that for drugs and biologics that will have important use in pediatric patients, it is the responsibility of the manufacturer to ensure that use is safe and effective. Although some such products may ultimately prove to be unsafe or ineffective, work on pediatric formulations of such products is not necessarily more wasteful than work on adult formulations. FDA does not agree that manufacturers will be required to develop several pediatric formulations for different

age groups. Even for a drug that was to be used in all pediatric age groups, a liquid formulation, e.g., might be usable in all age groups.

FDA has no basis to conclude that producing pediatric formulations will increase the cost of adult formulations or create disincentives for producing drugs and biologics with pediatric uses. No evidence was submitted to support either of these assertions.

40. Several comments discussed how to define "reasonable attempts" to produce a pediatric formulation. The AAP argued that difficulty in producing a pediatric formulation should be a basis for waiver only if the sponsor provides data showing that formulation experts encountered insurmountable problems of solubility, stability, compatibility, or palatability using accepted methods, and that cost be given only limited consideration. The AAP urged that such an assertion be corroborated by a panel of pediatric experts and FDA as well as formulation experts. Another comment agreed that formulations appropriate for younger age groups should be developed unless the manufacturer shows it would be virtually impossible. This comment argued that if a manufacturer wants to show that the cost is prohibitive, it should provide information allowing the financial and other costs of development to be seen in terms of the entire drug development process. Another comment argued that waivers should not be based on whether reasonable efforts to

develop a pediatric formulation have failed because this ground for a waiver would permit small companies to avoid producing pediatric formulations on cost grounds. This comment urged that waivers be allowed only if a pediatric formulation cannot be produced for scientific or technological reasons. One comment argued that even if producing a pediatric formulation is impossible, the manufacturer should be required to study the adult formulation in pediatric patients, because it will be used in pediatric patients.

One industry comment urged that the decision to require a pediatric formulation be made on a case-by-case basis. Another comment argued that pediatric formulations should be required only if a panel of pediatric experts concludes that there is a genuine pediatric need and substantial benefit.

FDA agrees that the burden should be on the manufacturer to provide evidence that experts in formulation chemistry had encountered unusually difficult technological problems in the development of a pediatric formulation. In determining whether those problems were sufficiently severe to warrant a waiver of pediatric studies, FDA will consider the potential importance of the product for pediatric patients. The more important the product, the more efforts should be made to develop a pediatric formulation. FDA will also, at its discretion, take to the Advisory Committee for Pharmaceutical Sciences questions about whether "reasonable attempts" have been made to produce pediatric

formulations in particular cases. Although FDA believes that it is appropriate to consider the cost to the manufacturer in determining whether attempts to produce a pediatric formulation have been reasonable, the agency received no helpful guidance on how to assess whether the costs of producing a pediatric formulation were unreasonable. In addition to any informative cost information provided by the manufacturer, FDA will take into account whether a product is still under patent or exclusivity protection. FDA will assume that manufacturers can incur greater costs for products that have significant patent life or exclusivity remaining.

41. One comment contended that FDA chemistry requirements have increased over the last 10 years. Another comment urged that FDA be more flexible in its review of formulations, e.g., by permitting generally recognized as safe (GRAS) substances in pediatric formulations.

FDA recently held a conference on pediatric formulations at which the agency sought input from industry on identifying the regulatory issues that affect the development of pediatric formulations for both new and approved marketed drugs. At this meeting, FDA also requested proposals for solutions to facilitate the development and approval of pediatric formulations. FDA is committed to removing unnecessary burdens on the review and approval of pediatric formulations.

42. Two comments urged manufacturers to provide formulas in product labeling for extemporaneous pediatric formulations made

by pharmacists. These comments stated that the current practice among hospital pharmacies is to use unvalidated formulas, resulting in a lack of consistency from one hospital to another, no stability testing, and, in some cases, reluctance to produce pediatric formulations at all because of the lack of guidance. One comment stated that information on extemporaneous formulations should be provided only where: (1) A commercial formulation is not possible or (2) the drug has extremely limited use in pediatric patients.

FDA is concerned that the availability of this approach may undermine efforts to produce standardized pediatric formulations. There are, however, one or two examples in which approved labeling carries directions for producing extemporaneous pediatric formulations. FDA will consider, on a case-by-case basis whether such an approach is appropriate, e.g., where it has not been possible to develop a stable commercial formulation.

J. Marketed Drug and Biological Products

FDA proposed in § 201.23 to codify its authority to require, in certain circumstances, a manufacturer of a marketed drug or biological product to submit an application containing data evaluating the safety and effectiveness of the product in pediatric populations. FDA proposed to impose such a requirement only where the agency made one of two findings: (1) That the product was widely used in pediatric populations and the absence of adequate labeling could pose significant risks to pediatric

patients; or (2) the product was indicated for a very significant or life-threatening illness, but additional dosing or safety information was needed to permit its safe and effective use in pediatric patients.

