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: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing new regulations requiring pediatric studies of certain new drug and biological products. Many new drugs and biological products represent treatments that are, at least at times, the best available treatment for children, but most of them 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. The proposed rule would attempt to partially address this lack of pediatric use information by requiring that manufacturers of a limited class of new drugs and new biological products provide sufficient data and information to support directions for pediatric use for the claimed indications, before or soon after approval. Manufacturers of a limited class of marketed drugs and biologics would also in compelling circumstances have to provide such data. This proposed rule is part of a comprehensive effort to increase

the number of new drugs and biological products with clinically significant use in children that carry adequate labeling for use in that subpopulation.

DATES: Written comments and recommendations by (insert date 90 days after date of publication in the FEDERAL REGISTER). Written comments on the information collection provisions should be submitted by (insert date 30 days after date of publication in the FEDERAL REGISTER). For further information of the agency's implementation plan, see section VII of "Supplementary Information" in this document.

ADDRESSES: Submit written comments and recommendations to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. Submit written comments on the information collection provision to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Introduction

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. According to the American Academy of Pediatrics, however, only a small fraction of all drugs and biological products marketed in the United States have had clinical trials performed in pediatric patients and a majority of marketed drugs are not labeled for use in pediatric patients or for use in specific pediatric age groups (Ref. 1). A recent FDA survey similarly concluded that most products that are indicated for diseases occurring in both adults and children have very little information about pediatric use in their labeling (Ref. 2). For some products, including vaccines and antibiotics, pediatric use information is generally adequate. Many drugs used in the treatment of both common childhood illnesses and more serious conditions, however, carry little information about use in pediatric patients. Less than half the drugs approved for treatment of human immunodeficiency virus (HIV) infection or accompanying opportunistic infections carry any pediatric safety or effectiveness information, and, of those that do, the data are often incomplete and limited to certain pediatric age groups. Pediatric labeling is also inadequate for such drug classes as steroids, drugs to treat gastrointestinal problems, prescription pain medications, antihypertensives, antidepressants, antirheumatic drugs, and drugs to treat ulcerative colitis.

Safety and effectiveness information for some pediatric age groups is particularly sparse. For example, there is almost no

information on use in patients under 2 years of age for most drug classes (Ref. 2).

Many of the drugs and biological products most widely used in pediatric patients carry disclaimers stating that safety and effectiveness in pediatric patients have not been established (Refs. 2 and 3). Based on 1994 data from IMS America, Ltd., a research firm that provides data on prescription drug usage, FDA compiled a list of the 10 drugs that were most widely prescribed for pediatric patients, on an outpatient basis, despite inadequate pediatric labeling. In each case, the label lacked any use information for the age group prescribed to, or the information was inadequate. The drugs were: Albuterol inhalation solution for nebulization for treatment of asthma (prescribed 1,626,000 times to pediatric patients under 12); Phenergan for treatment of allergic reactions (prescribed 663,000 times to pediatric patients under 2); ampicillin injections for treatment of infection (prescribed 639,000 times to pediatric patients under 12); Auralgan otic solution for treatment of ear pain (prescribed 600,000 times to pediatric patients under 16); Lotrisone cream for treatment of topical infections (prescribed 325,000 times to pediatric patients under 12); Prozac for treatment of depression and obsessive compulsive disorder (prescribed 349,000 times to pediatric patients under 16, including 3,000 times to infants under 1); Intal for treatment of asthma (solution prescribed 109,000 to pediatric patients under

2; aerosol prescribed 399,000 times to pediatric patients under 5); Zoloft for treatment of depression (prescribed 248,000 to pediatric patients under 16); Ritalin for treatment of attention deficit disorders and narcolepsy (prescribed 226,000 times to pediatric patients under 6); Alupent for treatment of asthma (184,000 times to pediatric patients under 6). These 10 drugs were thus prescribed over 5 million times in 1 year for pediatric patients in age groups for which the label carried a disclaimer or lacked adequate use information (Ref. 2).

The absence of pediatric labeling information may sometimes require the physician caring for children to choose between prescribing drugs without well-founded dosing and safety information or utilizing other, potentially less effective, therapy.

Inadequate pediatric labeling thus exposes children to the risk of unexpected adverse reactions or lack of optimal treatment. Even after a drug has been used in pediatric patients for some time, and there has been substantial clinical experience with the drug, directions for safe and effective use in pediatric patients are not provided on the label.

Children were once viewed as a population entirely distinct from adults, in whom safety and effectiveness of new drugs had to be established entirely independently. It has become increasingly clear, however, that children may be considered a demographic subpopulation with many similarities to the adult

population. In most cases, drugs and biological products behave similarly in demographic subgroups, including age and gender subgroups, even though there may be variations because of differences in, for example, pharmacokinetics. As FDA has already stated in a FEDERAL REGISTER document, where the disease and the drug's effects are similar in adults and children, adequate and well-controlled trials may not be needed in children to establish pediatric use information (59 FR 64240, December 13, 1994) (hereinafter referred to as the 1994 rule).

Although use of a drug in children is no longer considered a new indication (with the exception of specific "pediatric indications"), the development of additional information in pediatric patients is needed to provide appropriate dosing recommendations. Correct pediatric dosing cannot necessarily be extrapolated from adult dosing information using an equivalence based either on weight milligrams per kilogram (mg/kg) or body surface area (mg/square meter (m^2)). Potentially significant differences in pharmacokinetics may alter a drug's effect in pediatric patients. The effects of growth and maturation of various organs, maturation of the immune system, alterations in metabolism throughout infancy and childhood, changes in body proportions, and other developmental changes may result in significant differences in the doses needed by pediatric patients and adults. For example, studies have shown that fentanyl, a potent opioid, widely used in anesthetic management of infants

and small children but not labeled for use in pediatric patients under 2 years of age, demonstrates differences in clearance between the neonatal period and 2 or more months of age due to improving hepatic blood flow and hepatic microsomal maturation (Ref. 4). Comparable doses in adults and neonates (calculated on a microgram (μg)/kg basis) produce twofold to threefold higher plasma concentrations in neonates (Ref. 5). Pharmacokinetic differences of this kind demonstrate the importance of studying the pharmacokinetics of a drug in pediatric patients of different ages before they are widely exposed to it. Inadequate dosing information may expose pediatric patients to dangerously high doses or to ineffective treatment. The absence of pediatric testing may thus result in less than optimal treatment for many pediatric patients.

Pediatric patients receiving inadequately tested and labeled drugs are also exposed to the risk of unexpected adverse reactions. One of the earliest cases in which serious adverse events were observed in neonates following administration of a drug that had not been adequately studied in pediatric patients was the development of "gray baby syndrome" from chloramphenicol, an antibiotic (Ref. 6). After an initial report of 5 deaths and a subsequent report of 18 deaths in neonates, it was learned that the immature livers of these infants were unable to clear chloramphenicol from the body, allowing toxic doses of the drug to accumulate. Other cases in which inadequately studied drugs

have resulted in serious adverse effects in pediatric patients include teeth staining from tetracycline, kernicterus from sulfa drugs, withdrawal symptoms following prolonged administration of fentanyl in infants and small children, seizures and cardiac arrest caused by bupivacaine toxicity, development of colonic strictures in pediatric cystic fibrosis patients after exposure to high-dose pancreatic enzymes, and hazardous interactions between erythromycin and midazolam (Refs. 7, 8, 9, 10, 11, 12, 13, 14, 15, and 16). Many such adverse reactions could be avoided if pediatric studies were conducted before drugs were widely used in pediatric patients.

