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***COMMENTS: Background materials for the
pediatric labeling final rule.***

PEDIATRIC LABELING RULE

BACKGROUND. Most drugs and biologics entering the marketplace have not been adequately tested in children. As a result, product labeling frequently fails to provide directions for safe and effective use in children. Nevertheless, because children suffer from most of the same diseases as adults, they are by necessity treated with drugs and biologics lacking adequate directions for their use. The absence of pediatric labeling information poses a number of dangers to children, including the risk of under- or over-dosing leading to ineffective treatment or excessive or unanticipated adverse effects. There are many reported examples of serious adverse reactions in children exposed to inadequately tested drugs, including seizures and cardiac arrest caused by bupivacaine, an anesthetic, and withdrawal syndrome in infants and small children following prolonged administration of fentanyl, a pain killer used as an adjunct to anesthesia. The absence of adequate pediatric labeling may also result in failure to provide optimal treatment to children because of the lack of appropriate scientific data. For example, a survey on the use of protease inhibitors, newest and most promising AIDS drugs, found that, before these drugs were studied in children, fewer than 10% of children with AIDS were receiving protease inhibitors.

In recent years, FDA has undertaken several initiatives to encourage the voluntary addition of pediatric use information to drug labels. FDA has implemented a "Pediatric Plan" designed to focus attention on and encourage voluntary development of pediatric data during drug development. FDA has also identified the top 10 drugs used in children without adequate labeling instructions, and has written the manufacturers of these drugs requesting that they submit supplemental applications to add pediatric use information to their drug labels. In 1994, FDA issued a new rule that allowed pediatric use information to appear on label on the basis of substantially less data than before, and that required manufacturers to survey existing data to determine whether there was sufficient information to support pediatric use information in the drug's label.

Despite these efforts, the majority of new drugs and biological products still enter the marketplace insufficiently tested in the pediatric population and the labeling of drugs widely used in children carries little or no information on pediatric safety and effectiveness. For example, the 1994 rule requiring manufacturers to survey existing medical literature about the pediatric use of their products and to add pediatric use information to their labels produced only 65 supplements that contained adequate labeling information for all relevant pediatric age groups and another 35 with adequate labeling for some but not all age groups.

The medical and patient communities have strongly urged FDA to take effective steps to increase the quantity and quality of pediatric labeling.

The agency recognizes that a mixture of incentives and requirements is most likely to lead to improved pediatric labeling. The FDA Modernization Act of 1997 (FDAMA) included a provision providing financial incentives in the form of 6 months of market exclusivity to manufacturers who conduct pediatric studies on some drugs. Although FDA is hopeful that the FDAMA incentives to produce many additional pediatric studies, the agency believes that this final rule is still needed to significantly improve the current lack of adequate pediatric labeling. Because FDAMA exclusivity applies only to products that have exclusivity or patent protection under the Drug Price Competition and Patent Term Restoration Act and the Orphan Drug Act, it provides no incentive to conduct studies on certain categories of products, including most

antibiotics, biologics, and off-patent products. In addition, the voluntary nature of the incentive provided by FDAMA is likely to leave many drugs, age groups, and indications unstudied. For example, given limited resources to conduct pediatric studies, it is probable that manufacturers will elect to conduct pediatric studies on those drugs for which the incentives are most valuable, i.e., on drugs with the largest adult sales. This may leave unstudied drugs that are greatly needed to treat pediatric patients, but that have smaller markets. Manufacturers may also elect not to study drugs that require study in neonates, infants and young children, because studies of these age groups are particularly difficult and may require the development of new pediatric formulations. In addition, FDAMA provides exclusivity to a manufacturer who conducts a requested study, even if the results of the study are inconclusive and do not provide useful information on how to use the drug in children. Finally, FDAMA does not require manufacturers who conduct pediatric studies to put the information gained into their drug labels. FDA believes that the final rule will address many of the gaps left by the FDAMA incentives. Studies conducted under this rule are eligible for 6 months of exclusivity under FDAMA, if they otherwise comply with the statute.

PROVISIONS OF THE REGULATION. The final rule requires applications for new drugs and biological products to contain sufficient data and information to support directions for pediatric use for the claimed indications if they (1) provide a meaningful therapeutic benefit to children over existing treatments, or (2) are likely to be used in a substantial number of pediatric patients. The required study can be deferred until after approval if, for example, FDA finds that it is appropriate to delay pediatric studies until sufficient data are collected in adults, or if imposition of the requirement would delay the availability of a new drug for adults. The requirement can also be waived if FDA finds, among other things, that the product is likely to be unsafe or ineffective in pediatric patients, that pediatric studies are impossible or highly impractical, or that reasonable efforts to develop a pediatric formulation had failed. In response to comments, the scope of the final rule is broader than the proposed rule. The proposed rule would have applied only to "new chemical entities" and to never before approved biological products. Many comments argued that modifications of existing products, may be more clinically significant in the treatment of children than the original products. Therefore, the final rule applies to new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration.

The rule would also codify FDA's authority to require, in compelling circumstances described in the regulation, that manufacturers of already marketed drugs and biological products conduct studies to support pediatric use labeling for the already approved indications. FDA believes that, in exercising its discretion whether to require studies of already marketed drugs, it is appropriate to first learn whether manufacturers will undertake the needed studies voluntarily in response to FDAMA. Therefore, before exercising its authority to require studies of already marketed products, FDA intends to give the FDAMA incentives an opportunity to produce new pediatric studies. If manufacturers do not take advantage of the incentives, FDA will then require studies where there the compelling circumstances described in the regulation are met. FDA expects to require studies on about 2 drugs per year.

In the event that a manufacturer fails to carry out a required pediatric study, FDA would not seek to disapprove or withdraw approval of the product, because such an action could deprive adult patients of important therapies. Instead, FDA would anticipate seeking an injunction from a federal court requiring the manufacturer to conduct or fund the needed studies.

PEDIATRIC LABELING Qs and As

1. What does this rule require?

It requires the manufacturers of drugs and biological products that are widely used in children or that provide a meaningful therapeutic benefit to children to provide information on the safe and effective use of the products in children, including adequate dosing and safety information. The information may be required at the time the product is first approved, or may be deferred until a short time after approval if pediatric studies cannot be completed before the drug is ready for approval in adults. The rule also authorizes FDA to require manufacturers of marketed drugs and biologics to study their products in children in compelling circumstances.

2. Why are you doing this now?

Despite efforts in recent years to address this issue, most drugs still lack adequate pediatric labeling. Every year more than half of all newly approved drug and biologic products that are likely to be used in children lack information to support their safe and effective use in children. Thus, when new drugs enter the market, pediatricians lack information on dosing and safety necessary to prescribe these products to children who may need them. For products already on the market, information is eventually made available to physicians by journal articles, handbooks and other references, but usually years after a drug is approved (and even then the information isn't available on the label and may not be adequate for some age groups). An FDA survey of drugs prescribed during 1994 identified the 10 drugs prescribed most frequently to children without adequate labeling. Together, these 10 drugs were prescribed more than 5,000,000 times. Over the years, this lack of information has led to under-treatment and to serious adverse events in children.

3. Can't you achieve the same effect through voluntary compliance?

FDA has taken a number of steps in recent years to address inadequate pediatric labeling, including issuing a rule in 1994 requiring drug manufactures to survey existing data and determine whether those data are sufficient to give information on how to use a drug in pediatric populations. These attempts at voluntarily compliance have not worked, as illustrated by the fact that the majority of drugs important to children still lack adequate pediatric labeling. In response to the 1994 rule, FDA received approximately 430 supplementary applications for label changes, a small fraction of the total number of products on the market. Over half of the supplements submitted simply requested the addition of the statement "Safety and effectiveness in pediatric patients have not been established." Many others requested minor wording changes or submitted unorganized, unanalyzed collections of possibly relevant data. Only 15% of the small number of supplements received (approximately 65) provided adequate pediatric information for all relevant pediatric age groups, and another 8% (approximately 35) provided adequate pediatric information for some but not all relevant age groups.

4. How many comments were received on the proposal and what did they say?

FDA received 55 comments on the proposed rule from pediatricians, parents, medical societies, organizations devoted to specific diseases, and the pharmaceutical industry. The comments from the pediatric and medical communities and from parents supported the rule, and sought to broaden its coverage. Many of the comments from the pharmaceutical industry opposed the rule as unnecessary and beyond FDA's legal authority, although a few supported it.

5. What changes have been made in the final rule?

In response to comments that the scope of the proposal did not cover those drugs that would be of most importance to children, the rule now covers new active ingredients, indications, dosage forms, dosing regimens, and routes of administration. FDA has also responded to many comments seeking creation of a panel of outside pediatric experts to oversee implementation of the rule by agreeing to create such a panel and to seek its advice on a range of issues related to the rule.

6. Will this requirement hold up drug approvals?

No. FDA will not delay the approval of drugs that are ready to be approved for adults even if studies in children have not been completed. The rule provides for other methods of ensuring that the pediatric studies are completed in a timely way.

7. Given the financial incentives for pediatric studies in the FDA Modernization Act of 1997 (FDAMA) to encourage voluntary compliance, why is this rule necessary?

FDA believes that a combination of incentives and requirements provides the best hope for improving pediatric labeling. Although FDA is hopeful that the FDAMA incentives will encourage many new pediatric studies, those incentives are likely to leave a number of important drugs and age groups unstudied. For example, given limited resources to conduct pediatric studies, it is probable that manufacturers will elect to conduct pediatric studies on those drugs for which the incentives are most valuable, i.e., on drugs with the largest adult sales. This may leave unstudied drugs that are greatly needed to treat pediatric patients, but that have smaller markets. Manufacturers may also elect not to study drugs that require study in neonates, infants and young children, because studies of these age groups are particularly difficult and may require the development of new pediatric formulations. In addition, FDAMA provides exclusivity to a manufacturer who conducts a requested study, even if the results of the study are inconclusive and do not provide useful information on how to use the drug in children. Finally, FDAMA does not require manufacturers who conduct pediatric studies to put the information gained into their drug labels. FDA believes that the final rule will address many of the gaps left by the FDAMA incentives. Studies conducted under the rule are entitled to 6 months of exclusivity under FDAMA if they otherwise satisfy the terms of the statute.