Before requiring a study under this section, FDA proposed to consult with the manufacturer on the type of studies needed and on the length of time necessary to complete them, and would notify the manufacturer, by letter, of the agency's tentative conclusion that such a study was needed and provide the manufacturer an opportunity to provide a written response and to have a meeting with the agency. At the agency's discretion, such a meeting could be an advisory committee meeting. If, after reviewing any written response and conducting any requested meeting, FDA determined that additional pediatric use information was necessary, FDA proposed to issue an order requiring the manufacturer to submit a supplemental application containing pediatric safety and effectiveness data within a specified time. The proposal referred to the order in one place as a letter. FDA has clarified the final rule by stating that the manufacturer will receive "an order, in the form of a letter." A few other minor clarifying revisions have also been made in this section.

FDA sought comment on whether it should codify its authority to require the manufacturers of marketed drugs and biologics to conduct pediatric studies, and, if so, on the circumstances in which the agency should exercise that authority.

43. Many comments from the pediatric community agreed that FDA should codify its authority to require pediatric studies on marketed drugs. Several comments from the pharmaceutical industry argued that FDA lacked authority to require studies of marketed drugs and that the 1994 rule sufficiently addressed pediatric labeling for marketed drugs. Some comments argued that adding pediatric labeling for indications applicable to pediatric patients should be at the sponsor's discretion. Others claimed that incentives are better than requirements. One comment contended that the proposed requirement forces manufacturers "to take on unwanted liabilities in order to maintain an asset which was created and earned under a different set of rules." Other comments maintained that companies should not be required to conduct new studies, and that pediatric labeling should be based on existing data, such as marketing experience and dosing regimens generally accepted by experts. A comment from a pharmaceutical trade association argued that studies should not be required but that FDA should work with industry and others to "develop creative ways to obtain the needed labeling information" for marketed drugs.

FDA believes that it has ample authority to require pediatric studies of marketed drugs and biologics, as described in the preamble to the 1994 rule (59 FR 64240 at 64243) and in "Legal Authority" section IV of this document. FDA has also concluded, as described previously, that the response to the 1994

rule and other voluntary measures have not produced a significant improvement in pediatric labeling for many marketed drugs and biologics. In addition, as one pharmaceutical company conceded, manufacturers are unlikely to initiate clinical research on marketed drugs whose patents have expired, or are about to expire. FDA has therefore concluded that where pediatric information is critical to patient care, it is necessary to require that pediatric studies be carried out. FDA notes that new requirements are sometimes imposed on already marketed consumer products when such requirements are necessary to protect the public health. FDA emphasizes, however, that it will require studies of marketed products only in the compelling circumstances described in the regulation.

44. FDA received many comments on the grounds for requiring studies of marketed products. Comments from medical societies, pediatricians, and disease-specific organizations argued that the proposed grounds were too narrow. One comment stated that pediatric studies should be required of any marketed drug that is likely to be used in pediatric patients. Several comments argued that the phrase "very significant illness" was ill-defined. One comment stated that it was "so open-ended and subjective as to be impossible for use as a regulatory standard." Another comment suggested that any definition of "very significant illness" would be arbitrary and overbroad. Several comments urged that the same criteria that are applied to not-yet-approved drugs be applied to

marketed drugs. One of these comments argued that even if the criteria remain as proposed, "widely used" and "significant risk" should be defined in terms of the severity of the illness. According to this comment, if the consequences of no treatment are serious, the absence of labeling should be more readily found to present a significant risk. One industry comment maintained that the requirement should apply to marketed drugs only where there is a "compelling need" for pediatric data. One comment argued that the requirement should apply to all marketed drugs unless an expert panel concluded that studies were not required, while other comments urged that FDA utilize an expert panel to affirmatively identify and prioritize marketed drugs that should be studied in pediatric patients. Some of these comments suggested that there be no criteria and that the panel should determine which drugs should be studied on a case-by-case basis. One comment suggested that the list should be prioritized using the number of pediatric prescriptions.

FDA believes that criteria are necessary to assure consistency and fairness in deciding which marketed drugs and biologics are studied. FDA has reviewed the grounds for requiring pediatric studies of marketed drugs and biologics and has revised them in light of the comments. FDA has concluded that the phrase "very significant illness" is not sufficiently defined and agrees that it would be less confusing to use the same concepts that are used in defining which new products will

be subject to the pediatric study requirement. FDA has therefore replaced the concept of "very significant illness" and replaced it with "meaningful therapeutic benefit." The second criterion will now read:

* * * there is reason to believe that the drug product would represent a meaningful therapeutic benefit over existing treatments for pediatric patients for one or more of the claimed indications, but additional dosing or safety information is needed to permit its safe and effective use in pediatric patients.

FDA has also revised the first criterion to conform more closely to the criteria for requiring studies in not-yet-approved drugs and biologics, replacing "widely used" with "used in a substantial number of pediatric patients." FDA will use the same definition of "substantial number" for both marketed and not-yet-approved drugs and biologics. The first criterion will, however, continue to include the requirement that "the absence of adequate labeling could pose significant risks to patients." FDA believes that the pediatric study requirement may impose greater burdens on the manufacturers of marketed drugs and biologics than the manufacturers of not-yet-approved products, and that it is appropriate to require such studies only in the compelling circumstances described in the regulation. In determining which marketed products "could pose significant risks to patients," FDA

will consider such factors as the severity of the illness and the consequences of inadequate treatment, the number of pediatric prescriptions, and any available information on adverse events associated with use of the product.