Failure to conduct pediatric testing may, in unusual cases, deprive pediatric patients of significant therapeutic advances. Failure to develop a pediatric formulation of a drug, where younger pediatric populations cannot take the adult formulation, may also deny pediatric patients access to important therapeutic advances, or require pediatric patients to take the drug in homemade, poorly bioavailable formulations.

II. FDA Initiatives to Improve Pediatric Use Information

FDA has taken a number of steps in recent years to address inadequate pediatric drug testing and inadequate pediatric use information in drug labeling. Perhaps the most significant step was the issuance of the 1994 rule requiring drug manufacturers to survey existing data and determine whether those data are sufficient to support additional pediatric use information in the

drug's labeling (59 FR 64240). 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. The rule explicitly recognizes that controlled clinical studies to support pediatric use information need not have been carried out in pediatric patients where the course of the disease and the effects of the drug are sufficiently similar in children and adults to permit extrapolation from the adult effectiveness data to pediatric patients. In these cases, controlled clinical studies in adults together with pharmacokinetic and adverse reaction data in pediatric patients may be sufficient to establish pediatric safety and effectiveness.

Although the preamble to the 1994 rule recognizes FDA's authority to require drug manufacturers to conduct pediatric studies on a case-by-case basis, the rule does not impose a general requirement that manufacturers carry out studies if existing information is not sufficient to support pediatric use information. Instead, where there is insufficient information to support a pediatric indication or pediatric use statement, the rule requires the manufacturer to include in the drug's labeling the statement: "Safety and effectiveness in pediatric patients have not been established." Because the rule focuses on gathering existing information about pediatric use, rather than

carrying out new studies, supplements filed in response to the rule will be for marketed drugs. The rule does not apply to products first entering the marketplace, except to the extent that pediatric studies conducted on such products before approval can take advantage of the rule's explicit authorization to rely on pharmacokinetic data rather than adequate and well-controlled studies in pediatric patients, and that labeling statements about pediatric use must conform to the rule's labeling requirements.

FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation (CBER) 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. At specified points during the investigation of a new drug or biological product, FDA staff discuss with the sponsor the data needed to support pediatric labeling and encourage them to conduct needed studies. CDER and CBER have also begun to implement a program in which, after review of an NDA, biologics license application (BLA), or supplemental application, the FDA reviewer fills out a "pediatric page." The pediatric page does not itself impose any requirements, but describes the adequacy of product labeling for pediatric patients and plans for further pediatric studies. If pediatric labeling is found to be inadequate, the pediatric page states whether additional pediatric studies are needed. If pediatric studies are needed, the pediatric page states whether

the applicant has agreed to conduct the necessary studies and, if necessary, to develop a pediatric formulation. FDA is also developing a draft guidance document on pediatric pharmacokinetics.

In addition, FDA has taken steps to improve pediatric use information for marketed drugs under the pediatric plan. CDER has identified the 10 drugs most used in pediatric populations for which there is no pediatric use information or for which the pediatric use information is inadequate given the pattern of use in pediatric patients. The manufacturers of these drugs have been notified of the widespread use of their drugs in the pediatric population and asked to respond to the 1994 rule. CBER is currently identifying the biological products most frequently used in pediatric patients without labeling information. FDA has developed guidance to manufacturers on the content and format for pediatric use supplements under the 1994 rule and is tracking pediatric use supplements and commitments.

III. Results of Actions to Date and Need for Additional Steps

Although the actions taken by FDA to date have produced some gains in pediatric labeling, they have not yet substantially increased the number of drugs and biological products for which there is adequate pediatric use information. The percentage of new products entering the marketplace that contain adequate pediatric safety and effectiveness information has not shown consistent improvement in the last decade. An informal survey

conducted by the American Academy of Pediatrics in 1990 found that of all new molecular entities (NME's) approved between 1984 and 1990, 20 percent had information on pediatric use. Not all NME's have usefulness in pediatric patients, however. For example, for NME's approved in the years 1991-1996, 53 percent were regarded by FDA as having potential usefulness in pediatric patients. Presumably, if only the NME's with usefulness in pediatric patients had been considered in the survey, the percentage with pediatric labeling would have been somewhat higher, and as high as 42 percent.

FDA compared the number of 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 (9/16) 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 labeled for all age groups in which the drug was useful.) The manufacturers of an additional 17 drugs promised to conduct pediatric studies after approval. It is uncertain how many of these promises will result in pediatric labeling. Of the seven NME's approved in 1991 for which postapproval pediatric studies were promised, only one now has pediatric labeling.

These data indicate that voluntary efforts have, thus far, not substantially increased the number of products entering the marketplace with adequate pediatric labeling. Therefore, FDA has tentatively concluded that additional steps are necessary to ensure the safety and effectiveness of drug and biological products for pediatric patients. This proposed rule includes provisions that would require the manufacturers of certain new and marketed drugs and biological products to evaluate the safety and effectiveness of their products in pediatric patients, where existing information is not sufficient to support pediatric use labeling but the product is likely to be commonly used in pediatric patients, the product is a new drug or biological product which would provide a meaningful therapeutic benefit to pediatric patients over existing treatments, or the product is a marketed drug or biological product which is indicated for a very significant or life threatening illness.

Although this proposal would address the lack of pediatric labeling through the imposition of regulatory requirements, the agency solicits comment on whether there are other ways to assure that manufacturers reliably conduct pre- or postapproval studies in pediatric patients.

At the same time as it is issuing this proposed rule, FDA has initiated other actions that it hopes will encourage the development of adequate pediatric use information. FDA plans to develop guidance on clinical trial designs for assessing

pediatric safety and effectiveness. The agency has also discussed with the pharmaceutical industry a policy on user fees for pediatric studies designed to encourage the submission of these studies. Such a policy could be implemented through legislation at the time of reauthorization of the Prescription Drug User Fee Act of 1992. FDA has proposed that user fees be waived for supplements to add pediatric use labeling, unless the supplements contain adequate and well-controlled clinical trials. Thus, supplements that rely on pharmacokinetic data to extrapolate from existing adult studies would not be subject to user fees. FDA might also be prepared to waive the user fee for

supplements containing pediatric use studies for which FDA granted a request to defer submission until after approval.

Finally, FDA has issued a policy statement describing the types of evidence necessary to support supplements. In that

policy, FDA provides guidance to manufacturers on the circumstances in which FDA may approve a supplement in which confirmation 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 by studies without the extensive documentation ordinarily required.

The agency believes that financial and other incentives to manufacturers, although largely beyond FDA's current authority, could further increase the number of drugs and biologics with adequate pediatric labeling.