8. Have children been at risk in the past?

The lack of adequate pediatric labeling has resulted in the use of many products that have only been tested for adults, causing an increased risk of inappropriate and unexpected adverse effects. (For example, there were deaths that resulted in neonates from chloramphenicol, an antibiotic. Other cases in which inadequately studied drugs have resulted in serious adverse effects in pediatric patients include 1) seizures and cardiac arrest caused by bupivacaine toxicity, a local anaesthetic; 2) development of colonic strictures in pediatric cystic fibrosis patients after exposure to high-dose pancreatic enzymes; 3) hazardous interactions between erythromycin, an antibiotic, and midazolam, a short term anaesthetic; 4) teeth staining from the antibiotic tetracycline; 5) nuclear jaundice, a skin condition caused by sulfa drugs; and 6) withdrawal symptoms following prolonged administration of fentanyl, a pain killer used as an adjunct to anesthesia in infants and small children. These cases occurred from the 1950's through the 1990's.) Also, sometimes useful drugs not have been used in children because their effects in children were uncertain.

9. How many drugs that are commonly used in children lack this data?

FDA estimates that over one-half of the drugs approved in the past six years that had potential usefulness in kids had no pediatric labeling at the time of approval.

10. What kinds of drugs are commonly missing pediatric data?

Drugs such as anti-asthmatics, steroids, drugs to treat gastrointestinal problems, strong pain medications, antidepressants, anti-epilepsy drugs, and antihypertensives commonly lack appropriate pediatric labeling.

11. What drugs now have the best pediatric data?

Vaccines and antibiotics are the most adequately labeled drugs for children.

12. How many products will be affected by the rule?

FDA estimates that about 80 drugs and biological products will be studied in children under this regulation per year. (FDA estimates that a large proportion of these would probably have been studied voluntarily under the FDAMA incentives, although perhaps not as early.) The rule also gives the agency authority to review drugs already on the market to determine which ones should have pediatric studies. FDA intends to see whether manufacturers respond to the FDAMA incentives for conducting pediatric studies on marketed drugs before imposing any requirements on this category of products.

13. Does this regulation cover all drugs?

It covers all drugs and biological products that are used in a substantial number of pediatric patients or that will provide a meaningful therapeutic benefit to children. If a manufacturer shows

that a drug will not be used in a substantial number of pediatric patients and will not provide a meaningful therapeutic benefit to children, the pediatric testing requirement will be waived.

FDA will also waive the requirement if (1) the drug is likely to be unsafe or ineffective in children; (2) it is impossible or highly impractical to study the drug in children, because, e.g., the pediatric population is too small or geographically dispersed, or (3) reasonable efforts to develop a pediatric formulation (if one is needed) have failed.

14. How will these waivers work and won't they make the regulation meaningless?

The waivers are only intended to be used in those cases in which the drug would not be widely used and would not represent a meaningful benefit over existing treatment or where the studies are impossible or highly impractical or pose undue risks to pediatric patients.

15. What do doctors do when they don't have adequate pediatric safety and effectiveness information?

Many physicians rely on referenced pediatric handbooks for dosing and use information. (This information may or may not be based on adequate testing.) Others are reluctant to prescribe certain products to children without adequate pediatric labeling on the product.

16. Why haven't companies provided this information in the past?

Some companies do provide this information. However, pediatric labeling has not been required until now. Lack of familiarity with pediatric studies, need for a pediatric formulation, and cost may account for the lack of adequate pediatric information.

17. Would pediatric study participants' lives be at risk if they are entered in studies before all the data on adults are collected?

Pediatric patients will not be enrolled in studies until enough data on the drug have been obtained in adults and in animals so that the risk to the pediatric patients does not outweigh the potential benefits. Children are currently entered into studies of some drugs, for example of antibiotics, before the drugs are approved in adults. The considerations that will determine when enough data have been collected in adults to begin pediatric studies under the rule are the same as those currently used in deciding when to begin studies in children. The timing of pediatric studies will depend, among other things, on the type of drug being studied, the severity of the disease for which it will be used, the availability of other adequate treatments, and what is known about the safety of the drug.

18. How much will this cost drug manufacturers?

The costs of pediatric studies will be less than 1% of the total costs of developing a drug.

Although some drugs may require more than one study, e.g., for different pediatric age groups, FDA estimates that an individual pediatric study costs between \$100,000 to \$150,000. FDA also estimates that if a company must produce a pediatric formulation, the new formulation an average of \$1,000,000. FDA estimates that the total annual industry costs will be approximately \$47 million per year (for an industry with domestic U.S. sales in excess of \$66 billion per year). FDA also estimates that the benefits of the rule will exceed \$100,000,000 in reduced health care costs for children.

FDA has also developed a rough estimate that the FDAMA incentives will be worth approximately \$350-\$400 million/year to the pharmaceutical industry.

19. Will drug prices increase as a result of this regulation?

Because the cost of pediatric studies to manufacturers is expected to be small, it is anticipated that there will be no significant price increases to patients.

20. What kind of "legal action" can FDA take to force companies to provide this data on approved drugs?

FDA can go to court and ask the court to order the company to comply with the regulations. If the company does not comply, the court can impose penalties.

21. Why doesn't it cover medical devices? Do we not have this kind of problem with medical device pediatric data?

Once the agency gains experience in requiring pediatric studies for drugs and biologics, it will assess the need for such labeling for devices.

22. What kind of improvement can we expect in our children's health as a result of this regulation?

We expect safer and more effective medicines for children. The primary benefits expected are the reductions in avoidable adverse drug reactions and under or over treatments that would result from better informing health care practitioners about whether, and in what dosages, a given drug was safe and effective for use in children.

23. When will this regulation go into effect?

The rule becomes effective 120 days after publication in the Federal Register. Manufacturers of new drug and biologic products who are required to conduct studies under the rule will have 2 years from the date of publication to comply with the pediatric study requirement. FDA will not delay the approval of any applications otherwise ready to be approved for adults while awaiting the submission of pediatric studies required under the rule.

24. When can parents expect that information to support safe and effective use of products in children will become available?

We believe that, in some cases, the information already exists and the drug companies merely need to analyze and compile it. In these cases, the information can be made available on the labeling of the products fairly quickly. In other cases, studies need to be conducted. Under the requirements of our 1994 regulation, where the effects of the product and the disease for which it is indicated are sufficiently similar in both adults and children, the studies needed can be done within one year.

DRAFT

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 312, 314, and 601

[Docket No. 97N-0165]

RIN 0910-AB20

Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing new regulations requiring pediatric studies of certain new and marketed drug and biological products. Most drugs and biologics have not been adequately tested in the pediatric subpopulation. As a result, product labeling frequently fails to provide directions for safe and effective use in pediatric patients. This rule will partially address the lack of pediatric use information by requiring that manufacturers of certain products provide sufficient data and information to support directions for pediatric use for the claimed indications.

DATES: Effective date. The regulation is effective (insert date 120 days after date of publication in the FEDERAL REGISTER).

Compliance dates. Manufacturers must submit any required assessments of pediatric safety and effectiveness 20 months after the effective date of the rule, unless the assessments are waived or deferred by FDA.

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SUPPLEMENTARY INFORMATION:

I. Introduction

In the FEDERAL REGISTER of August 15, 1997 (62 FR 43900) (hereinafter referred to as the proposal), FDA proposed to require that manufacturers of certain new and marketed drugs and biologics conduct studies to provide adequate labeling for the use of these products in children. As described in the proposal, children are subject to many of the same diseases as adults, and are, by necessity, often treated with the same drugs and biological products as adults. However, many drugs and biological products marketed in the United States that are or could be used in children are inadequately labeled for use in

pediatric patients or for use in specific pediatric subgroups (Refs. 1 and 2). Indeed, many of the drugs and biological products that are widely used in pediatric patients carry disclaimers stating that safety and effectiveness in pediatric patients have not been established (Refs. 2 and 3). Safety and effectiveness information for some pediatric age groups is particularly difficult to find. For example, there is almost no information on use in patients under 2 years of age for most drug classes (Ref. 1).

As described in more detail in the proposal, the absence of pediatric labeling information poses significant risks for children. Inadequate dosing information exposes pediatric patients to the risk of adverse reactions that could be avoided with an appropriate pediatric dose. The lack of pediatric safety information in product labeling exposes pediatric patients to the risk of age-specific adverse reactions unexpected from adult experience. The proposal cited reports of injuries and deaths in children resulting from use of drugs that had not been adequately tested in the pediatric population. The absence of pediatric testing and labeling may also expose pediatric patients to ineffective treatment through underdosing, or may deny pediatric patients therapeutic advances because physicians choose to prescribe existing, less effective medications in the face of insufficient pediatric information about a new medication. Failure to develop a pediatric formulation of a drug or

biological product, where younger pediatric populations cannot take the adult formulation, may also deny pediatric patients access to important new therapies, or may require pediatric patients to take the drug in extemporaneous formulations that may be poorly or inconsistently bioavailable.

The proposed rule described previous steps taken by FDA in recent years to address the problem of inadequate pediatric testing and inadequate pediatric use information in drug and biological product labeling. FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research have implemented a "Pediatric Plan" designed to focus attention on, and encourage voluntary development of, pediatric data both during the drug development process and after marketing. In addition, in the FEDERAL REGISTER of December 13, 1994 (59 FR 64240) (hereinafter referred to as the 1994 rule), FDA issued a regulation requiring manufacturers of marketed drugs to survey existing data and determine whether those data were sufficient to support additional pediatric use information in the drug's labeling. Under the 1994 rule, if a manufacturer determines that existing data permit modification of the label's pediatric use information, the manufacturer must submit a supplemental new drug application (NDA) to FDA seeking approval of the labeling change.

Although the preamble to the 1994 rule recognizes FDA's authority to require drug and biological product manufacturers to

conduct pediatric studies on a case-by-case basis, the rule does not impose a general requirement that manufacturers carry out studies when existing information is not sufficient to support pediatric use information. Instead, if there is insufficient information to support a pediatric indication or pediatric use statement, the rule requires the manufacturer to include in the product's labeling the statement: "Safety and effectiveness in pediatric patients have not been established."

The response to the 1994 rule has not substantially addressed the lack of adequate pediatric use information for marketed drugs and biological products. Pediatric labeling supplements were submitted for approximately 430 drugs and biologics, a small fraction of the thousands of prescription drug and biological products on the market. Of the supplements submitted, approximately 75 percent did not significantly improve pediatric use information. Over half of the total supplements submitted simply requested the addition of the statement "Safety and effectiveness in pediatric patients have not been established." Others requested minor wording changes or submitted unorganized, unanalyzed collections of possibly relevant data. Approximately 15 percent (approximately 65) of the supplements provided adequate pediatric information for all relevant pediatric age groups, and another 8 percent (approximately 35) provided adequate pediatric information for some but not all relevant age groups.

The absence of adequate pediatric use information remains a problem for new drugs and biologics as well as for marketed products. The proposal presented data from 1988 through the 1990's showing that the percentage of new products entering the marketplace with adequate pediatric safety and effectiveness information has not increased in the last decade.