FDA agrees that an expert panel can provide useful experience and guidance in developing a prioritized list of marketed drugs and biologics that meet the criteria for required studies. FDA intends to seek advice on developing such a list from a pediatric panel, as described in section III.M of this document ("Pediatric Committee").

FDA also notes that FDAMA requires the agency to publish a list of marketed drugs for which "additional pediatric information may produce health benefits in the pediatric population." FDA published this list within 180 days of the enactment of FDAMA, as required by that statute. Although the products on the list designated as high priority may be appropriate candidates for required studies under this rule, the list of high priority products is not necessarily exhaustive. Other products that might be subject to a requirement under this rule might not appear on the list. FDA also emphasizes that there is no implication that the agency will require studies of any particular product on the list.

45. One comment claimed that the proposal requires studies only from manufacturers of innovator drugs (sponsors of the original application for the drug), while the major market share

for many of these drugs is now held by generic manufacturers. This comment argued that a waiver should be granted if ANDA holders fail to share the costs of required studies. Another comment argued that the pediatric study requirement should apply only to the sponsor of the original application.

Where the agency requires pediatric studies on a multi-source marketed drug, each manufacturer of that drug, whether innovator or generic, will be responsible for satisfying the study requirement. To avoid duplication of research, FDA will encourage all the manufacturers to jointly fund an appropriate study. If, however, a joint study is not agreed to, each manufacturer will be responsible for submitting adequate studies.

K. Ethical Issues

In the proposal, FDA noted that because pediatric patients represent a vulnerable population, special protections are needed to protect their rights and to shield them from undue risk. To address ethical concerns in research on pediatric patients, both the AAP (Ref. 17) and the Department of Health and Human Services (DHHS), 45 CFR part 46, subpart D, have developed guidelines for the ethical conduct of clinical studies in pediatric patients. FDA advised in the proposal that sponsors should adhere to these guidelines for pediatric studies conducted under this rule. The agency also sought comment on ethical issues raised by the proposal.

46. A few comments addressed appropriate ethical guidelines for pediatric studies. Several comments said that existing ethical guidelines provide an adequate framework for pediatric studies. A comment from the AAP stated that ethical conduct should be guided by the DHHS and AAP guidelines, and that IRB approval that explicitly ensures protection of vulnerable subjects should be obtained. This comment also stated that the AAP guidelines provide a means to ensure ethical conduct of studies without impeding pediatric research. One comment said that DHHS ethics regulations may not provide sufficient protection for pediatric patients and suggested incorporating AAP guidelines for ethical conduct of pediatric studies into FDA's human subjects protections regulations. Another comment contended that pediatric studies should strictly adhere to regulations currently in effect for studies of human subjects who are unable to give consent, and urged FDA to further define requirements for investigation in vulnerable populations.

FDA believes that adherence to the DHHS and AAP guidelines will provide sufficient protection to pediatric patients from the risks of research. FDA will, however, seek advice from a panel of pediatric experts on whether additional protections are necessary.

47. Several comments addressed the ethics of requiring pediatric studies as described in the proposal. Two comments asserted that children are overmedicated and that administering

drugs to children is unacceptable and "ungodly." Comments from the pharmaceutical industry claimed that the rule as drafted would result in unethical testing of pediatric patients. One comment maintained that the regulations do not adequately protect pediatric patients from the risks of research because they impose a "general rule that a deferral of testing in pediatrics will only be granted in narrow and limited circumstances."

In contrast, comments from the pediatric community maintained that far more serious ethical concerns are raised by using untested drugs in pediatric patients than by conducting pediatric research. A comment from the AAP stated that there is no greater ethical dilemma than whether to give a drug with insufficient safety and effectiveness data to a child, or to withhold treatment and let the disease progress unabated.

Some comments suggested specific points in drug development at which pediatric testing becomes ethical. One comment argued that testing in pediatric patients before efficacy is demonstrated in adults may unnecessarily expose pediatric patients to a product's risks before its benefits are established. Another comment contended that it is unethical to begin studying drugs in pediatric patients that are not intended primarily for pediatric patients until the drug is adequately characterized in adult patients, including choice of appropriate adult dose and establishment of reasonable evidence of safety and efficacy with an acceptable therapeutic margin. A pharmaceutical

trade association argued that it is unethical to begin trials in pediatric patients until enough adult safety and effectiveness data have been gathered to conclude that the drug "is likely to be approved for use in adults."

FDA believes that some of the comments from the pharmaceutical industry misstate the application of the rule. As described fully previously, deferral of pediatric studies is specifically permitted in those cases where data should be collected in adults before exposing pediatric patients to the agent. There is no suggestion in either the proposed or final rule that deferral will be granted only in "narrow and limited circumstances." FDA believes that, as drafted, the deferral provisions of the rule permit ethical pediatric testing that does not expose pediatric patients to inappropriate risks.