IV. Public Hearing

Because of the importance of ensuring the safety and effectiveness of the medications administered to children and the need to address the absence of pediatric labeling in the most effective manner possible, FDA intends to hold a public hearing at which recognized experts in the field, members of the pharmaceutical industry, and other interested parties will have an opportunity to discuss the issues raised by this proposal.

V. Description of the Proposed Rule

The proposed rule is designed to ensure that new drugs and biological products that are likely to be commonly used in children or that represent a meaningful therapeutic benefit over existing treatments for children contain adequate pediatric

labeling for the approved indications at the time of, or soon after, approval. The rule would therefore require a manufacturer of a drug classified as a "new chemical entity" or a new (never-before-approved) biological product to submit, before approval, safety and effectiveness information on relevant pediatric age groups for the claimed indications. The submission of information could be deferred until after approval if, for example, pediatric studies should not begin until information on adults was collected, or where the collection and filing of pediatric data would delay the availability of a product that provides a significant therapeutic advantage to adults. The requirement would be waived for some or all pediatric age groups, if: (1) The product did not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and was unlikely to be used in a substantial number of pediatric patients, (2) studies on the product were impossible or highly impractical because, for example, the population was too small or geographically dispersed, (3) the product were likely to be unsafe or ineffective in pediatric patients, or (4) reasonable efforts to develop a pediatric formulation (if one were needed) had failed.

The rule is also intended to assist in improving pediatric use information for already marketed drugs and biological products where there is a compelling need for more information. The rule would therefore codify FDA’s authority, discussed in the

1994 rule, to require, in compelling circumstances, that manufacturers of already marketed drugs and biological products conduct studies to support pediatric use labeling for the claimed indications.

The proposed rule also contains provisions designed to encourage discussions of the need for pediatric studies early in the drug development process, as well as 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.

FDA notes that the Federal Food, Drug, and Cosmetic Act (the act) authorizes FDA, under certain circumstances, to grant periods of exclusive marketing to manufacturers who obtain approval of labeling supplements adding pediatric use information to a drug's label. First, a manufacturer is entitled to 3 years of exclusive marketing under section 505(c)(3)(D)(iii) and (j)(4)(D)(iv) of the act (21 U.S.C. 355(c)(3)(D)(iii) and (j)(4)(D)(iv)) for obtaining approval of pediatric use labeling based on clinical studies, other than bioavailability studies. Second, a manufacturer may be entitled to 7 years of exclusive marketing under the Orphan Drug Amendments for obtaining approval of an application for use of a drug to treat a disease or condition affecting a pediatric population of less than 200,000.

A. Scope

The proposed rule would cover only original applications for those drugs classified as "new chemical entities," including antibiotics, and new biological drug products that have 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. (An "active moiety," also defined in § 314.108(a), is the molecule or ion, excluding certain appendages, that is responsible for the physiological or pharmacological action of the drug.) New chemical entities and new biological products are generally the most innovative and therapeutically significant of the new drug products approved by FDA.

In an effort to limit the scope of the rule to those products for which pediatric labeling is most urgently needed and to minimize the burden on manufacturers and on agency resources available to review new product applications, FDA has tentatively concluded that the pediatric study requirement would not apply to subsequent applications for the drug or biological product, e.g. to supplements for new indications or dosage forms. FDA recognizes that, in some cases, a change to an approved product, particularly a new indication, may have clinically significant use in children. FDA seeks 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, and, if so, how the

rule could be applied in a manner that does not impose undue burdens on manufacturers or agency resources.

The proposed rule would require an assessment of safety and effectiveness in one subpopulation (pediatric patients) only for the indications already claimed by the manufacturer. It would not require a manufacturer to study its product for unapproved ("off-label") indications, even if the product were widely used in pediatric patients for those indications. Although the proposed rule would not apply to unapproved pediatric indications, nothing in the rule would diminish the physician's power to prescribe drugs and biological products for such unapproved indications.

B. Not-Yet-Marketed Drug and Biological Products

1. Sections 312.23(a)(3)(v), 312.33(a)(8), and 312.47(b)(1)(i) and (b)(2) (21 CFR 312.23(a)(3)(v), 312.33(a)(8), and 312.47(b)(1)(i) and (b)(2))--Early Discussion of Plans for Pediatric Studies

In the development of a new drug or biological product, decisions about appropriate populations to study and the design of such studies must often be made well before the submission of an NDA or BLA. FDA has identified several critical points in the drug development process, before submission of an NDA or BLA, during which the sponsor and FDA should focus on the sponsor's plans to assess pediatric safety and effectiveness. These time points include: Any pre-investigational new drug application

(IND) meeting or "end of phase 1" meeting for a drug designated under subpart E of part 312 (21 CFR part 312), the IND submission, the IND annual report, any "end of phase 2" meeting, the presentation of the IND to an FDA drug advisory committee, and any pre-NDA or pre-BLA meeting. Of these, the pre-IND meeting, the "end of phase 1" meeting, the IND submission, the IND annual report, the "end of phase 2" meeting, and the pre-NDA meeting are codified in part 312, FDA’s regulations governing IND's.

FDA has already proposed to amend the IND annual report requirement to include discussion of pediatric studies (60 FR 46794, September 8, 1995). FDA is proposing to amend the remaining regulations to specify that these meetings and reports should include discussion of the assessment of pediatric safety and effectiveness. To assist manufacturers in planning for studies that may be required under this proposed rule, FDA is also proposing to inform manufacturers at the "end of phase 2" meeting, or at the earliest appropriate opportunity, of the agency’s best judgment, at that time, of the pediatric studies that will be required for the product and when the studies should be submitted.

In addition to the discussions of pediatric testing codified in this proposed rule, FDA will also assist manufacturers by providing early consultations on chemistry and formulation issues raised by requirements under this rule.

2. Sections 314.50(g)(1) and 601.27--Required Studies

Under proposed §§ 314.50(g) and 601.27(a), an original application for a drug classified as a new chemical entity or an application for a new biological product would be required to contain data adequate to assess the safety and effectiveness of the drug product for all pediatric age groups for the claimed indications, unless FDA granted a deferral or full or partial waiver of the requirement. Assessments required under this section for a product that represented a meaningful therapeutic benefit over existing treatments would have to be carried out using appropriate formulations for the age group(s) for which the assessment is required (see "Pediatric Formulations," in section V.E of this document), unless reasonable efforts to produce a pediatric formulation had failed (see "Waivers," in section V.B.4 of this document).

The proposed rule does not mandate particular types of studies. The sponsor should consult with FDA on the types of data that will be considered adequate to assess pediatric safety and effectiveness. 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 children, FDA may conclude that pediatric safety and effectiveness can be based on adult effectiveness data together with pharmacokinetic and safety

data in pediatric patients. The proposed 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.