For example, FDA compared the number of new molecular entities (NME's) approved in 1991 and 1996 with potential usefulness in pediatric patients and looked at the adequacy of pediatric labeling for those drugs. Fifty-six percent (9/17) of the NME's approved in 1991 with potential usefulness in pediatric patients had some pediatric labeling at the time of approval. In 1996, only 37 percent (15/40) of the NME's with potential usefulness in pediatric patients had some pediatric labeling at the time of approval. For both 1991 and 1996, those drugs counted as having pediatric labeling may not have been studied in all age groups in which the drug was potentially useful. The manufacturers of an additional 7 of the 1991 drugs and 17 of the 1996 drugs promised to conduct pediatric studies after approval. Since publication of the proposal, figures for 1997 NME's have become available. In 1997, 39 NME's were approved. Twenty-seven had potential usefulness in pediatric patients, and 33 percent of these (9/27) had some pediatric labeling at the time of approval. Postapproval studies were requested or promised for an additional six. It is uncertain how many of the commitments made for

postapproval studies of the 1996 and 1997 drugs will result in pediatric labeling. Of the seven NME's approved in 1991 for which sponsors made commitments to conduct postapproval pediatric studies, pediatric labeling has been added to only one. This figure reflects both studies that resulted in positive labeling, i.e., safety and dosing information, and studies that resulted in warnings against pediatric use. It does not reflect studies that failed to provide any useful information about pediatric use or studies that were completed but the sponsor failed to seek a change in its pediatric use labeling.

These data indicate that voluntary efforts have, thus far, not substantially increased the number of products entering the marketplace with adequate pediatric labeling. FDA has therefore concluded that additional steps are necessary to ensure the safety and effectiveness of drug and biological products for pediatric patients. This rule requires the manufacturers of new and marketed drugs and biological products to evaluate the safety and effectiveness of the products in pediatric patients, if the product is likely to be used in a substantial number of pediatric patients or would provide a meaningful therapeutic benefit to pediatric patients over existing treatments.

In addition to issuing this rule, FDA has initiated other actions that it hopes will encourage the development of adequate pediatric use information. FDA plans to develop additional guidance on how to develop effectiveness, safety, and dosing

information to support pediatric labeling. The agency also supported a provision in the reauthorized Prescription Drug User Fee Act (PDUFA) eliminating user fees for pediatric supplements to encourage the submission of these supplements.

Finally, FDA has issued a guidance document entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," describing the kinds of studies that can support effectiveness in supplemental or original applications. In that document, FDA provides guidance to manufacturers on the circumstances in which FDA may approve an initial or supplemental claim in which substantiation of the results of an adequate and well-controlled trial is provided by information other than a second adequate and well-controlled trial precisely replicating the first trial, or the circumstances in which studies without the extensive documentation ordinarily required could be utilized. This guidance will often be relevant to the data needed to support claims in a pediatric population.

Since the issuance of the proposal, Congress has enacted a bill that has an impact on pediatric studies of certain drugs. The Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105-115) contains provisions that establish economic incentives for conducting pediatric studies on drugs for which exclusivity or patent protection is available under the Drug Price Competition and Patent Term Restoration Act (Pub. L. 98-417) and the Orphan Drug Act (Pub. L. 97-414). These

provisions extend by 6 months any existing exclusivity or patent protection on a drug for which FDA has requested pediatric studies and the manufacturer has conducted such studies in accordance with the requirements of FDAMA. FDAMA also specifically recognizes FDA's intention to require pediatric studies by regulation and extends by 6 months any existing exclusivity or patent protection on a drug whose manufacturer submits pediatric studies in compliance with this rule, if the studies meet the completeness, timeliness, and other requirements of section 505A. Under FDAMA, a manufacturer who submits pediatric studies required under this rule may receive a 6-month extension of exclusivity or patent protection granted to the manufacturer for that drug.

Although FDA expects the exclusivity offered by FDAMA to provide a substantial incentive for sponsors to conduct some pediatric studies, the agency nonetheless believes that this final rule is necessary to significantly increase the number of drug and biological products that have adequate labeling. Certain limitations on the scope and effect of the exclusivity offered by FDAMA are likely to leave significant gaps in pediatric labeling. For example, because FDAMA exclusivity applies only to products that have exclusivity or patent protection under the Drug Price Competition and Patent Term Restoration Act and the Orphan Drug Act, it provides no incentive

to conduct studies on certain categories of products, including most antibiotics, biologics, and off-patent products.

In addition, the voluntary nature of the incentive provided by FDAMA is likely to leave many drugs, age groups, and indications unstudied. Given limited resources to conduct pediatric studies, it is probable that manufacturers will elect to conduct pediatric studies preferentially on those drugs for which the incentives are most valuable, i.e., on drugs with the largest sales. This may leave unstudied drugs that are greatly needed to treat pediatric patients, but that have smaller markets. For similar reasons, manufacturers are less likely to seek FDAMA exclusivity by conducting studies on drugs that require studies in neonates, infants, or young children. The youngest pediatric populations are more difficult to study and may require pediatric formulations, making pediatric studies of these groups more expensive, thereby reducing the value of the incentives provided by FDAMA. Thus, where there is a great medical need for data on drugs with relatively small markets or for studies on neonates, infants, or young children, it may be necessary to require the collection of such data, rather than rely on incentives.

Finally, manufacturers are eligible for FDAMA exclusivity when they submit a study to FDA that is consistent with FDA's written request for such a study. The study results are not required to provide useful information on pediatric use (e.g.,

the results may be inconclusive), and the sponsor is not required to obtain approval of a supplement adding the information gained in the study to the drug's label. Thus, FDAMA provides no guarantee that the studies conducted under the statute will result in improved pediatric labeling.

For these reasons, FDA believes that there remains an important need for this rule. FDA has concluded, however, that with respect to already marketed drugs eligible for exclusivity under FDAMA, the publication of the list required by section 505A(b) and the availability of pediatric exclusivity may diminish the need to exercise the agency's authority to require studies. Under the rule, FDA has discretion whether to require studies of marketed drugs (see § 201.23 (21 CFR 201.23)). FDA believes that, in exercising its discretion under § 201.23, it is appropriate to determine whether manufacturers will undertake the needed studies voluntarily. FDA will therefore allow an adequate opportunity for manufacturers voluntarily to submit studies for drugs listed by FDA as having a high priority. If, following such an opportunity, there remain marketed drugs for which studies are needed and the compelling circumstances described in the rule are met, the agency will consider exercising its authority to require studies. With respect to marketed drugs and biologics that are not eligible for exclusivity under FDAMA, FDA intends to exercise its authority to require studies as of the effective date of the rule in the circumstances described in the

regulation. FDA emphasizes that the appearance of a drug or biologic on the list published under section 505A(b) carries no implication that FDA will require studies on that drug or biologic under this rule. FDA intends to reserve its authority to require studies of marketed drugs and biologics to situations in which the compelling circumstances described in the regulation are present.

FDA intends to issue further regulations and guidance implementing the pediatric exclusivity provisions of FDAMA, which will, among other things, provide guidance on the interaction of this rule and FDAMA exclusivity.

II. Highlights of the Final Rule

This final rule is designed to ensure that new drugs and biological products contain adequate pediatric labeling for the approved indications at the time of, or soon after, approval. The final rule establishes a presumption that all new drugs and biologics will be studied in pediatric patients, but allows manufacturers to obtain a waiver of the requirement if the product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients. The rule also authorizes FDA to require pediatric studies of those marketed drugs and biological products that: (1) Are used in a substantial number of pediatric patients for the claimed indications, and where the absence of adequate labeling could

pose significant risks; or (2) would provide a meaningful therapeutic benefit over existing treatments for pediatric patients, but whose labels do not provide adequate information to support safe and effective use in pediatric patients for the approved indications.

A. Scope of Rule

The proposed rule would have required an application for a drug classified as a "new chemical entity" or a new (never-before-approved) biological product to contain safety and effectiveness information on relevant pediatric age groups for the claimed indications. Based upon comments observing that changes in already marketed chemical entities, such as new indications or dosage forms, can have as much or more therapeutic significance for pediatric patients than the original product, the final rule expands the scope of the rule to include new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration for which an applicant seeks approval. The final rule does not, however, require the submission of pediatric data for a drug for an indication or indications for which orphan designation has been granted under section 526 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360bb).

B. Types of Studies Needed

As described in the 1994 final rule, gathering adequate data to establish pediatric safety and effectiveness may not require

controlled clinical trials in pediatric patients. Where the course of the disease and the product's effects are similar in adults and pediatric patients, FDA may conclude that pediatric safety and effectiveness can be supported by effectiveness data in adults together with additional data, such as dosing, pharmacokinetic, and safety data in pediatric patients. The rule also does not necessarily require separate studies in pediatric patients. In appropriate cases, adequate data may be gathered by including pediatric patients as well as adults in the original studies conducted on the product.

The specific pediatric information needed in each case will depend on the nature of the application, what is already known about the product in pediatric populations, and the underlying disease or condition being treated. The final rule requires an assessment of safety and effectiveness in pediatric patients only for the indications claimed by the manufacturer. It does not require a manufacturer to study its product for unapproved or unclaimed indications, even if the product is widely used in pediatric patients for those indications. In the proposed rule, the pediatric study requirement for drugs was contained in § 314.50(g) (21 CFR 314.50(g)). In the final rule, the requirement is located in new § 314.55, because § 314.50 does not contain other specific study requirements. The location of the requirement for biological products (§ 601.27 (21 CFR 601.27)) remains unchanged in the final rule.

C. Age Groups

The final rule requires pediatric studies in each age group in which the drug or biological product will provide a meaningful therapeutic benefit or will be used in a substantial number of pediatric patients for the indications claimed by the manufacturer. The relevant age groups will, however, be defined flexibly, depending on the pharmacology of the drug or biological product, rather than following the fixed age categories defined in the 1994 rule and identified in the preamble to the proposed rule. For drugs and biological products that offer a meaningful therapeutic benefit, the rule requires manufacturers to develop pediatric formulations, if needed, for those age groups in which studies are required. Manufacturers may, however, avoid this requirement if they demonstrate that reasonable attempts to develop a pediatric formulation have failed.

D. Not-Yet-Approved Products

1. Deferral of Studies Until After Approval

The final rule permits the submission of pediatric information to be deferred until after approval if there is an adequate justification for deferral, e.g., because pediatric studies should not begin until some safety and/or effectiveness information on adults has been collected, or awaiting the completion of pediatric studies would delay the availability of a product to adults. When trials should begin in particular cases, and whether deferral will be necessary, will depend upon the

seriousness of the disease for which the drug or biological product is indicated, the need for the product, the amount of safety and effectiveness data available, and what types of pediatric studies are needed.