48. A few comments urged that placebo-controlled trials in pediatric patients be used rarely if at all. The AAP stated that placebo controls should not be used where that design would impose a substantial increase in risk to the child or would impede the ability to perform useful clinical trials. This comment urged that alternatives to placebo controls be used wherever possible and that where placebo controls are used, the study design should incorporate safeguards to avoid undue risk.

The question of appropriate control group arises only when there is a need for controlled trials to establish efficacy in the pediatric population. FDA agrees that alternatives to

placebo-controlled trials should be used wherever they can provide sufficient information to establish effectiveness. FDA often accepts data from active control studies for certain therapeutic classes, such as anti-infectives and oncologic drugs. (See 21 CFR 314.126.) In some cases, new treatments can also be studied against a placebo together with a background of existing therapy, i.e., studied in "add-on" trials.

49. One comment argued that parents should not be given money or equivalent compensation for participation in drug studies. This comment suggested that any compensation could be put in the child's IRA.

The IRB overseeing a research study, rather than FDA, is responsible for determining whether compensation offered to the subjects of the study is ethically appropriate.

L. Remedies

If a manufacturer failed, in the time allowed, to submit adequate studies to evaluate pediatric safety and effectiveness required under proposed § 201.23(c) or § 314.55 (proposed § 314.50(g)), FDA proposed to consider the product misbranded under section 502 of the act or an unapproved new drug under section 505(a) of the act (see "Legal Authority," in section IV of this document). Although proposed § 201.23 expressly covered both drugs and biologics, FDA inadvertently omitted in that section a reference to actions against biologics that have not obtained a license under section 351 of the Public Health Service

Act. Such a reference has been added in the final rule. 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. FDA may also seek an injunction or bring a prosecution under the Public Health Service Act. In the proposal, FDA advised that it would bring an enforcement action for injunctive relief for failure to submit a required assessment of pediatric safety or effectiveness. Violation of the injunction would result in a contempt proceeding or such other penalties as the court ordered, e.g., fines. As noted in the proposal, FDA does not intend to deny or withdraw approval of a product for failure to conduct pediatric studies, except possibly in rare circumstances, because removal of a product from the marketplace could deprive other patients of the benefits of a useful medical product. Such circumstances might arise where the predominant use of the product was in pediatric patients rather than adults, and there were life-threatening risks associated with use of the product in pediatric patients when used without proper dosing and safety information in the labeling.

To assist FDA in determining whether pediatric assessments are needed or are being carried out with due diligence, FDA proposed to amend § 314.81(b)(2) (21 CFR 314.81(b)(2)) (annual postmarketing reports) to require that 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. FDA also proposed to require that, where possible, the annual report contain an estimate of patient exposure to the drug product, with special reference to the pediatric population.

50. Several comments agreed with the agency that withdrawal or denial of approval is infeasible and supported the use of injunctive remedies. One comment argued that if FDA provides no incentives, disincentives to avoid pediatric trials must be strong, and that withdrawal and denial of approval must therefore be used as a remedy.

FDA continues to believe that refusal to approve or removal from the market is generally an unsatisfactory remedy from a public health perspective because it denies adequately studied populations access to safe and effective medicines.

51. Several comments supported the imposition of monetary fines. One comment urged that fines be imposed in the amount of a percentage of the profits to ensure that large and small companies had an equal disincentive. Several comments argued that fines should be used by FDA to fund pediatric studies carried out by government or private agencies. One comment contended that monetary penalties, such as fines or shortening of

exclusivity, are the only practical remedy because industry and government are economically driven, but that injunctions are too costly.

Although FDA continues to believe that court-imposed fines are an appropriate remedy for failure to submit pediatric assessments, the agency has no authority itself to impose fines for violation of this rule, to set the amount of such fines, or to take the fines and direct them to specific activities.

52. Two comments opposed treating violative products as "misbranded" because this could limit access to the drugs or could delay availability of the products for adult use. According to one comment, FDA should consider a misbranding charge only if the sponsor failed to meet a phase 4 commitment. Another comment argued that injunction or prosecution are appropriate only as a final response, and that other, unspecified means are more efficient to elicit compliance. This comment also argued that seizure would serve only to deprive patients of safe and effective drugs.

The comments arguing that a misbranding charge could limit access or delay approval provided no basis for concluding that these results would occur, and FDA is aware of none. FDA agrees that injunction and prosecution are appropriate remedies only after the sponsor has been given an adequate opportunity to meet its obligations under the rule. FDA emphasizes, however, that providing adequate pediatric labeling cannot be long-delayed

without putting the health of pediatric patients at risk and that the agency will not accept unwarranted delays in submitting required studies. FDA also notes that it does not intend ordinarily to use seizure as a remedy for failure to conduct required studies.