3. Sections 314.50(g)(2), 314.81(b)(2)(vii), and 601.27(b)--Deferred Submission and Postmarketing Reports

In some cases, pediatric testing should not begin until certain safety and/or effectiveness information in adults has been collected. FDA believes that in certain cases it may be appropriate to defer submission of pediatric studies. For example, in such cases, an NDA or biological product license could be ready for approval for adult use before pediatric studies were completed. Also, where a product was needed to treat a serious or life-threatening disease for which there were not satisfactory alternative therapies or where the product represented an meaningful therapeutic benefit over existing therapies, it would be contrary to the public health to delay approval until pediatric studies were submitted.

Proposed §§ 314.50(g)(2) and 601.27(b) would permit FDA 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. 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. FDA would consult with the sponsor in determining a deadline for the deferred submission, but would ordinarily require the submission not more than 2 years after the date of the initial approval. The deadline for submission of studies would take account of likely or actual difficulties encountered in recruiting pediatric patients to the study. FDA seeks comment on the circumstances in which FDA should permit deferral. FDA also seeks comment on factors that should be considered in determining whether a

product is among those that should be studied in adults before children.

To ensure that deferral would not unnecessarily delay the submission of pediatric use information, FDA has tentatively concluded that a request for deferred submission should 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. To permit FDA to monitor the conduct of postapproval studies to ensure that they were carried out with due diligence, FDA is proposing to amend § 314.81(b)(ii) of the postmarketing reports requirements to require applicants to include in their annual reports whether they have been required to conduct postmarket pediatric studies and, if so, to report the status of those studies. (Additional postmarketing reporting requirements are described under "Remedies," in section V.G of this document.) FDA seeks comment on the types of evidence FDA should examine to ensure that deferred studies are carried out in a timely fashion.

4. Sections 314.50(g)(3) and 601.27(c)--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 widely used in pediatric patients. FDA also does not intend to require pediatric assessments in other situations where the study(ies) necessary to

carry out the assessment are impossible or highly impractical or would pose undue risks to pediatric patients. Thus, §§ 314.50(g)(3) and 601.27(c) would require FDA to grant a waiver of the pediatric study requirement on its own initiative or at the request of the applicant if: (1) The product (a) did not represent a meaningful therapeutic benefit over existing treatments, and (b) was not likely to be used in a substantial number of pediatric patients as a whole, or was not likely to be used in a substantial number of one or more pediatric subpopulations, or (2) necessary studies were impossible or highly impractical, because, for example, the number of such patients was so small or geographically dispersed, or (3) there were evidence strongly suggesting that the product would be ineffective or unsafe in some or all pediatric populations. If a waiver were granted because there was evidence that the product would be ineffective or unsafe in pediatric patients, this information would be included in the product's labeling.

An applicant could request a full waiver of all pediatric studies if one or more of the grounds for waiver applied to the pediatric population as a whole. A partial waiver permitting the applicant to avoid studies in particular pediatric age groups could be requested if one or more of the grounds for waiver applied to one or more pediatric age groups. In addition to the other grounds for waiver, the proposed rule would authorize FDA to grant a partial waiver for those age groups for which a

pediatric formulation was required (see "Pediatric Formulations," in section V.E of this document), if reasonable attempts to produce a pediatric formulation had failed.

The proposed rule would require the applicant to include in the request for a waiver an adequate justification for not providing pediatric use information for one or more pediatric populations. For example, the waiver request could demonstrate that the product was indicated for a disease that does not occur in a substantial number of pediatric patients (e.g., drugs for breast or prostate cancer). The waiver request could demonstrate that the product was a member of a drug class known to be unsafe in specific pediatric age groups (e.g., chloramphenicol, an antibiotic, which has caused serious adverse events in neonates. Also, it is widely known that, except for serious or life threatening diseases where alternative therapy is needed, quinolones, anti-malarial agents, are not recommended in young children due to concerns about cartilage and bone development). Animal toxicity data or imautere metabolic pathways for newborns are examples of data that may be used to demonstrate that the product was a member of a drug class known to be unsafe in specific pediatric age groups.

FDA would grant the waiver request if the agency found that there was a reasonable basis on which to conclude that any of the grounds for a waiver had been met. A full waiver would be appropriate where, for example, the product did not represent a

meaningful therapeutic advance and was not likely to be used in a substantial proportion of any pediatric age group. A partial waiver would be appropriate where, for example, the product was likely to be used in substantial numbers in some pediatric age groups but not others, where the product was likely to be unsafe or ineffective in some age groups, or where reasonable efforts to develop a pediatric formulation necessary for some age groups had failed. If a waiver were granted on the ground that it was not possible to develop a pediatric formulation, the waiver would cover only those pediatric age groups requiring a pediatric formulation.

The agency solicits comments on the proposed grounds for waiving the pediatric study requirement and whether additional grounds may exist, such as whether cost should justify waiver of the pediatric study requirement. Additionally, FDA seeks comment on defining the term "meaningful therapeutic benefit". Comment is also requested on, what should be considered a "substantial number" of pediatric patients, i.e., how the agency should establish a level of expected use in pediatric patients below which pediatric labeling would not be required for a drug that did not represent a meaningful therapeutic advance. FDA is considering two possible methods. The first method would focus on the number of times the drug was expected to be used in pediatric patients, annually. Under this method, FDA has tentatively concluded that 100,000 or more prescriptions or uses

per year in all pediatric age groups would be considered a substantial number. Products that might require studies under this test include anesthetics, anticonvulsants, asthma drugs, antidepressants, antimicrobials and antivirals, vaccines, and drugs to treat certain skin conditions. FDA has also tentatively concluded that a partial waiver for a particular pediatric age group would be available under this method if the product were expected to be prescribed or used fewer than 15,000 times per year in that age group.

The second possible method for establishing the level of expected use would focus on the number of pediatric patients affected by the disease or condition for which the product is intended. Physician mention data from the IMS National Disease and Therapeutic Index[1], shows pediatric use of certain products generally falling within two ranges (i.e., those products either exceeding 100,000 physician mentions for pediatric use per year or those falling below 15,000 physician mentions for pediatric use per year. Thus, under this method, FDA has tentatively concluded that 100,000 pediatric patients affected by the disease or condition for which a product was indicated would be considered a "substantial number" of pediatric patients. A partial waiver for a particular pediatric age group would be

[1]IMS, National Disease and Therapeutic Index, IMS America; Plymouth Meeting, PA.

available under this method if fewer that 15,000 patients in that age group were affected by the disease or condition. FDA seeks

comment on these methods of assessing expected pediatric exposure and on the specific numerical thresholds suggested.

5. Section 314.50(d)(7)--Pediatric Use Section of Application

Under proposed § 314.50(d)(7), applicants would be required to include in their applications a section summarizing and analyzing the data supporting pediatric use information for the claimed indications. The proposed new section of the application would contain an integrated summary of the clinical pharmacology studies, controlled clinical studies, uncontrolled clinical studies, or other data or information that are relevant to the safety and effectiveness, and benefits and risks of the drug in pediatric populations. Because full descriptions of all such studies must already be provided under § 314.50(d)(3) and (d)(5), the new pediatric use section would be required to contain only brief summaries of the studies together with a reference to the full description of each provided elsewhere in the application.