In general, FDA expects that studies of drugs or biological products for diseases that are life threatening in pediatric patients and that lack adequate therapy could begin earlier than studies of drugs that are less urgently needed, ordinarily as early as the availability of preliminary safety data in adults (frequently referred to as phase 1 data), even if data from well-controlled studies are not yet available. For less critical drugs and biologics, pediatric studies could ordinarily begin when additional safety and/or effectiveness data from the initial well-controlled trials in adults (frequently referred to as phase 2 data) became available. Of course, studies of products for exclusively pediatric diseases ordinarily need not await the development of adult data. The timing of individual pediatric studies will, however, necessarily depend on the specific information available about the product in question. For example, a study of a noncritical drug in adolescents might begin after the initial safety studies in adults, if all the parties involved agreed that initiation was appropriate in light of the results of the adult and animal safety studies.

In other cases, studies should not begin in pediatric patients until significantly more adult data are collected. For

example, FDA does not believe that early study or use in pediatric patients is appropriate for some so-called "me-too" drugs that are expected to be widely used but are members of a drug class that already contains an adequate number of approved products with pediatric labeling. Such drugs may not have been shown to provide any benefit over other products in the same class, and may introduce new risks that are not apparent until the drug has been in wide use after marketing. Studies of such drugs will therefore usually be deferred until the safety profiles of the drugs are well established through marketing experience. To encourage use of properly labeled drugs in pediatric patients, FDA may require the pediatric use section of the approved labeling of such a me-too drug to contain a statement recommending preferential use of other drugs that are adequately labeled for pediatric use.

2. Waiver of the Study Requirement

The pediatric study requirement applies to all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration, unless FDA waives the requirement. Under criteria established in the rule, FDA may waive the study requirement for some or all pediatric age groups. The burden is on the sponsor to justify a waiver. A waiver will be granted if the waiver request demonstrates that the product meets both of the following conditions: (1) The product does not represent a meaningful therapeutic benefit for

pediatric patients over existing treatments, and (2) the product is not likely to be used in a substantial number of pediatric patients. There was some confusion in the comments on the proposed rule over these waiver criteria. FDA emphasizes that the study requirement applies to a product that offers a meaningful therapeutic benefit even if it is not used in a substantial number of pediatric patients, and vice versa.

In response to comments, FDA has refined its definitions of "meaningful therapeutic benefit" and "substantial number of pediatric patients." To define meaningful therapeutic benefit for both drugs and biologics covered by this rule, FDA has relied, in part, on CDER's current administrative definition of a "Priority" drug, applied to pediatric populations. The administrative definition of "Priority" products for biologics relies on different criteria (Ref. 2). Use of CDER's Priority drug definition to help define "meaningful therapeutic benefit" is not intended to affect the administrative definition of a Priority biologic. The Priority classification for drugs is determined based on CDER's estimate, at the time of NDA submission, of a drug's therapeutic, preventive, or diagnostic value. A Priority drug is defined as one that, if approved, would be a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products approved for that use. In establishing meaningful therapeutic benefit for pediatric use, the comparison will be to other

products adequately labeled for use in the relevant pediatric population. If there are no such products, a new product would usually be considered to have a meaningful therapeutic benefit. Improvement over existing products labeled for pediatric use 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. Evidence of improvement over existing therapies need not in all cases come from head-to-head trials.

To help ensure that pediatric patients have a sufficient range of treatments available, a product will also be considered to provide a meaningful therapeutic benefit if it is in a class of products or for an indication for which there is a need for additional therapeutic options, notwithstanding the fact that it might not be a priority drug. In contrast to the range of therapies for a given indication often available to adults, there are relatively few instances in which therapeutic alternatives are studied and labeled for pediatric patients. For some diseases, however, it is therapeutically important to have a range of available treatment options, e.g., because there are frequent treatment failures. The Priority definition would cover the first product labeled for pediatric use, but might not cover the second or third product for a given indication or in a given

class, if the subsequent product did not offer an advantage over existing therapies. 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 will seek further guidance on applying this criterion from a panel of pediatric experts.

Thus, new products will meet the definition of a meaningful therapeutic benefit if: (1) They provide a significant improvement over existing adequately labeled therapies; or (2) if they are indicated for diseases or conditions, or are in product classes, in which there are currently few products labeled for pediatric use and more therapeutic options are needed. FDA expects that over time, as the number of products adequately labeled for pediatric patients grows, the number of new products meeting the second criterion will diminish. FDA emphasizes that the addition of the second criterion for defining meaningful therapeutic benefit under this final rule is not intended to alter the definition of a Priority drug, and that products meeting the second criterion will not thereby be eligible for Priority status. FDA also notes that the rule's definition of meaningful therapeutic benefit is intended to apply only in the pediatric study context.

FDA has also revised the proposed definition of "a substantial number of pediatric patients." Several comments argued that FDA should rely on the definition of a rare disease

in the Orphan Drug Act as a disease affecting fewer than 200,000 patients, because Congress could be said to have considered more than 200,000 a substantial number for purposes of developing a new indication. Developing adequate directions for use of a drug or biologic in pediatric populations usually represents a substantially smaller task than establishing the effectiveness and safety of a product in the first instance. Although in some cases, controlled trials may be needed, this will not often be the case and, where needed, a single controlled trial would usually suffice. More commonly, what will be needed would be safety experience and pharmacokinetic or pharmacodynamic studies. Reflecting this considerably smaller effort, FDA will use the percentage of the population under 16 years of age, calculated using recent U.S. Census data, (approximately 23 percent in 1998) (Ref. 3) and multiply 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 would currently be considered a substantial number. This definition of "a substantial number of pediatric patients" (percentage of population under 16 years of age multiplied by 200,000) has not been codified, however, and FDA may modify it, after consulting with a panel of pediatric experts. Any modification will be issued in a guidance document with an opportunity for comment.

FDA will also waive the pediatric study requirement where:

(1) The applicant shows that the required studies on the product are impossible or highly impractical because, for example, the population is too small or geographically dispersed; (2) the product is likely to be unsafe or ineffective in pediatric patients; or (3) reasonable efforts to develop a pediatric formulation (if one is needed) have failed.

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.

E. Marketed Products

The final rule is also intended to improve pediatric use information for already marketed drugs and biological products. The rule codifies FDA's authority, discussed in the 1994 rule, to require, in the compelling circumstances described in the regulation, that manufacturers of already marketed drugs and biological products conduct studies to support pediatric-use labeling for the claimed indications. The criteria for requiring studies of marketed products have been revised slightly in response to comments.

F. Early Discussions and Pre- and Postmarket Reports

The final rule contains provisions designed to encourage discussions of the need for pediatric studies early in the drug development process, as well as pre- and postmarketing reporting requirements designed to assist FDA in determining whether

pediatric studies are needed for particular products and whether required studies are being carried out with due diligence.

G. Pediatric Committee

Many comments on the proposed rule urged FDA to form a committee of outside experts to assist in various aspects of the implementation of the rule. FDA has concluded that such a panel could provide useful advice and experience. FDA will convene a panel of pediatric experts, including at least one industry representative, and seek its advice on a range of issues related to implementation of the rule, including: (1) The agency's implementation of all aspects of the final rule, including its waiver and deferral decisions; (2) which marketed drugs and biological products meet the criteria for requiring studies; (3) when additional therapeutic options are needed for a given disease or condition occurring in pediatric patients; (4) ethical issues raised by clinical trials in pediatric patients; (5) the design of trials and analysis of data for specific products or classes of products; and (6) issues related to the progress of individual studies.

H. Remedies for Violation of the Rule

For violations of this rule, FDA would ordinarily expect to file an enforcement action for an injunction, asking a Federal court to find that the product is misbranded under section 502 of the act (21 U.S.C. 352) or is an unapproved new drug under section 505(a) of the act (21 U.S.C. 355) or an unlicensed

biologic under section 351 of the Public Health Service Act, and to require the company to submit an assessment of pediatric safety and effectiveness for the product. Violation of the injunction would result in a contempt proceeding or such other penalties as the court ordered, e.g., fines. FDA does not intend, except possibly in rare circumstances, to disapprove or withdraw approval of a drug or biological product whose manufacturer violates requirements imposed under this rule.

III. Comments on the Proposed Rule

FDA received 54 written comments on the proposed rule from pediatricians, professional societies, parents, members of the pharmaceutical industry, organizations devoted to specific diseases, and patient groups. A significant majority of the comments, primarily those from pediatricians, professional societies, parents, organizations devoted to specific diseases, and patient groups, supported regulations requiring that drugs and biologics be studied in children. Many of these comments described the problems faced by the pediatric community and parents resulting from inadequate pediatric labeling and the absence of pediatric formulations, and argued that a pediatric study requirement was long overdue. Some comments, primarily those from the pharmaceutical industry, opposed a pediatric study requirement, arguing that existing voluntary measures and incentives were sufficient to ensure adequate pediatric labeling.

Finally, a number of comments addressed FDA's legal authority to require pediatric testing of drugs and biologics.

FDA also held a day-long public hearing on October 27, 1997, in Washington, DC, at which recognized experts in the field, members of the pharmaceutical industry, and other interested parties were given an opportunity to discuss the issues raised by the proposed rule. There were three panels, each of which comprised representatives from industry, the pediatric community, organizations devoted to specific diseases, patient groups, and a bioethicist. The panels considered the following three issues: (1) When pediatric studies are needed, (2) what types of studies are needed, and (3) special challenges in testing pediatric patients. Those who spoke were nearly unanimous in their support for some kind of regulation requiring pediatric studies of some drugs and biologics. There was, however, a wide range of views on which drugs and biologics should be the subject of required studies and on how the requirement should be implemented.

Many written and oral comments raised specific issues for consideration by the agency. These comments are addressed below.

A. Purpose of Rule

1. FDA received many comments arguing that this rule is needed to ensure adequate medical care for children. Many comments from pediatricians stated that they regularly must prescribe to young children drugs that are not labeled for

children under 6 or even 12, and for which pediatric dosage forms do not exist. One comment stated that, without adequate testing and labeling, physicians must estimate appropriate pediatric doses, and that even at "appropriate" doses, it is not known whether use in children is as safe as use in adults. One comment argued that the absence of pediatric labeling puts children at greater risk for adverse drug reactions (ADR's) and therapeutic failures than adults. According to another comment, most common and severe ADR's in pediatric patients would be eliminated by adequate testing, and that perhaps 2 percent of all pediatric hospitalizations are due to ADR's. One comment concluded that the failure to conduct pediatric studies results in a different standard of care for children and adults in this country.