53. Some comments offered additional or alternative remedies for failure to conduct required studies. One comment urged that failure to provide information to support pediatric labeling result in highly visible warnings on prescription and OTC labels that the drug has not been approved by FDA for pediatric use. Two comments argued that the label should disclose the status of pediatric studies, whether waivers or deferrals had been requested or granted, and the timetable for full compliance. Another comment contended that incentives are more effective than penalties, and that FDA discussions with sponsors during drug development will achieve the results sought in the proposal.

FDA agrees that publicity can sometimes be a useful tool for encouraging compliance. FDA does not believe, however, that it is feasible to include in labeling detailed information on the status of pediatric trials, because that information could change frequently. As described in section III.M of this document, FDA will, in appropriate cases, bring issues related to the progress of pediatric studies before a panel of pediatric experts, and may utilize other forms of publicity to provide the public with

information about the status of required pediatric studies. FDA notes, e.g., that FDAMA contains provisions concerning disclosure of information on the status of postmarketing studies. FDA may also consider the use of prominent warnings about the absence of data on pediatric use, if necessary in particular cases.

M. Pediatric Committee

A large number of comments recommended that FDA form a panel of pediatric experts to provide advice on a range of topics related to implementation of this rule. Two comments recommended that an expert panel give advice on all facets of the rule. Several comments suggested more specific roles for the panel. For example, the AAP recommended that the panel provide advice on waiver requests, which marketed drugs require study, whether a drug is "widely used," whether to accept a manufacturer's failure to develop a pediatric formulation, relevant age groups for study, the appropriateness of deferral, and appropriate timetables for completion of deferred studies. A disease-specific organization urged that a pediatric committee assist in establishing "pediatric guidelines and practice," including a list of drugs for which studies would be required, protocol design, formulations, and age ranges. Two industry comments recommended that the panel review which drugs require testing and labeling, at what phase of drug development pediatric patients should be exposed, when waivers should be granted, what methods should be used to evaluate safety and effectiveness, the economic

burdens on industry, and liability issues. Several comments, including comments from a pharmaceutical trade association, a disease-specific organization, a medical society, and pediatricians, recommended that the panel give advice on which drugs should be studied in pediatric patients. One comment suggested that FDA appoint a pediatric pharmacology expert to each of the existing drug advisory committees, except possibly the Fertility and Maternal Health Advisory Committee.

FDA has concluded that a panel of pediatric experts could provide useful advice and experience on several aspects of the implementation of the rule. FDA will therefore convene a panel of pediatric experts, including at least one industry representative, and seek its advice on a range of issues. Such a panel may be composed of pediatric experts appointed to each of FDA's existing drug advisory committees. As described in section III.E of this document under "Waivers," FDA does not believe that it would be practical to ask such a committee to review every waiver or deferral request. However, the agency will ask the panel to provide annual oversight of the agency's implementation of the final rule, including the agency's record of granting or refusing waivers and deferrals. FDA will also seek the advice of the panel in identifying specific marketed drugs and biological products that should be studied in pediatric patients, and the age groups in which they should be studied. FDA will also ask for advice on assessing when additional therapeutic options are

needed in treating specific diseases and conditions occurring in pediatric patients. As described previously, FDA will seek the panel's advice on ethical issues raised by clinical trials in pediatric patients, and whether additional rules should be implemented in this area. Where a manufacturer is not carrying out required studies according to the agreed upon timetable, FDA may seek the advice of the panel on whether the manufacturer is acting with due diligence. In addition, FDA may bring before the panel other issues that arise in the implementation of the rule, including the design of trials and analysis of data for specific products and classes of products.

N. Other Comments

54. Several comments suggested various forms of oversight for the implementation of the rule. One comment suggested that FDA establish a plan to prospectively evaluate these regulations, including their effect on the cost of drug development and on the time to new drug approval, and the number and success of pediatric studies actually performed. Another comment urged FDA to appoint a "Children's Studies Ombudsman." One comment asked that the rule include an appeals mechanism to resolve disputes between sponsors and agency reviewers.

As described previously, FDA intends to convene a panel of pediatric experts, including at least one representative of the pharmaceutical industry, to, among other things, review the agency's implementation of the rule. FDA notes that it already

has procedures for resolution of disputes between sponsors and FDA reviewing divisions, 21 CFR 312.48 and 314.103, and that these procedures will be available for disputes that arise under this rule.

55. Several comments contended that the rule is inconsistent with requirements in Canada, Europe, and Japan for pediatric studies. These comments argued that the rule was at odds with harmonization efforts and urged FDA to harmonize its requirements with those of other countries. One comment recommended that the United States, the European Union (EU), and Japan adopt pediatric drug development as a topic for global discussion and harmonization.

Although FDA is not required to harmonize its labeling regulations and enforcement with those of our International Conference on Harmonization (ICH) partners, harmonization is a goal that the agency strives to achieve. FDA intends to work through the ICH process to harmonize methods for conducting pediatric studies.

56. A few comments sought additional incentives for pediatric studies. One industry comment suggested that FDA should provide: (1) Priority reviews for applications containing pediatric data or ongoing studies; (2) waiver of user fees for pediatric effectiveness supplements; and (3) application of the subpart E regulations (21 CFR part 312, subpart E) to pediatric development of new drugs and biological

products, to address the issues associated with small sample size and therapeutic need.