C. Marketed Drug and Biological Products

1. Section 201.23--Required Studies

As discussed in the preamble to the 1994 rule, FDA has the authority, under certain circumstances, to require the manufacturers of marketed drugs that are used in pediatric patients to submit pediatric studies assessing safety and effectiveness for the already approved indications (59 FR 64240 at 64243). Proposed § 201.23 would authorize FDA to require a manufacturer of a marketed drug or biological drug product to

submit an application containing data evaluating the safety and effectiveness of the product in pediatric populations, in compelling circumstances. FDA has tentatively concluded that it should impose such a requirement only where the agency made one of two findings that: (1) The product was widely used in pediatric populations and the absence of adequate labeling could pose significant risks to pediatric patients; or (2) the product was indicated for a very significant or life threatening illness, but additional dosing or safety information was needed to permit its safe and effective use in pediatric patients.

Before requiring a study under § 201.23, the appropriate center, CDER or CBER, would consult with the manufacturer on the type of studies needed and on the length of time necessary to complete them and would notify the manufacturer, by letter, of the center's tentative conclusion that such a study was needed and provide the manufacturer an opportunity to provide a written response and to have a meeting with the center. At the center's discretion, such a meeting could be an advisory committee meeting. If, after reviewing any written response and conducting any requested meeting, CDER or CBER determined that additional pediatric use information were necessary, the center director would issue an order requiring the manufacturer to submit a supplemental application containing pediatric safety and effectiveness data within a specified time. The manufacturer would be able to request reconsideration by the Commissioner for

Food and Drugs (the Commissioner) of the order under the provisions at 21 CFR 10.33.

Proposed § 201.23(c) would require FDA to grant full or partial waivers of study requirements on their own initiative or at request of the applicant for reasons analogous to those which would entitle not-yet-marketed drug and biologic products to waivers.

FDA seeks comment on whether it should codify its authority to require the manufacturers of marketed drugs to conduct pediatric studies, and, if so, the circumstances under which the agency should exercise that authority. The agency also solicits comment on the proposed grounds for waiving the pediatric study requirement for already marketed drug and biological products and whether additional ground may exist, such as whether cost should justify waiver of the pediatric study requirement. Comment is also sought on defining the term "very significant illness".

D. Studies in Different Pediatric Age Groups

Because the pharmacokinetics and pharmacodynamics of a drug or biological product may be different in different pediatric age groups or stages of development, it could be necessary to conduct studies in more than one pediatric age group. The following age categories for the pediatric population are commonly distinguished: (1) Neonates; (2) infants; (3) children, and (4) adolescents. In the 1994 rule, FDA defined neonates as birth up to 1 month, infants as 1 month to 2 years, children as 2 years to 12 years, and adolescents as 12 years to 16 years (59 FR

64242). The need for studies in more than one age group would depend on whether the drug or biological product was likely to be used in each age group (see "Waivers," in sections V.B.4 and V.C.1 of this document) and whether safety and effectiveness in one age group could be extrapolated to other age groups. The metabolism and elimination of the drug and the stage of development of the child may be important in determining which age groups should be tested. There would generally need to be sufficient data, including pharmacokinetic data to establish dosing and safety for each group. (Pharmacokinetic data are generally collected from pediatric patients receiving the drug or biologic as treatment rather than from healthy children.) In cases where the product was expected to have similar pharmacokinetics in more than one age group, pharmacokinetic data

from one age group could be sufficient to support labeling for other age groups. Such extrapolation would not be routine.

FDA recognizes that studies in neonates and young infants present special problems. On one hand, failure to adequately test drugs in this age group has led to both under treatment and, conversely, some of the most serious therapeutic mishaps known to have occurred among pediatric patients. On the other hand, studies in this age group may be significantly more difficult to carry out in the period before or soon after approval than studies in older age groups. However, FDA recognizes that for some conditions, early study would be advantageous. FDA would therefore expect to apply the study requirement to patients in this age group with caution and would, whenever appropriate, permit such studies to occur after the product has been successfully studied in older children. The agency seeks comment on the issues raised by requiring studies in this age group.

E. Pediatric Formulations

In some cases, testing of a product in pediatric patients could require the development of a pediatric formulation. Many children below a certain age are unable to swallow pills and may require a liquid, chewable or injectable form of the product. The need to develop a pediatric formulation does not necessarily mean that the product would not have been used in children in its adult dosage form. In many cases, physicians prescribing tablets to young children direct the parent to grind up the tablet and sprinkle the powder into the child’s food. In other cases,

pharmacists may compound tablets into pediatric formulations of their own choosing. These methods of administering adult dosage forms to children may be unsatisfactory, however, because the bioavailability of any particular product in this form is untested and dosing may be highly variable. A standardized

pediatric formulation ensures bioavailability and consistency of dosing, and permits meaningful testing of safety and effectiveness.

FDA has tentatively concluded that it would be reasonable to expect a manufacturer of a product to produce a pediatric formulation, if one were necessary, only in those cases where a new drug or new biological product provided a meaningful therapeutic benefit over existing treatments, and where the study requirement had not been waived in the age group requiring the pediatric formulation. Proposed §§ 201.23, 314.50(g)(1) and 601.27(a) contain this requirement. The type of formulation needed would vary depending on the age group in which the product were to be used and the disease being treated. Young children unaccustomed to taking drugs may need liquid or chewable formulations, while children with serious and chronic diseases may need only smaller tablets.

The difficulty and cost of producing a pediatric formulation may vary greatly depending upon such factors as solubility of the compound and taste. FDA would waive the requirement for pediatric studies (see "Waivers," in section V.B.4 of this document) in age groups requiring a pediatric formulation, if the manufacturer provided evidence that reasonable attempts to produce a pediatric formulation had failed.

FDA solicits comment on whether it is appropriate to require a manufacturer to develop a pediatric formulation and, if so, the circumstances in which it would be appropriate to impose such a

requirement. For example, should the cost of developing a pediatric formulation justify a waiver of the pediatric study requirement? Should the number of patients affected by the disease or condition in the relevant age group be considered in determining whether to require the development of a pediatric formulation for that age group? Is it appropriate to ask the manufacturer of a not-yet-approved product to allocate resources to developing pediatric formulation(s)? Where cost is a significant issue, would it be appropriate to defer development of a pediatric formulation until after approval of the product? What should be considered "reasonable attempts" to develop a pediatric formulation?

As noted above, FDA was unable to quantify the potential benefits of this rule due to the unavailability of relevant data and studies. Nevertheless, the agency will attempt to assess the benefits of the final rule and solicits comment on the appropriate design and methodology of such measurement. In particular, FDA seeks information and data that would help the agency to: (1) Quantify the societal costs of the adverse drug events experienced by pediatric populations and (2) assess the proportion of these adverse drug events that would be eliminated by the new information that would result from the rule. In addition, FDA seeks information and data that would help the agency to: (1) Quantify the societal costs of the underused or

inadequate drug therapies prescribed to pediatric populations and to (2) assess the proportion of these costs that would be

eliminated by the new information that would result from the rule.