A comment from a pharmaceutical trade association argued, however, that most of the toxicity problems identified by FDA as caused by inadequate pediatric labeling were from the 1950's and that these "dated" examples are not relevant to current practice. As an example, the comment cited chloramphenicol, a drug referred to by FDA in the proposed rule because, when it was used in the 1950's in neonates without adequate testing, it was responsible for many infant deaths (Ref. 4). According to the comment, it is now known that chloramphenicol can be used in neonates if the dose is correct. The comment also stated that practicing physicians have access to adequate dosing information from case reports in the medical literature.

FDA agrees that the absence of adequate pediatric labeling puts pediatric patients at risk for adverse drug reactions and ineffective dosing. FDA believes that the reference to new dosing information that permits use of chloramphenicol in infants illustrates the need for this final rule. Had adequate safety and dosing information been available earlier, many babies' lives could have been saved. Instead, adequately supported dosing information was not available until after the drug had been used in a large number of babies, with tragic consequences. FDA also disagrees with the comment that the remaining reports cited in the proposal of unexpected toxicity in pediatric patients from inadequately tested drugs are "dated." Contrary to the assertion in the comment, a majority of these reports are from the 1980's and 1990's (Refs. 5 through 14).

FDA also does not believe that case reports scattered through the medical literature are an adequate substitute for organized and complete pediatric labeling information. To the extent that published experience is informative and credible, it should be used to improve labeling. The comments received from pediatricians reflect their view that there is often no adequately supported dosing and safety information for the drugs they use routinely in their patients. Even where case reports are available, they describe a limited number of pediatric patients and cannot provide sufficient information to establish the safety profile of a drug in pediatric patients.

2. Some comments argued that pediatric studies are needed because differences between children and adults can make extrapolation from adult data treacherous. One comment pointed out that research on antiarrhythmics in pediatric patients has revealed many surprises in dosing and side effects. For example, drugs that bind to milk may cause safety or effectiveness problems in pediatric patients not detected in adults.

FDA agrees that pediatric dosing cannot necessarily be extrapolated from adult dosing information using an equivalence based either on weight milligram/kilogram (mg/kg) or body surface area (mg/m²). There are potentially significant differences in pharmacokinetics, or unique drug-food interactions, that may alter a drug's blood levels in pediatric patients. Moreover, there can be pharmacodynamic differences between adults and pediatric patients.

3. Several comments argued that voluntary measures have not resulted in a significant increase in pediatric labeling, and that new products continue to enter the market without adequate, or any, pediatric labeling. Pediatricians, professional societies, parents, organizations devoted to specific diseases, and patient groups provided many examples of diseases and drug classes for which pediatric labeling was long-delayed, inadequate, or nonexistent. Acquired immune deficiency syndrome (AIDS) drugs were frequently cited as an example of the industry's failure to obtain adequate pediatric labeling at or

near the time of approval. One comment pointed to protease inhibitors, which are theoretically most effective in newborns but have not been tested or approved for use in this group. Even for older children, the comment observed that it has taken over a year after adult approval to obtain pediatric labeling for these life-saving drugs. Another comment stated that the absence of drugs for human immunodeficiency virus (HIV) infection that are appropriately labeled and formulated for pediatric patients causes parents to give children inappropriate doses, sometimes giving up part of their own dose if the child's physician will not prescribe it.

Other comments pointed out that epilepsy is considered a pediatric disease but claimed that many new epilepsy drugs are approved without information for use in pediatric patients. These comments urged that anti-epileptic drugs be added to the list of drug classes with inadequate labeling. A comment from a specialist in pulmonary medicine stated that although asthma is a common disease in pediatric patients, adult formulations are often released first, leaving pediatric patients without effective treatments. Other comments observed that not one of the standard immunosuppressive medications used in pediatric patients has been tested in pediatric patients. One comment contended that poor information about the pharmacokinetics of these drugs in pediatric patients has led to inadequate dosing to achieve effectiveness and possibly unnecessary toxicity.

The American Psychiatric Association commented that significant psychiatric diseases are increasingly diagnosed in pediatric patients, who may be treated with drugs despite the lack of pediatric labeling. According to this comment, most psychoactive medications are underutilized in pediatric patients due to the lack of pediatric labeling and to fear of overdosing. In the case of anti-hyperactivity drugs, however, the comment states that as many children are overtreated as undertreated, especially among pre-school age children. A comment from the National Institute of Mental Health (NIMH) stated that the rule was much needed to provide essential data on the safety and effectiveness of psychiatric medications in pediatric patients. This comment attached seven NIMH reviews of the existing data on psychotropic medications for pediatric patients, identifying many critical knowledge gaps that remain to be addressed by pediatric research.

One comment stated that pediatric nephrologists frequently prescribe drugs to pediatric patients for life-threatening conditions, including antihypertensive medications, diuretics, lipid-lowering agents, and immunosuppressive agents, even for pediatric patients less than 2 years of age, without benefit of formal studies. This comment further stated that drug therapy for chronic conditions like kidney failure is currently based only on experience gained from drug usage in children after approval for the indication in adults, and that discovering

"inadequate dosing or severe side effects by empiric use of these drugs is not desirable or safe." Another comment provided the results of a survey of 4,898 pediatric patients with end-stage renal disease on the medications they receive. Ninety-seven percent received prednisone or prednisolone, 91 percent received cyclosporine, and 84 percent received azathioprine. According to the comment, none of these drugs was studied in pediatric patients and no information on the pharmacokinetics of these drugs in pediatric patients is available.

In contrast, several comments from the pharmaceutical industry argued that voluntary measures, the 1994 rule, and the incentives provided by FDAMA are adequate to assure adequate pediatric labeling and that FDA has not given these steps sufficient time to work. Several comments argued that to obtain pediatric studies, FDA should use encouragement and early discussion with sponsors, together with incentives, rather than imposing new requirements. These comments contended that sponsors should make "phase 4 commitments" (commitments to conduct pediatric studies after approval) and FDA should track these commitments. According to one comment, these methods have not been systematically used by FDA. According to another comment, FDA did not describe its present experience in getting manufacturers to conduct pediatric studies. Other comments argued that FDA has not allowed the 1994 rule sufficient time to produce results and that the agency should wait until it has

reviewed and acted upon all supplements submitted under that rule before imposing new requirements. One comment contended that if the 1994 rule was successful in producing pediatric labeling for marketed drugs, the new rule should apply only to new drugs. One comment argued that incentives, including exclusivity, waiver of user fees, tax credits, and expedited reviews of pediatric supplements, and liability protection for research physicians, Institutional Review Boards (IRB's), universities, pharmaceutical firms, and parents, are the best means of obtaining pediatric labeling. A few comments argued that excessive litigation will follow imposition of this rule.

Two comments argued that the 53 NME's approved in 1996 demonstrate that pediatric labeling efforts by the industry are adequate, and that new requirements are not needed. Although the figures used in the 2 comments do not agree exactly, these comments stated that 20 or 21 of the 53 have potential for pediatric use. According to these comments, of these, 4 have approved pediatric labeling, 14 have planned or ongoing studies, 1 is switching to over-the-counter (OTC) use, and 1 or 2 have no immediate plans for pediatric labeling activities. One comment contended that, between 1990 and 1997, a 28 percent increase occurred in the number of new drugs in development for pediatric uses, but provided no data to support this claim.

FDA believes that the current state of pediatric labeling for drugs and biologics in the United States, as amply

illustrated by comments from the pediatric community, is unsatisfactory. The agency's failure to obtain a significant increase in labeling for either new or marketed drugs or biologics through other measures implemented over the last several years demonstrates the need for a requirement that sponsors conduct pediatric studies of drugs and biologics that represent a meaningful therapeutic benefit to pediatric patients or that will be widely used in pediatric patients. As described in section I of this document, the response to the 1994 rule has not produced a significant improvement in pediatric labeling for marketed drugs. FDA received labeling supplements only for a small fraction of the drugs and biologics on the market. Of those supplements it did receive, over half of the submissions merely sought to add a statement to the product's labeling that "safety and effectiveness in pediatric patients have not been demonstrated," and less than a quarter provided adequate pediatric information for some or all relevant age groups.

The agency's experience in attempting to obtain pediatric labeling for new drugs entering the marketplace through voluntary measures has also been disappointing. As described in the proposal, the percentage of NME's with adequate pediatric labeling has not increased since 1991, when the agency began systematic efforts to obtain better pediatric labeling. Although the number of requests by the agency and commitments by sponsors to conduct phase 4 (postapproval) pediatric studies may have

increased, these requests and commitments have so far infrequently resulted in pediatric labeling. Table 1 of this document displays the results of commitments or requests to conduct pediatric studies postapproval between 1991 and 1996. FDA notes that the table does not reflect any labeling supplements under review.

Table 1.--Pediatric Labeling							
Status of pediatric labeling	1991	1992	1993	1994	1995	1996	Totals
NME's approved	30	25	25	22	28	53	183
Pediatric studies not needed	14	11	11	7	14	13	70
Label includes some pediatric use information or pediatric studies complete at time of approval	9	4	5 ¹	6 ¹	5	15	44
Postapproval pediatric studies promised or requested	7	10	10 ²	10 ^{2,3}	10 ²	17	64
Pediatric labeling added after approval	1	0	2	4	2	2	11

¹ In one case, pediatric use information provided for one of two approved indications

² In one case, pediatric data requested for second of two approved indications

³ In one case, pediatric data requested for additional age groups

As Table 1 of this document reflects, FDA's figures disagree with those of the comments for the number of 1996 NME's with potential for pediatric use, the number with some pediatric labeling at the time of approval and the number for which commitments or requests for postapproval studies have been made. The comments did not identify specific drugs, so it is not possible to determine why the two sets of figures conflict. Nevertheless, the historical experience reflected in the table suggests that most of the postapproval pediatric studies for which commitments were made for the 1996 NME's will not result in pediatric labeling. Of the 17 commitments to conduct pediatric studies in 1996, there have thus far been only 2 additions of pediatric labeling. Although some additional studies supporting labeling changes may be submitted in the future, the experience reflected in Table 1 of this document suggests that this will not be a large number. For example, the 18 promised or requested studies for the 1991 through 1993 cohorts have resulted in just 3 additions of pediatric labeling 5 to 7 years after approval. Thus, FDA does not agree that the experience with 1996 NME's demonstrates the adequacy of current efforts to obtain pediatric labeling.

None of the comments claiming that the rule will result in excessive litigation provided any evidence suggesting a

relationship between pediatric testing and increased litigation or liability. As shown in the number of NME's with pediatric labeling at the time of approval, a significant minority of drug and biologic manufacturers already conducts pediatric testing. FDA is aware of no evidence that excessive litigation has been associated with this testing.