Since the publication of the proposal, two significant new incentives have become available for pediatric research. First, as described elsewhere in this document, FDAMA provides 6 months of exclusive marketing to certain applicants who conduct pediatric studies. Second, as a result of changes made during the reauthorization of the PDUFA, user fees are no longer required for supplements that are solely for the purpose of adding a new indication for use in pediatric populations.

IV. Legal Authority

In the proposal, FDA cited as authority for the requirements in the rule sections 502(a), 502(f), 505(d)(7) of the act, and § 201.5 (21 CFR 201.5), which require adequate directions for use and prohibit false or misleading labeling; section 201(n) of the act, which defines as misleading labeling that fails to reveal material facts related to consequences of the customary or usual use of a drug; sections 201(p), 301(a) and (d) (21 U.S.C. 331(a) and (d)), and 505(a) of the act, which subject a drug to enforcement action if it is not recognized as safe and effective or approved for the conditions prescribed, recommended, or suggested in the labeling; section 502(j) of the act, which prohibits drugs that are dangerous to health when used in the manner suggested in their labeling; sections 505(i) and 505(k) of the act, which authorize FDA to impose conditions on the

investigation of new drugs, including conditions related to the ethics of an investigation, and to require postmarketing reports; section 701(a) of the act, which authorizes FDA to issue regulations for the efficient enforcement of the act; and section 351 of the Public Health Service Act, which formerly required biological products to meet standards designed to insure their "continued safety, purity, and potency." FDA notes that section 351 was amended by FDAMA, and now requires biological products to be "safe, pure, and potent."

FDA has authority under section 302 of the act and under the Public Health Service Act to seek an injunction requiring studies of certain marketed drugs on the grounds that the absence of pediatric safety and effectiveness information in the labeling renders the product misbranded or an unapproved new drug. The act also authorizes seizures of misbranded or unapproved drugs under section 304 of the act. Misbranding drugs and introducing unapproved new drugs into interstate commerce are prohibited acts under sections 301(a), (d), and (k) of the act. The statutory definition of "drug" is set out at section 201(g) of the act.

57. Several comments agreed that FDA has authority to require pediatric testing of drugs and biological products. One comment argued that the act already gives FDA the authority to require that all drugs be tested in pediatric patients, and that the rule, which permits waivers and deferred testing in some cases, weakens the agency's existing statutory authority. One

comment contended a provision of FDAMA granting exclusivity to "any pediatric study [that] is required pursuant to regulations promulgated by the Secretary [and that meets certain other requirements]" shows that Congress agrees that FDA has authority to require pediatric studies. This comment also argued that, to the extent that FDA's position on its authority to require pediatric studies has changed, the change in position is justified because the proposal articulates a reasoned basis for the change.

FDA agrees that it has the authority to require pediatric testing of drugs and biologics. For the reasons cited in the preamble to the proposed and final rules, FDA has concluded that the requirements in the rule appropriately balance the need for adequate pediatric labeling and the limitations on resources available for pediatric testing and agency review. FDA also agrees that the reference in FDAMA, which was enacted after the proposal was issued, to pediatric studies required by FDA, demonstrate that Congress is aware of FDA's position that it has the authority to issue this rule and agrees that the agency has such authority. Finally, FDA agrees that it has articulated a reasoned basis for its position that the agency has authority to require pediatric studies, but notes that FDA previously stated its position that it has the authority to require pediatric studies in 1994 (59 FR 64240 at 64243).

58. Several comments argued that FDA lacks authority to require pediatric studies of drugs. A few comments cited remarks by former Commissioner David Kessler during a 1992 speech. In that speech, David Kessler stated his opinion that FDA does not have "the authority to require manufacturers to seek approval for indications which they have not studied." Other comments argued that FDA has no authority to require the study of any indications or populations other than those proposed by the manufacturer. One comment challenged FDA's reliance on section 201(n) of the act for not-yet-approved drugs, claiming that the agency cannot know what will be the "customary or usual uses" of an unmarketed drug. A few comments argued that the agency's legal theory would authorize the agency to require studies of all off-label indications.

FDA disagrees that any of these arguments show that FDA lacks authority to issue this rule. Under FDA's longstanding policy, statements made in speeches, even by Commissioners, are informal expressions of opinion and do not constitute a formal agency position on a matter. As such they are not binding on the agency. (See, e.g., 21 CFR 10.85(k).)

FDA also disagrees that it has no authority to require a drug or biologic to be studied in a population that is expected to use the product for the claimed indication, or that this is a new position. The agency has repeatedly stated that an application for marketing approval should contain data on a

reasonable sample of the patients likely to be given the product once it is marketed (59 FR 64240 at 64243; 58 FR 39406 at 39409). The agency has also previously asserted its authority to require studies in pediatric patients and in other subpopulations for both not-yet-approved products and marketed products. In the preamble to the 1994 rule, FDA made the following statement:

If FDA concludes that a particular drug is widely used, represents a safety hazard, or is therapeutically important in the pediatric populations, and the drug sponsor has not submitted any pediatric use information, then the agency may require that the sponsor develop and/or submit pediatric use information.