F. Ethical Issues

Ethical concerns may have contributed to reluctance to conduct studies in pediatric patients. To address these concerns, both the American Academy of Pediatrics (Ref. 1) and the Department of Health and Human Services, 45 CFR part 46, subpart D, have developed guidelines or regulations for the ethical conduct of clinical studies in pediatric patients. Because pediatric patients represent a vulnerable population, special protections are needed to protect their rights and to shield them from undue risk. As the American Academy of Pediatrics has observed, however, administration of untested drugs "may place more children at risk than if the drugs were administered as part of well-designed, controlled clinical trials" (Ref. 1 at p. 286). The ethical guidelines currently

in place are designed to protect children's rights and protect them from undue risk. Sponsors should adhere to these guidelines for pediatric studies conducted under this rule. The agency seeks comment on ethical issues that may be raised by this proposal.

G. Remedies

FDA has tentatively concluded that the most practical remedy for failure to submit a required study is an injunctive action brought under the "misbranding" or "new drug" provisions of the act. Denying or withdrawing approval of an otherwise safe and effective drug or biological product is not a satisfactory remedy, because removal of a product from the marketplace could deprive other patients of the benefits of a useful medical product. FDA does not intend to deny or withdraw approval of a product for failure to conduct pediatric studies, except possibly in rare circumstances.

If a manufacturer failed, in the time allowed, to submit adequate studies to evaluate pediatric safety and effectiveness, under proposed §§ 201.23(d) or 314.50(g), FDA could consider the product misbranded under section 502 of the act (21 U.S.C. 352) or an unapproved new drug under section 505(a) of the act (see "Legal Authority," in section VI of this document). When a product is misbranded or an unapproved new drug, sections 302, 303 and 304 of the act (21 U.S.C. 332, 333, and 334) authorize injunction, prosecution or seizure. For violations of this rule,

should it become final, FDA would ordinarily expect to file an enforcement action for an injunction, asking a Federal court 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.

To assist FDA in determining whether pediatric assessments are needed or are being carried out with due diligence, FDA is proposing to amend § 314.81 (other postmarketing reports) to require that annual reports filed by the manufacturer contain information on labeling changes that have been initiated in response to new pediatric data, analysis of clinical data that have been gathered on pediatric use, assessment of data needed to ensure appropriate labeling for the pediatric population, and information on the status of ongoing pediatric studies. Where possible, the annual report would also contain an estimate of patient exposure to the drug product, with special reference to the pediatric population.

FDA seeks comment on appropriate remedies for failure to conduct a required pediatric study and the circumstances, if any, in which the agency should deny or withdraw approval of a drug product.

VI. Legal Authority

Therapeutic tragedies in pediatric patients have prompted some of the most important federal legislation to ensure that

drugs are safe and effective. For example, the act was enacted in 1938 in the wake of a tragedy in which many pediatric patients died after taking an untested medicine called Elixir of Sulfanilamide. The legislative history of this enactment demonstrates that Congress intended to ensure that children, as well as adults, received adequately tested and appropriately labeled drugs. (See, e.g., 78 Congressional Record 567-573 (1934) (statement of Sen. Copeland).)

> Every mother is anxious that the food and medicine given her baby shall be above suspicion. The welfare of every man, woman, and child is involved in the quality and preparation of the foods and drugs sold in America * * *. [T]he purpose of this legislation * * * is to protect the public, to protect the mothers and the children * * *

81 Congressional Record 7312 (1937) (remarks of Rep. Coffee)

The agency has stated, in the context of both pediatric studies and studies in women, that an application for marketing approval should contain data on a reasonable sample of the patients likely to be given a drug or biological product once it is marketed (59 FR 64240 at 64243; 58 FR 39406 at 39409, July 22, 1993). The agency has further stated that in some cases it could require studies in pediatric patients and in women for both not-yet-approved products and marketed products (Id).

The primary rationale for such a requirement is the same for women and pediatric patients. In most cases, drugs and biological products behave similarly in demographic subgroups, including age and gender subgroups, even though there may be variations among the subgroups, based on, for example, differences in pharmacokinetics. Thus, where a drug or biological product is indicated for a disease suffered equally by men, women, and children, and is not contraindicated in women or pediatric patients, the product will be widely prescribed for all three subgroups even if it were studied only in, or labeled only for, men. As described above, there is extensive evidence that many drugs labeled only for adult use are in fact widely used in pediatric patients for the same indications.

FDA notes that this proposal addresses only use of drug products for their approved indications in a significant subpopulation. The proposed rule does not address "off-label" or unapproved uses of approved drugs and biological products, in which an approved product is used for diseases or conditions other than those in the label. This rule would apply only where a product was expected to have clinically significant use in pediatric populations for the indications already claimed by the manufacturer.

In addition to the provisions cited below as authority for the proposed rule, the agency relies on section 701(a) of the act

(21 U.S.C. 371(a)), which authorizes FDA to issue regulations for the efficient enforcement of the act.

A. New Drug and Biological Products

Biological drug products are subject both to section 351 of the Public Health Service Act (the PHS Act) and to the provisions of the act and implementing regulations applicable to drugs, except that manufacturers of biological products covered by approved BLA's are not required to submit NDA's under section 505 of the act. References to "drugs" in the following sections include biological drugs.

1. Sections 502(a), 502(f), 505(d)(7), and 201(n) of the Act

A drug is misbranded under section 502(a) of the act if its labeling is "false or misleading in any particular." Similarly, a new drug application must contain labeling that is not false or misleading (section 505(d)(7) of the act). Section 201(n) of the act (21 U.S.C. 321(n)) defines labeling as misleading if it "fails to reveal facts material * * * with respect to consequences which may result" not only from use of the product as labeled, but "from the use of the [product] * * * under such conditions of use as are customary or usual." Information on dosing and adverse effects are facts "material" to the consequences that may result from customary use in pediatric patients. A drug product is misbranded under section 502(f) of the act, if its label fails to provide adequate directions for each intended use. 21 CFR 201.5 states that adequate directions

must be provided for each use recommended in the labeling *and* each use "for which the drug is commonly used." Thus, FDA may require a product to carry labeling that provides safety and effectiveness information on use in subpopulations in which the product is customarily or commonly used.

There is extensive evidence that drugs for diseases that affect both adults and pediatric patients are routinely used in pediatric patients despite the absence of pediatric labeling, and even in the face of disclaimers stating that safety and effectiveness have not been established in children. FDA may therefore consider pediatric use to be "customary or usual" or "commonly used" where the drug is indicated for a disease or condition that affects both adults and children, and the drug is not contraindicated in pediatric patients. In many cases, the use in pediatric patients of a drug labeled only for adults will increase over time, as physicians become aware of the drug’s potential usefulness in children and familiar with the drug’s uses and effects. Thus, FDA may conclude that a drug that was appropriately labeled for adult use at the time of approval is, at some later date, no longer appropriately labeled.