With respect to the argument that the incentives provided by FDAMA will be sufficient to ensure adequate pediatric labeling, FDA believes that a mixture of incentives and requirements is most likely to result in real improvements in pediatric labeling. FDA is hopeful, e.g., that the FDAMA incentives will make more resources available for pediatric studies. As described earlier, FDA does not believe, however, that incentives alone will result in pediatric studies on some of the drugs and biologics where the need is greatest. The incentives provided by FDAMA are available only for drugs already by the exclusivity or patent protection provided by sections 505 and 526 of the act. Thus, the FDAMA incentives are not available for many already marketed drugs, or for many antibiotics or biologics. In addition, limited resources available to conduct pediatric studies and fiduciary obligations to shareholders may cause manufacturers to conduct pediatric studies preferentially on those drugs where the incentives are most valuable, rather than on those drugs or biological products where studies are most needed.

4. Two comments argued that the rule is inconsistent with a 1977 FDA document entitled "General Considerations for the Clinical Evaluation of Drugs in Infants and Children," which recommended, among other things, that "reasonable evidence of efficacy generally * * * be known before infants and children are exposed to [a drug]."

As described in more detail in section III.D of this document under "Deferral," FDA expects that for drugs and biologics other than those for life-threatening diseases without adequate treatment, clinical trials in pediatric patients will ordinarily begin no earlier than when initial data from well-controlled trials in adults (frequently referred to as phase 2 data) become available to ensure that reasonable preliminary evidence of safety and/or effectiveness is available before pediatric patients are exposed to the drug or biological product. How much evidence of safety or effectiveness is "reasonable evidence" that should be available before pediatric trials may begin will be determined on a case-by-case basis. Thus, FDA believes that this rule is substantially consistent with the 1977 document.

FDA notes that the 1977 document was based upon a report prepared for FDA under a contract with the American Academy of Pediatrics (AAP). The AAP is currently developing proposed revisions to this document concerning the types of data needed to support pediatric labeling. The 1977 document, which falls under

the general category of guidance documents, does not bind FDA or the public, but represents the agency's current thinking on a particular issue. Alternative approaches may be used if the alternative satisfies the requirements of the applicable statute and regulations (62 FR 8961, February 27, 1997) (Good Guidance Practices document). Until such time as an updated guidance on the clinical evaluation of drugs in infants and children is published, sponsors are encouraged to confer with the agency before initiating pediatric studies.

5. Several comments challenged FDA's use of the 1994 IMS National Disease and Therapeutic Index (NDTI) data on the 10 drugs used most frequently in pediatric patients without adequate labeling, arguing that the data incorrectly imply that physicians have no labeling information, when in fact prescribing information is now, or will be, available for most of the 10 drugs listed.

These comments misunderstand the purpose for which FDA cited the 1994 data. Those data provided a snapshot of the labeling information available to physicians for 10 widely used drugs at a given point in time. Even if additional information had been added to the labels of these drugs in the 4 years since the survey was conducted, there was none available during a year in which the drugs, together, were prescribed to pediatric patients over 5 million times. FDA notes, moreover, that, contrary to the suggestion in the comments, adequate labeling has been added for

only 1 of the 10 drugs for the age group described in the proposal.

6. Two comments disputed the estimated number of times their products were prescribed to pediatric patients. One manufacturer argued that the total units sold of Auralgan were less than the listed number of prescriptions. Another manufacturer disputed the estimates of Ritalin usage. This manufacturer also complained that it was not contacted by FDA about use of Ritalin despite the statement in the proposal that FDA had contacted the manufacturers of the top 10 drugs used without adequate labeling in pediatric patients.

Limitations on the data used to estimate number of prescriptions may have resulted in the discrepancy noted by the manufacturers of Auralgan or Ritalin. The number of prescriptions is estimated from data provided by IMS America, Ltd. IMS NDTI surveys a sample of physicians (more than 2,940 physicians representing 27 specialities) to determine the number of times that, during patient contacts, physicians mentioned specific drugs for particular age groups. Physician mentions may not correlate exactly with actual usage. In addition, the NDTI numbers taken from the sample of physicians are extrapolated to the nation as a whole, using a given formula. With respect to the claim that FDA has not contacted the manufacturer of Ritalin, FDA notes that it has scheduled meetings with the manufacturer to

discuss use of the drug in children, which have been canceled at the manufacturer's request.

7. One comment challenged FDA's use of quinolones as an example of a class of drug that does not need to be studied in pediatric patients. The comment claimed quinolones do need to be studied in pediatric patients because of their important use in cystic fibrosis patients.

FDA agrees that fluoroquinolones may provide important therapeutic benefits to patients with cystic fibrosis. At present, all approved fluoroquinolones are labeled with the following statement: "Safety and effectiveness in children and adolescents less than 18 years of age have not been established." In addition, the label includes a statement advising that the fluoroquinolones cause arthropathy in juvenile animals. Historically, the agency has recognized a potential therapeutic role for the fluoroquinolones in children with cystic fibrosis and hematology/oncology disorders. Indeed, FDA recently approved ciprofloxacin labeling containing a discussion of cystic fibrosis experience in the pediatric use subsection. These actions show that the agency recognizes that there may be a need to study fluoroquinolones in some pediatric patients.

8. One comment from a pharmaceutical company argued that serious ethical, legal, medical, and technical difficulties often prevent conducting pediatric studies. The comment cited difficulties in enrolling pediatric patients in sufficient

numbers, unwillingness of parents to enroll children, and the absence of pediatric patients with the disease near convenient and qualified study centers. According to the comment, studies have been successfully conducted in pediatric patients in the past where there was a medical need for the drug in pediatric patients, but this rule will require pediatric studies of drugs intended for adults that may or may not be administered to pediatric patients. The comment also contended that the rule will necessitate a massive infusion of resources for industry, FDA, and medical speciality organizations, and that the agency should start with a small list of diseases with similar pathophysiology in adults and children, and a small list of drug classes known to have similar metabolism, and plan a graduated approach.

Contrary to the suggestion in the comment, this rule is designed to require studies only in those settings in which there is a significant medical need or where usage among pediatric patients is likely to be substantial. FDA acknowledges the difficulties encountered in some cases, but agrees that where there is a need for studies these difficulties have been overcome and that pediatric studies have been successfully conducted in many situations. FDA believes that the number of such studies already conducted each year, for example of antibiotics, vaccines, and roughly 25 percent of NME's, support the view that such studies are not medically, ethically, or technically

impossible. FDA also emphasizes that this rule will not require studies in settings where ethical or medical concerns militate against studies. As with all studies regulated by FDA, no pediatric study may go forward without the approval of an IRB, which is responsible for ensuring that the study is ethical and adequately protects the safety of the subjects. In addition, the deferral provisions of the rule are specifically designed to ensure that no pediatric study begins until there are sufficient safety and effectiveness data to conclude that the study is ethically and medically appropriate.

B. Scope

The proposal would have covered only original applications for those drugs classified as "new chemical entities," including antibiotics, and new biological products that had never been approved for any indication. A "new chemical entity," defined in 21 CFR 314.108(a), is a drug that contains no previously approved active moiety. Under the proposal, chemical modifications that did not change the active moiety, such as the formation of a different salt or ester of the moiety, would not have required further study. New indications or dosage forms of a previously approved moiety also would not have required further studies. FDA sought comment on whether the requirement should apply more broadly, e.g., to applications for minor chemical variations of approved products, new indications, new dosage forms or new routes of administration.

9. A majority of those who commented on the scope of the rule recommended that the final rule cover all new drugs and biologics, including new dosage forms and indications, because modifications in existing drugs may be as therapeutically significant to pediatric patients as the original drug or biologic. These comments included pediatricians, medical societies, one pharmaceutical company, and one disease-specific organization. Several comments, including two companies, an IRB, the AAP, a disease-specific organization, and a professional society recommended including new indications and dosage forms on a case-by-case basis, generally if their inclusion were recommended by an expert panel. Several comments supported the narrow scope of the proposal, including a pharmaceutical trade association, a professional society, and several companies. The pharmaceutical trade association suggested that the rule might also apply to new formulations uniquely suited to pediatric patients.

FDA has reconsidered the scope of the rule in light of the comments and has concluded that, in some cases, the need for pediatric studies is as great for modifications of existing products and new claims as for the original products. A new indication or dosage form for a previously approved drug, e.g., could be far more relevant to pediatric patients than the originally approved product. From a public health standpoint, FDA cannot justify the distinction in the proposal between new

chemical entities and never-before approved biologics, on one hand, and significant modifications of those products, on the other hand. Therefore, FDA has revised proposed §§ 314.55 (proposed 314.50(g)) and 601.27(a) to cover applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration. The final rule exempts from its coverage any drug for an indication or indications for which orphan designation has been granted under the Orphan Drug Act (21 U.S.C. 360bb). FDA believes this exemption is appropriate because the purpose of the Orphan Drug Act is to encourage the development of drugs for patient populations that are so small as to make the manufacture and sale of the drug unprofitable if not for the incentives offered by the Orphan Drug Act. Imposition of a pediatric study requirement on an orphan drug could conflict with the balance struck by the Orphan Drug Act, by further raising the cost of marketing the drug. This exemption does not apply after marketing under § 201.23 of this final rule.

FDA's decision to expand the scope of the rule does not mean, however, that pediatric studies would always be needed for a new product entering the marketplace, or for a new claim. The waiver criteria will apply equally to modifications of existing drugs and biological products. Thus, FDA will require studies only of those new drugs and biologics that offer a meaningful therapeutic benefit to pediatric patients or that are expected to be used in a substantial number of pediatric patients. In many

cases, moreover, new dosage forms might need relatively little pediatric data, such as pharmacokinetic data alone.

10. One comment sought clarification of the applicability of the rule to generic drugs. The comment argued that the collection of pediatric data was unwarranted where a generic manufacturer was copying a drug with an adult dose, and that FDA should require a pediatric bioequivalence study only where the innovator submits a supplement for a new dose or regimen in the pediatric population. Another comment from a generic drug trade association argued that bioequivalence studies in children should never be required to support approval of a generic drug.

This rule does not impose any requirements on studies submitted in support of applications for generic copies of approved drugs that meet the requirements of section 505(j) of the act. FDA also does not currently require bioequivalence studies to be conducted in children for generic drugs. FDA notes that petitions submitted under section 505(j)(2)(C) for a change in active ingredient, dosage form, or route of administration may be denied if "investigations must be conducted to show the safety and effectiveness of" the change. Thus, if a petition is submitted for a change that would require a pediatric study under this rule, the petition may be denied.