If FDA has made a specific request for the submission of pediatric use information because of expected or identified pediatric use, and the sponsor fails to provide such information, the agency may consider the product to be a misbranded drug under section 502 of the act, or a falsely labeled biological product under section 351 of the PHS Act, as an unapproved new drug or unlicensed biological product. (See 21 U.S.C. 355 and 42 U.S.C. 262.)

(59 FR 64240 at 64248; see also 58 FR 39406 at 39409)

The act and implementing regulations require drugs to be adequately labeled for their intended uses. See sections 502(f)

of the act and § 201.5. "Intended uses" encompass more than the uses explicitly included in the manufacturer's proposed labeling. Id., 21 CFR 201.128. In determining the intended uses of a drug for which it must be adequately labeled, FDA may consider both the uses for which it is expressly labeled and those for which the drug is commonly used, § 201.5. FDA may also consider the actual uses of the drug of which the manufacturer has, or should have, notice, even if those uses are not promoted by the manufacturer, 21 CFR 201.128. Section 201(n) of the act defines labeling as misleading if it fails to include material facts about the consequences of "use of the [drug] * * * under such conditions of use as are customary or usual." Sections 201(p) and 505(d) of the act authorize FDA to require evidence establishing the safety and effectiveness of uses "suggested" by the manufacturer's labeling as well as those expressly recommended in the labeling. Thus, the agency has authority to require a manufacturer to establish the safety and effectiveness of, and adequately label its product for, use of the product in a subpopulation for which the product is not labeled if that use is common or suggested in the labeling.

As described in the proposal, there is extensive evidence that drugs and biologics indicated for diseases that affect both adults and pediatric patients are routinely used in pediatric patients despite the absence of pediatric labeling, and even in the face of disclaimers stating that safety and effectiveness

have not been established in pediatric patients. FDA may therefore consider pediatric use to be "customary or usual" or "commonly used" where the drug is indicated for a disease or condition that affects both adults and children, and the drug is not contraindicated in pediatric patients. FDA may also consider pediatric use to be "suggested" in a drug's labeling even where such use is not expressly recommended or is even disclaimed. The medical community generally expects that drugs and biological products will behave similarly in demographic subgroups, including age and gender subgroups, even though there may be variations among the subgroups, based on, e.g., differences in pharmacokinetics. Thus, where a drug or biological product is indicated for a disease suffered equally by men, women, and children, and is not contraindicated in women or pediatric patients, the product will be widely prescribed for all three subgroups even if it were studied only in, or labeled only for, men.

FDA disagrees that it can know nothing, in advance of marketing, about whether a drug or biological product will be used in pediatric patients. The evidence cited in the proposal and confirmed by comments from the pediatric community is overwhelming that products indicated for diseases that affect both adults and children are and will be commonly used in pediatric patients. Indeed, pediatricians often have no choice but to use these products in pediatric patients. A drug product

that provides a meaningful therapeutic benefit either because it represents a significant improvement in therapy or because it is a necessary therapeutic option can be expected to be routinely used in the treatment of pediatric patients. Under the rule, the decision that a product will provide a meaningful therapeutic benefit or will be used in a substantial number of pediatric patients is made on a case-by-case basis, depending upon such factors as the number of pediatric patients affected by the disease for which the product is indicated, the availability and adequacy of other therapeutic options to treat pediatric patients for the disease, and whether similar products, e.g., products in the same drug class, have been widely used in pediatric patients.

Finally, FDA emphasizes that this rule applies only where a product is expected to have clinically significant use in pediatric populations for the indications already claimed by the manufacturer. The record before the agency documents widespread evidence of actual use of products in the pediatric population for indications labeled for adults. This record supports FDA's conclusion that it has authority to require pediatric studies of drugs and biologics that have or are expected to have clinically significant use among pediatric patients for the claimed indications. The agency has not examined evidence concerning the use of approved products for diseases or conditions not in the label, and the rule does not apply in those situations.

59. Two comments addressed the agency's reliance on section 701(a) of the act. One comment argued that 701(a) of the act, in combination with the substantive statutory provisions cited by FDA, authorizes this rule because the agency has demonstrated that the rule is reasonably related to the purposes of the act. Another comment argued that 701(a) of the act does not authorize the agency to enforce requirements beyond those imposed by the act.

Section 701(a) of the act gives the Secretary authority to issue regulations for the efficient enforcement of the act. Consonant with the Supreme Court's determination that the language of the act should not be read restrictively, but in a manner consistent with the act's purpose of protecting the public health, a regulation issued under section 701(a) of the act will be sustained so long as it is reasonably related to the purposes of the act. United States v. Nova Scotia Food Products Corp., 568 F.2d 240, 246 (2nd Cir. 1977). FDA believes that it has demonstrated that this regulation is reasonably related to the purposes of the act.