C. Required Studies

FDA proposed to amend its regulations related to the content of NDA and biologic license applications (BLA's) to include

required information on pediatric studies for certain applications. Under the proposal, an application for a new chemical entity or never before approved biologic would have been required to contain data adequate to assess the safety and effectiveness of the product for all pediatric age groups for the claimed indications, unless FDA granted a deferral or full or partial waiver of the requirement. As described in section III.B of this document under "Scope", FDA has revised § 314.55(a) (proposed § 314.50(g)(1)) and § 601.27(a)) to cover applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration. Under the final rule, all covered applications will be required to contain data adequate to assess the safety and effectiveness of the product, unless FDA has granted a waiver or deferral of the requirement (see "Waiver" and "Deferred Submission" in section III.D and E of this document).

Assessments required under this section for a product that represents a meaningful therapeutic benefit over existing treatments must be carried out using appropriate formulations for the age group(s) for which the assessment is required, unless reasonable efforts to produce a pediatric formulation had failed (see "Waiver" in section III.E of this document). Comments on issues related to formulation are addressed under "Pediatric Formulations" in section III.I of this document.

The proposal did not mandate particular types of studies. The proposal recommended that the sponsor consult with FDA on the types of data that would be considered adequate to assess pediatric safety and effectiveness in particular cases.

FDA received several comments on the design and conduct of clinical trials in pediatric patients.

11. One comment asked for clarification of what is meant by "adequate evidence" to demonstrate safety and effectiveness. The comment argued that FDA should not require two adequate and well-controlled trials for pediatric studies, and that the amount of evidence required should depend on the ability of the data to be extrapolated from adult to pediatric patients, the seriousness of the illness to be treated, the ability to assess meaningful measures of efficacy in pediatric patients, and the feasibility of conducting adequate trials in relatively uncommon pediatric disease states. Another comment claimed that the ability to extrapolate from adult efficacy data is limited and argued that well-controlled trials in pediatric patients should be the norm. This comment also stated that safety cannot be extrapolated from adult data and recommended studying 300 pediatric patients for an adequate period to identify frequent ADR's. Other comments questioned the appropriateness of extrapolating from adult effectiveness data in a variety of settings. One comment argued that in the area of blood products, in addition to extrapolating from pharmacokinetic data, it may be appropriate to extrapolate

from adult data using relative blood volume replacement. Several comments urged reliance on a variety of other sources of data, including published studies and reports, and actual use information. One comment urged FDA to rely on advanced scientific and statistical methods that optimize safety, convenience, and informativeness, while minimizing unnecessary or uninformative clinical trials.

FDA agrees that "adequate evidence" of safety and effectiveness for pediatric patients does not necessarily require two adequate and well-controlled trials. One of two central purposes of the 1994 rule was to make it clear that pediatric effectiveness may, in appropriate circumstances, be based on adequate and well-controlled studies in adults with supporting data in pediatric patients that permit extrapolation from the adult data. FDA agrees, however, that extrapolation from adult effectiveness data would not always be appropriate and that it may not be appropriate to extrapolate pediatric safety from adult safety data. FDA has specifically noted, in the FDA guidance document entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," that if further controlled trial data were needed in a population subset, it would usually be sufficient to conduct a single additional controlled trial. FDA also agrees that useful information can come from data other than adequate and well-controlled trials, and encourages the submission of valid and reliable data from a

variety of sources. The type and amount of data required in any particular case will depend upon many factors, including those cited in the comments.

12. One comment urged FDA, in the final rule, to encourage sponsors to use Computer-Assisted Trial Design (CATD), allowing them to reduce number of actual trials in pediatric patients.

FDA encourages the use of any validated scientific method for designing, conducting, or analyzing clinical trials.

13. One comment questioned whether there will be a sufficient pool of pediatric subjects to complete trials, in light of the increase in the number of trials occasioned by the rule.

FDA believes that with appropriate organization, the pool of pediatric patients available for studies should be adequate. The Pediatric Pharmacology Research Units (PPRU's), a network of groups instituted to conduct pediatric research, some of which are located outside of major population centers, have an established record of recruiting pediatric patients and completing valid studies. Even where the number of pediatric patients affected by a disease is small, valid studies have sometimes been successfully conducted. It should also be reemphasized that many of the studies contemplated under the rule are pharmacokinetic studies, dose-response studies with short-term endpoints (pharmacodynamic studies) and safety studies that are likely to impose relatively little burden on individual

patients. Where, however, patient recruitment is so difficult as to make the study impossible or highly impractical, the rule permits a waiver of the study requirement (§§ 314.55(c) and 601.27(c)).

14. One comment urged that the final rule include a broader research requirement, and sought to have drug interactions and drug metabolism taken into consideration. Another comment sought to have the final rule codify minimal requirements for studies, such as toxic overdose and pharmacokinetic data. One comment urged FDA not to codify specific requirements for clinical trials, but to establish these requirements in consultation with an expert pediatric committee.

FDA declines to codify specific requirements for pediatric studies. Flexibility is necessary to assure that required studies are appropriate for each product. FDA will, however, consult with a pediatric committee on specific pediatric study issues.

15. One comment from a professional pharmacy organization urged that all protocols for pediatric studies be reviewed by pediatric experts, including a pharmacist knowledgeable about pharmacodynamic factors in each age group.

FDA reviews protocols for pediatric studies submitted in investigational new drug applications (IND's), and its reviewers include experts in pediatrics and pharmacology.

D. Deferred Submission

The proposal recognized that there would be circumstances in which it would be appropriate to permit the submission of pediatric data after approval. Two such circumstances were described in the preamble to the proposal: (1) Where adult safety or effectiveness data need to be collected before the product could be appropriately studied in pediatric patients, and (2) where the product was ready for approval in adults before studies in pediatric patients were completed. Although not included in the text of the proposal, these examples have been added to the final rule. Under the proposal, FDA would have the authority to defer the submission of some or all of the required pediatric data until after approval of the product for adult use, on its own initiative or at the request of the applicant. Under the proposed provisions, if the applicant requested deferral, the request would be required to contain an adequate justification for delaying pediatric studies. If FDA concluded that there were adequate justification for deferring the submission of pediatric use studies, the agency could approve the product for use in adults subject to a requirement that the applicant submit the required pediatric studies within a specified time after approval. It is important to appreciate that deferred submission of pediatric data refers to the date on which the data are submitted, not when the studies are initiated. Thus, deferred studies will generally be initiated before approval, unless it is

concluded that the full adult data base or marketing experience are needed before pediatric studies may appropriately begin.

FDA stated in the proposal that it would consult with the sponsor in determining a deadline for the deferred submission, but tentatively concluded that it would require the submission not more than 2 years after the date of the initial approval. To ensure that deferral would not unnecessarily delay the submission of pediatric use information, FDA proposed that a request for deferred submission include a description of the planned or ongoing pediatric studies, and evidence that the studies were being, or would be, conducted: (1) With due diligence, and (2) at the earliest possible time. FDA sought comment on the circumstances in which FDA should permit deferral, and on the factors that should be considered in determining whether a given product was one that should be studied in adults before pediatric patients. FDA received many comments on the deferral provisions in the proposal.

16. A few comments stated that the deferral provisions are an appropriate means of assuring that pediatric patients are not studied before adequate safety data have been gathered. A number of comments from the pharmaceutical industry asserted, however, that the proposal would require concurrent testing in adults and pediatric patients despite medical and ethical reasons for delaying testing pediatric testing. For example, a comment from a pharmaceutical trade association claimed that the rule:

* * * would require testing of new medical compounds in children before safety in adults has been studied adequately, before effectiveness in adults has been established, and in young children and neonates without adequate information about the effects of the drug in older pediatric patients.

These industry comments appear to have either ignored the explicit deferral provisions of the rule or perceived them as rare exceptions to a usual requirement that adults and children be studied at the same time. Nothing in the rule requires concurrent testing in adults and pediatric patients, nor testing in infants and neonates before testing in older children. As stated previously and in the proposal, the deferral provisions were specifically included to, among other things, ensure that pediatric studies could be delayed when necessary to assure that appropriate safety and/or effectiveness data were available to support pediatric testing.

17. Most of the comments on deferral focused on whether the need for safety and/or effectiveness data in adults before initiating pediatric studies should be a basis for deferral. Comments from disease-specific organizations, medical societies, including the AAP, and pediatricians argued that deferrals should be granted rarely if at all on this basis. One comment argued that delaying availability of life-saving drugs to children

cannot be rationalized scientifically, legally, or ethically, and contended that deferral should not be permitted for serious and life-threatening diseases where there is no substantial difference between the disease or the anticipated effect of the drug in children or adults. Another comment argued that deferral should be used sparingly in all age groups, including infants and neonates, and that its use should be evaluated in the context of the seriousness of the condition to be treated, the therapeutic advance the drug represents, and the likelihood that the drug will be given to children as soon as it is approved. According to this comment, the risks of research in pediatric patients may be outweighed by the risks that the drug will be given to them without data.

One comment argued that pediatric studies of important drugs should be conducted in parallel to adult studies, especially in children under 12. Several comments from the pediatric community, however, supported the development of some adult safety and/or effectiveness data before initiation of pediatric studies. One comment from an organization devoted to pediatric AIDS stated that while the general assumption should be that pediatric studies will be submitted at the same time as adult studies, it may be appropriate to have some testing in adults before children. The AAP stated that it is appropriate to begin studies in pediatric patients after phase 1 and phase 2 studies in adults have defined routes of clearance and metabolic

pathways. Thus, the comment urged that pediatric studies be conducted during phases 2 and 3, not 4. A comment from a nephrology organization argued that drugs for organ-specific diseases should be studied in phase 3, as soon as phase 1 and 2 trials have shown safety in adults. This and another comment stated that deferring studies until after approval compromises clinical trial enrollment, citing the experience with recombinant erythropoietin. According to these comments, erythropoietin was not studied in pediatric patients until after its approval for adults, and enrollment was so difficult that pediatric studies were not completed for 5 years.

Several comments from the pediatric community also cited limited circumstances in which they believed deferral to be appropriate. A medical society argued that data should be collected after adult studies only for drugs with narrow therapeutic indices, unusual accumulation in the body, where the drug study requires extensive blood sampling, or where the study design places young patients at risk for limited information gain.

Many comments from the pharmaceutical industry argued, in contrast, that deferral should be the rule, rather than the exception. Most of these comments contended that it was unethical to begin studying drugs in pediatric patients, other than those that are intended primarily for pediatric patients, until the drugs are shown to be reasonably safe and effective in

adult patients. All argued that pediatric studies must not be initiated until substantial data in adults are available, but cited different initiation points, e.g., after phase 2, after safety and effectiveness is established in adults and an approvable letter is received, after approval, after 1 year of marketing.