V. Implementation Plan

FDA proposed that the rule would become effective 90 days after the date of its publication in the FEDERAL REGISTER. For new drug and biologic product applications submitted before the effective date of the final rule, the agency proposed a compliance date of 21 months after the effective date of the

final rule (for a total of 2 years after issuance of the final rule). For new drug and biologic product applications submitted on or after the effective date of the final rule, the agency proposed a compliance date of 15 months after the effective date of the final rule (for a total of 18 months after issuance of the final rule). FDA has revised the final rule to become effective 120 days after publication in the FEDERAL REGISTER, to allow additional time for comment on the revised information collection requirements. FDA has also revised the compliance dates. All applications will have a compliance date of 20 months after the effective date of the rule (for a total of 2 years after publication of the final rule).

60. Two industry comments argued that the proposed effective dates were too short. One of these suggested that 15 and 21 months were too short to develop a pediatric program and formulation, conduct trials, analyze data, and submit an application. Two comments asked that FDA clarify what "compliance" means. According to one of these comments, 15 months would be adequate for initiation of discussions with a sponsor about plans, but inadequate for completion of studies. This comment also argued that it is not in children's interest to rush through pediatric studies to meet an arbitrary deadline. Another comment offered the example of Ritonavir, a drug to treat HIV infection, for which pediatric studies reportedly took 21 months even after development of a pediatric formulation.

According to the comment, it took 15 months to agree on a protocol, 3 months to recruit patients, and 3 months to the first interim analysis of data. One disease-specific organization argued that the effective dates were too long. This comment proposed 12 months from the effective date of final rule, which could be extended by 6 months if genuine difficulties occurred. This comment also urged that compliance with the early discussion requirements be immediate. One comment argued that pending applications should be granted a full waiver and treated as marketed products.

"Compliance," as referred to in the proposal, means the submission of an assessment of pediatric safety and effectiveness under § 314.55(a) (proposed § 314.50(g)(1) or 601.27(a)), unless a waiver or deferral for all relevant age groups has been granted. FDA has reconsidered the compliance dates and has concluded that applications submitted on or after the effective date of the final rule should be given 20 months from the effective date of the final rule to achieve compliance. Although FDA does not believe that development of, and agreement on, a protocol should take 15 months, protocol development, recruitment, enrollment, and data analysis may together take up to 2 years. There is no reasonable basis on which to distinguish between an application submitted 1 day before the effective date of the final rule, and one submitted a day later.

All other provisions of the rule will become effective on the effective date of the rule. One hundred twenty days from the date of publication in the FEDERAL REGISTER is sufficient time to meet these new requirements.

VI. Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520). The title, description, and respondent description of the information collection requirements are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

With respect to the following collection of information, FDA invited comment on: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of

automated collection techniques, when appropriate, and other forms of information technology.

OMB filed a Notice of Action, not approving the proposed collection of information. OMB requested that, as part of the final rule, FDA address all comments received on the information collection requirements contained in the rule, particularly with respect to the reporting burden imposed by the rule. FDA received one comment concerning the proposed burden estimates of this rulemaking under the PRA. The comment contended that FDA underestimated the time required to comply with the annual reporting requirements of the proposed rulemaking.

Concerning § 314.50(d)(7), the comment stated that in order to comply with this requirement, "one company" estimated that, for one pediatric reporting project, medical staff had spent at least 118 hours, rather than the 8 hours that FDA had estimated, reviewing the medical literature and summarizing the findings. FDA does not believe that this comparison is fully appropriate because § 314.50(d)(7) does not require an applicant to review the medical literature, or other studies, de novo. It simply requires an applicant to provide a brief summary of data that have already been fully reported and analyzed elsewhere in the same application. However, because the data to be summarized may be more extensive than originally estimated, FDA has, in response to the comment, increased its estimate of the reporting burden for this requirement from 8 hours to 50 hours.

Concerning § 314.55(a), the comment contended that FDA's estimate of 10 companies submitting NDA's annually for NME's is too low. The comment implied that, based on data for 1996, 50 companies would be a more realistic estimate. The comment also contended that FDA's estimate of 16 hours for a manufacturer to prepare the report of the data supporting the safety and effectiveness of the drug for the indication for the pediatric population is too low.

Concerning § 314.55(b), the comment stated that FDA's estimate of 9 manufacturers requesting deferrals of the submission of pediatric study data and the estimate that this would take 8 hours to complete are too low.

Concerning § 314.81(b)(2)(i), the comment contended that FDA's estimate of 1.5 hours for manufacturers to submit pediatric information in their annual reports is too low.

Concerning § 314.81(b)(2)(vi)(c), the comment contended that FDA's estimate of 1.5 hours for manufacturers to submit in their annual reports the analysis of available safety and efficacy data conducted or obtained in the pediatric population as well as proposed labeling changes is too low. The comment stated that even an estimate of 15 hours would be too low. Although the comment did not provide an estimate of the hours required to satisfy § 314.81(b)(2)(i) and (b)(2)(vi)(c), FDA has increased its estimates to 8 and 24 hours, respectively.