Although many of these industry comments argued that pediatric studies should be conducted exclusively as phase 4 (postapproval) commitments, a significant number of industry comments acknowledged that pediatric studies could begin before approval, generally after phase 2, and that there were circumstances in which deferral was not appropriate. One comment argued that because early pediatric studies often require pediatric formulations and because up to 50 percent of drugs are abandoned before phase 3, it is wasteful to require companies to manufacture a pediatric formulation and begin studies before the end of phase 2. Another comment argued that no pediatric studies should begin before the decision to proceed to phase 3, except where: (1) The disease affects only pediatric patients; (2) the disease mainly affects pediatric patients, or the natural history or severity of the disease is different in pediatric patients and adults; or (3) the disease affects both pediatric patients and adults and lacks adequate treatment options. One comment urged that the final rule state that "in most cases, pediatric testing should not begin with any drug or biological

product until certain adult safety and/or effectiveness information has been collected." According to this comment, there could be exceptions where no other therapy was available and there was a potential for the drug to be lifesaving. A pharmaceutical trade association argued for a presumption that pediatric studies not begin until the end of phase 2 or 3, but listed circumstances in which deferral should not occur: (1) Where the disease is life threatening and there is no alternative therapy, (2) where the drug is intended for a pediatric indication, (3) where the drug presents no major safety issues, (4) where the drug class is well studied in pediatric patients, or (5) where a large amount of "off-label" use in pediatric patients is anticipated.

In general, FDA expects that some data on adults will be available before pediatric studies begin, but that less data will usually be required to initiate studies of drugs and biologics for life-threatening diseases without adequate treatment than for less serious diseases. Pediatric studies of drugs and biologics for life-threatening diseases may in some cases be appropriately begun as early as the initial safety data in adults become available, because the urgency of the need for such products may justify early trials despite the relative lack of safety and effectiveness information. In such cases, deferral of submission of pediatric studies until after approval will be unnecessary, unless drug development is unusually rapid and the product is

ready for approval in adults before completion of the pediatric studies.

Pediatric studies on products for less serious diseases should generally not begin until more adult data have been collected, ordinarily no earlier than the availability of data from the initial well-controlled studies in adults. As noted earlier in this document, there may occasionally be exceptions to this principle where all parties agree that earlier initiation is appropriate. Whether deferral of submission of the data until after approval will be necessary for such products will depend upon when pediatric studies can scientifically and ethically begin in each case and how difficult the studies are to complete.

In some cases, FDA expects that scientific and ethical considerations will dictate that studies not begin until after approval of the drug or biological product. For example, pediatric studies of "me-too" drugs that do not offer a meaningful therapeutic benefit and that are members of a drug class that already contains an adequate number of approved products with pediatric labeling may be deferred until well after approval. In cases where a drug has not been shown to have any benefit over other adequately labeled drugs in the class, the therapeutic need is likely to be low and the risks of exposing pediatric patients to the new product may not be justified until its safety profile is well established in adults through marketing experience. Because the basis for the deferral in such

cases will be concern that the drug presents risks to pediatric patients that will not be known until there is widespread marketing experience, without offsetting benefit, FDA is revising the proposal to advise sponsors that FDA may require, in appropriate cases, that such drugs carry labeling statements recommending preferential use in pediatric patients of products that are already adequately labeled. Such a statement might read:

The safety and effectiveness of this product have not been established in children. There are alternative therapies that have been shown to be safe and effective for use in children with [indicated condition]. Ordinarily, products already labeled for use in children should be used in preference to [name of this product].

Some drugs with no demonstrated advantage over available therapy can nonetheless be expected to have wide use in pediatric patients. Pediatric studies of such drugs should be initiated relatively early, even if they are not completed at the time of approval.

18. A comment from a pharmaceutical company listed several circumstances in which it argued FDA should permit deferral: (1) The pediatric population is so small that enrollment and completion of trials cannot be accomplished in parallel with

adult trials, (2) the natural course of the disease is different in adults and children, (3) analytic tools and clinical methodologies cannot be easily adapted to the pediatric population, (4) the drug has complex pharmacokinetic properties in adults making it hard to extrapolate a pediatric dosage range, (5) the scope and nature of nonclinical studies support only adult clinical studies, (6) two or more attempts to develop a pediatric formulation have failed, or (7) unique drug-drug or drug-food interactions in children confound drug development. Another comment added to this list: (1) Where fewer than 200,000 pediatric patients are affected by the disease being treated, and (2) drugs with a low therapeutic index.

FDA agrees that some of these circumstances could make completion of studies prior to approval in adults difficult, but does not agree that they would make studies impossible or impractical in all cases. The need for deferral must be considered case-by-case. A small pediatric population, e.g., might make completion of controlled trials very slow, but might not prevent obtaining pharmacokinetic data. Simply citing a pediatric population under 200,000 will not be sufficient to justify deferral; a small fraction of this number participating in trials may be sufficient to support timely pediatric studies, depending on the nature of the studies. As an example, over 70 percent of the estimated 6,000 pediatric patients with cancer each year are enrolled in clinical trials (Ref. 15). There does

not seem to be any reason to conclude that deferral is warranted solely because the natural course of the disease is different in adults and children. FDA also disagrees that deferral is necessarily warranted where analytic tools and clinical methodologies cannot be easily adapted to pediatric patients. Deferral may be necessary in some cases where the infants and toddlers are unable to provide subjective outcome data, but it may also be possible to utilize alternative endpoints or to extrapolate effectiveness data from older pediatric age groups, obtaining pharmacokinetic data from the younger age groups to determine an appropriate dose. Drugs with a low therapeutic index that do not fulfill an urgent need should, in general, be studied in pediatric patients later in drug development.

With respect to complex pharmacokinetic properties that prevent extrapolation of adult data to pediatric patients, low-therapeutic index drugs, and unique drug-drug or drug-food interactions in pediatric patients, FDA believes that the need for pediatric studies before approval is even greater where these conditions are present; moreover, none of them represents a significant impediment to studies. Recognizing that drugs and biologics approved for adults are regularly prescribed to pediatric patients despite the absence of adequate dosing and safety data, information positively suggesting that dosing and safety cannot be extrapolated from adult data increases the importance of conducting pediatric studies before the product is

widely used in pediatric patients. The absence of supporting nonclinical studies (e.g., studies in young animals) should not usually be a basis for deferral. These studies, if needed, are readily conducted. Moreover, a full adult data base provides pertinent safety information that might make further preclinical data unnecessary. Difficulties in developing an adequate pediatric formulation may, in some cases, justify deferral of studies in young pediatric patients. In other cases, however, it may be appropriate to study a less-than-optimal formulation, e.g., an injection, if one is available, in pediatric patients while awaiting the development of a more desirable pediatric formulation.

19. One comment argued that it was "unacceptable" to defer pediatric studies to avoid delaying approval for adult use. Instead, the comment urged FDA to provide a "limited approval" for adult use until pediatric data are available and impose a monetary penalty for failure to comply. Another comment argued that permitting deferral to avoid delay in adult marketing could be applied to most applications, creating a de facto situation in which pediatric data were understood to be not required until 2 years after approval. One comment stated that while pediatric dosing schedules are essential, pediatric studies should not delay approval of drugs for a major population, adults.

FDA continues to believe that deferral is appropriate where awaiting the completion of pediatric studies would delay the

availability of a safe and effective drug or biological product for adults. Granting a deferral does not automatically mean, however, that pediatric studies need not be submitted for 2 years or that initiating them should be long delayed. The proposal suggested 2 years as the maximum period for a deferral. Where pediatric studies are supposed to be nearing completion at the time a product is ready for approval in adults, FDA expects that the period of deferral would be significantly shorter than 2 years. Where some useful pediatric information, e.g., safety information, is available at the time of approval, even if some required studies are not complete, FDA may require that the pediatric use section of the product's labeling include that information, to the extent consistent with 21 CFR 201.57(f)(9). FDA also notes that it has no authority to impose a monetary penalty for failure to submit a required study of a drug or biological product. FDA must ask a court to impose such a penalty in a contempt proceeding.

20. Several comments argued that pediatric trials should be conducted sequentially, beginning with the oldest pediatric age group, and ending with the youngest. One comment stated that IRB's would question testing a drug in younger children before older children. The AAP argued that there is little defense for studying pediatric patients sequentially from oldest to youngest, and that such a policy will result in approvals without data in neonates. This comment argued that the timing of studies should

give consideration to safety, but without consideration of sequence. Another comment argued that FDA should not routinely require that drugs for serious and life-threatening diseases be studied sequentially. In HIV, according to this comment, drug testing should be "as simultaneous as possible" because safety and dosing may be initiated in each age group in a dose escalating manner regardless of the results in previously tested groups.

FDA agrees that age-dependent sequential studies are not necessarily appropriate. Particularly where there is urgent need for a product, there may be good reason to study older and younger children at the same time.

21. A few comments objected to FDA's tentative decision to require the submission of studies ordinarily no later than 2 years after the initial approval. One comment stated that deferral of up to 2 years was excessive, citing the "critical" need to ensure timely performance of pediatric studies in populations where the drug is likely to be used. Another comment stated that 2 years may be adequate for collecting pharmacokinetic data, but not necessarily for collecting safety data. According to this comment, the size of the clinical data base will be the principal determinant of when data should be submitted. A comment from the American Red Cross stated that the extensive IRB review of studies of blood products involving pediatric patients, and the difficulty in enrolling such

patients, makes the 2-year deferral deadline unrealistic for this category of product.

FDA agrees with the comments that the 2-year deadline suggested by the proposal may not be appropriate, and that the length of the deferral should be decided on a case-by-case basis. The timing of the deferred submission will depend upon such factors as the need for the drug or biologic in pediatric patients, when sufficient safety data become available to initiate pediatric trials, the nature and extent of pediatric data required to support pediatric labeling, and substantiated difficulties encountered in enrolling patients and in developing pediatric formulations. FDA may also extend the date for submission of studies at the time of approval, e.g., where other drugs in the class have been approved during the pendency of the NDA and the new drug is no longer needed as a therapeutic option.

E. Waivers

FDA does not intend to require pediatric assessments unless the product represents a meaningful therapeutic benefit over existing treatments or is expected to be used in a substantial number of pediatric patients. FDA also does not intend to require pediatric assessments in other situations where the study or studies necessary to carry out the assessment are impossible or highly impractical or would pose undue risks to pediatric patients. Thus, FDA proposed to add § 314.50(g)(3) (now