2. Sections 201(p), 301(a), and 505(a) of the Act

Under section 301(a) and (d) of the act (21 U.S.C. 331(a) and (d)) and section 505(a) of the act, a drug product is subject to enforcement action if it is a "new drug" for which no NDA has been approved. A product is a new drug under section 201(p) of

the act if it is not recognized to be safe and effective under the conditions "prescribed, recommended, or suggested" in the drug's labeling. There is widespread evidence that, despite the absence of pediatric labeling, drugs are routinely used in pediatric patients for the labeled indications. FDA may therefore consider pediatric use to be "suggested" in a drug's labeling where the drug is indicated for a disease or condition that affects both adults and pediatric patients, unless the drug is specifically contraindicated for pediatric patients. As described above, because pediatric use of new drugs often increases over time, FDA may conclude that labeling that is appropriate at the time of approval is later no longer appropriate.

3. Section 502(j) of the Act

Section 502(j) of the act defines as misbranded those drugs that are dangerous to health when used in the manner prescribed, recommended, or suggested in their labeling. FDA may consider pediatric use to be "suggested" in a drug's labeling where the drug is indicated for a disease or condition that affects both adults and pediatric patients, unless the drug is specifically contraindicated for pediatric patients. As described earlier in this notice, the absence of pediatric testing and labeling poses risks to children including the risk of unanticipated adverse reactions, and under-and over-dosing.

4. Section 505(i) and (k) of the Act

Section 505(i) of the act that authorizes the issuance of regulations governing the use of investigational drugs, and the proviso in 505(k) of the act, which requires regulations issued under 505(i) to have "due regard * * * for the interests of patients," together authorize FDA to impose conditions on the investigation of new drugs, including conditions related to the ethics of a proposed investigation and to the interests of patients. Fairness in distribution of the burdens and benefits of research is one of the ethical principles underlying federal regulations on investigational drugs. (See, e.g., 44 FR 23192 at 23194, April 18, 1979 ("Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research").) Because exclusion of pediatric patients from clinical trials may deny them an equitable share of the benefits of research, section 505(i) and (k) authorize FDA to require their inclusion in clinical trials.

5. Section 351 of the Public Health Service Act

Section 351 of the PHS Act (42 U.S.C. 262) provides authority to regulate the labeling and shipment of biological products. Under section 351(d), licenses for biological products are to be issued only upon a showing that they meet standards "designed to insure the continued safety, purity, and potency of such products" prescribed in regulations. The "potency" of a biological product includes its effectiveness (21 CFR 600.3(s)).

B. Marketed Drug Products

1. Section 502(f) of the Act and 21 CFR 201.5

A drug product is misbranded under section 502(f) of the act, if its label fails to provide adequate directions for each intended use. 21 CFR 201.5 states that adequate directions must be provided for each use recommended in the labeling *and* each use "for which the drug is commonly used." Where there is evidence that a drug product is widely used in pediatric patients, failure to provide adequate directions for the use could misbrand the product.

2. Sections 502(a) and 201(n) of the Act

A drug is misbranded under section 502(a) of the act if its labeling is false or misleading. Section 201(n) of the act defines labeling as misleading if it fails to reveal facts that are material in light of the consequences of the customary or usual use of the product. Where a drug is widely used in pediatric patients, FDA may consider pediatric use to be "customary." Failure to provide adequate information on dosing and adverse effects in the pediatric population could render the product misbranded, even where the manufacturer does not promote the product for that subpopulation.

3. Section 502(j) of the Act

Section 502(j) of the act defines as misbranded those drugs that are dangerous to health when used in the manner prescribed, recommended, or suggested in their labeling. FDA may consider pediatric use to be "suggested" in a drug’s labeling where the drug is indicated for a disease or condition that affects both adults and pediatric patients, unless the drug is specifically contraindicated for pediatric patients. As described earlier in this notice, the absence of pediatric testing and labeling poses risks to children including the risk of unanticipated adverse reactions, and under-and over-dosing.

4. Section 505(k) of the Act

Section 505(k) of the act authorizes FDA to order the holder of an approved NDA to submit reports of data necessary to determine whether there are grounds to withdraw approval of the

NDA. FDA has in the past issued regulations under section 505(k) of the act (formerly section 505(j) of the act) requiring postapproval studies of certain drugs (see, e.g., 21 CFR 310.303 ("Continuation of long-term studies, records, and reports on certain drugs for which new drug applications have been approved")(1972); 21 CFR 310.304 ("Drugs that are subjects of approved new drug applications and that require special studies, records, and reports")(1972); and 21 CFR 310.500 ("Digoxin products for oral use; conditions for marketing")(1974)). Section 505(k) of the act also authorizes the agency to require other postmarketing reports on drug products.

5. Section 351 of the Public Health Service Act

Section 351(d) of the PHS Act authorizes FDA to ensure the "continued safety, purity, and potency" of biological products. Section 351(b) of the PHS Act prohibits false labeling of a biological product.

VII. Implementation Plan

All applications for drug and biological products covered by the final rule would be required to contain an assessment of pediatric safety and effectiveness for the claimed indications, unless the applicant has obtained a waiver or deferral of this requirement from FDA.

FDA proposes that the final rule become effective 90 days after the date of its publication in the FEDERAL REGISTER. For new drug and biologic product applications submitted before the

effective date of the final rule, the agency proposes a compliance date of 21 months after the effective date of the

final rule. For new drug and biologic product applications submitted on or after the effective date of the final rule, the agency proposes a compliance date of 15 months after the effective date of the final rule. The agency solicits comments on the proposed effective date and proposed compliance dates.

VIII. Paperwork Reduction Act of 1995

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

FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Pediatric Safety and Effectiveness Reporting Requirements for Certain Drugs and Biological Products.

Description: FDA is proposing reporting requirements that include: (1) Reports on planned pediatric studies in investigational new drug applications (IND's) (proposed § 312.23(a)(10)(iii)); (2) Reports assessing the safety and effectiveness of certain drugs and biological products for pediatric use in new drug applications (NDA's) and biologic license applications (BLA's) or in supplemental applications (proposed § 314.50(g)(1)); (3) Analyses of data on pediatric safety and effectiveness in NDA's (proposed § 314.50(d)(7)); (4) Postmarketing reports of analyses of data on pediatric safety and effectiveness (proposed § 314.81(b)(2)(vi)(C)); (5) Postmarketing reports on patient exposure to certain marketed drug products, analyzed and age (proposed § 314.81(b)(2)(i)); (6) Postmarketing reports on labeling changes initiated in response to new pediatric data (proposed § 314.81(b)(2)(vi)(C)); and (7) Postmarketing reports on the status of required postapproval studies in pediatric patients (proposed § 314.81(b)(2)(vii)). The purpose of these reporting requirements is to address the lack of adequate pediatric labeling of drugs and biological products by requiring the submission of evidence on pediatric safety and effectiveness for products with clinically significant use in children.

Description of Respondents: Sponsors and manufacturers of drugs and biological products.

Table 1.--Estimated Annual Reporting Burden

CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
201.23	2	1	2	16	32
314.50 (d)(7)	150	1	150	8	1,200
314.50 (g)(1)	10	1	10	16	160
314.50 (g)(2)	9	1	9	8	72
314.50 (g)(3)	15	1	15	8	120
314.81 (b)(2)(i)	625	1	625	1.5	937.5
314.81 (b)(2) (vi)(c)	625	1	625	1.5	937.5
314.81 (b)(2) (vii)	625	1	625	1.5	937.5
601.27(a)	1	1	1	16	16
601.27(b)	1	1	1	16	16
601.27(c)	1	1	1	16	16
Total:					4,444.5

There are no capital or operating and maintenance costs associated with this collection of information.

The agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding information collection by (insert date 30 days after date of publication in the FEDERAL REGISTER) to the Office of Information and Regulatory

Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA.

IX. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8), (a)(11), and (e)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

X. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act (Pub. L. 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the agency must analyze regulatory options that would minimize the impact of the rule on small entities. The Unfunded Mandates Reform Act (Pub. L. 104-4) (in section 202) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an

annual expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation).

The agency has reviewed this proposed rule and has determined that the proposed rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866, and these two statutes. This proposal is a significant regulatory action as defined by the Executive Order due to the novel policy issues it raises. With respect to the Regulatory Flexibility Act, the Commissioner certifies that the rule will not have a significant economic impact on a substantial number of small entities. Since the proposed rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in an annual expenditure of $100,000,000 or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act.

A. Purpose

The FDA is proposing that a limited class of important new drugs and biologicals that are likely to be used in pediatric patients contain sufficient data and information to support directions for this use. As the approved labeling for many of these new products lack relevant pediatric information, any use in children greatly increases the risk of inappropriate dosing, unexpected adverse effects, and suboptimal therapeutic outcomes. The proposed rule is designed to ensure that new drugs, including

biological drugs, that are therapeutically important and/or likely to be widely used in children contain adequate pediatric labeling at the time of, or soon after, approval.

B. Number of Affected Products and Required Studies

Neither the precise number of new drugs that would require additional pediatric studies nor the cost of these studies can be predicted with certainty. To develop plausible estimates, FDA examined the pediatric labeling status at time of approval for each NME and important biological approved from 1991 to 1995, and used these estimates to project the cost that would have occurred had the proposed rule been in place over that period. The agency assumes that future costs would be reasonably similar. As shown in Table 2, each new drug was assigned to one of three categories: (1) Therapeutically important, some potential pediatric use, (2) other approvals, potential for wide pediatric use, and (3) all other approvals. (The first two categories include all products that the agency believes would have met the therapeutic importance and pediatric use threshold criteria set forth in this proposed rule. The third category includes all products that would not have met these criteria.) For NME's, these category assignments were based on pediatric pages completed by CDER's reviewing division at the time of each approval, the priority review designation for each drug, and

physician mention data from the IMS National Disease and Therapeutic Index.[2] All priority NME's were assumed to be therapeutically important, and assigned to the first category, unless the drug’s pediatric page specifically noted a low potential for pediatric use or the IMS data indicated no pediatric use. For nonpriority NME's, FDA assumed that wide

[2]IMS, National Disease and Therapeutic Index, IMS America; Plymouth Meeting, PA. FDA’s analysis does not include data from 1996 because the IMS data are not yet available.

pediatric use would have been expected for only those products that exceeded 100,000 physician mentions for pediatric use during 1995. Assessments of therapeutic importance for biologicals were developed retrospectively by CBER.

As shown, 60 of the 142 approvals (42 percent) over this 5-year period fell into the first two categories; that is, 47 drugs were classified as therapeutically important with at least some potential pediatric use and 13 less therapeutically important drugs were designated as offering a potential for wide pediatric use based on physician mentions. The 82 drugs (58 percent) grouped under the third category would presumably not have met the therapeutic importance and pediatric use criteria of the proposed rule.

Table 2.--Estimated Number of NME's and Biologicals Approved in 1991-95 (That Would Have Been Affected by the Proposed Rule)

Pediatric Labeling Status	Number of Approved Drugs	Percent of Approved Drugs
Therapeutically important, some potential pediatric use	**47**	33%
Some pediatric labeling	16	
No pediatric labeling	31	
Other approvals, potential for wide pediatric use	**13**	9%
Some pediatric labeling	7	
No pediatric labeling	6	
Subtotal	60	42%
Some pediatric labeling	23	
No pediatric labeling	37[1]	
All other approvals	**82**	58%
TOTAL APPROVALS	**142**	100%
[1]Pediatric page shows seven ongoing pediatric studies		

In assessing the amount of additional research that would have been required for the 60 drugs from the first two categories (those that would have potentially been affected by the proposed rule), FDA believes that most would not have required extensive additional clinical trials. As FDA explained in the 1994 final rule (59 FR 64240), extrapolations from adult effectiveness data based on pharmacokinetics studies and other safety data can be sufficient to provide the necessary dosing pediatric information for those drugs that work by similar mechanisms in adults and children. The agency estimates that the majority of these 60

drugs could, to some extent, rely on such extrapolations. Although the proposed rule identifies four pediatric subgroups: (1) Neonates, (2) infants, (3) children, and (4) adolescents, the need for studies in more than one age group depends on the likely use of the drug in each age group and on whether relevant data can be extrapolated to other age groups. As a rule, individual clinical trials would rarely be required for each age group for a given drug.

Estimates of the size of the studies that would have been required to support pediatric labeling for these 60 drugs vary from 20 patients where the simplest type of pharmacokinetic study would be adequate, to 70 to 120 pediatric patients for studies where some safety and effectiveness data would be needed, to several hundred pediatric patients for studies where more substantial safety and effectiveness data would be required. Thus, for the purpose of developing order-of-magnitude cost estimates, FDA further subdivided the 60 potentially affected drugs into three distinct groupings. The first group of 30 drugs would have required the least amount of new data and includes both the 7 drugs for which the CDER pediatric pages indicate that pediatric trials were already underway and the 23 drugs that already had at least some pediatric labeling at the time of approval. Based on a review of those labels at approval time, FDA estimated that up to half, or 15 of these 30 drugs may have

needed limited additional data that would have involved new studies with, on average, 50 pediatric patients each.

Next, FDA assumed that 23 drugs (about three quarters of the remaining 30) would have required new pediatric studies with data from about 100 patients each. Finally, FDA assumed that the remaining 7 drugs would have needed more extensive safety and effectiveness data, requiring 300 pediatric patients for each drug. Consequently, FDA estimates that, if this proposed rule had been in effect from 1991 to 1995, sponsors of 45 of the 60 potentially affected drugs would have needed to obtain additional data from about 5,150 pediatric patients (15 drugs x 50 patients + 23 drugs x 100 patients + 7 drugs x 300 patients). The proposed regulation, therefore, would have required additional pediatric research for an estimated average of 9 new drugs and about 1,030 pediatric patients per year.

In addition, the proposed rule permits the agency to request pediatric data for certain drugs that are already marketed. While the precise impact of this regulatory provision is uncertain, FDA expects that it would affect no more than two drugs per year. If the submission for one of these drugs relied on data from 100 pediatric patients and the other from 300 pediatric patients, the total number of drugs that would have required additional research reaches 11 per year and the total number of pediatric patients about 1,430 per year.

Other costs for pediatric research may accrue to drugs that ultimately fail to gain regulatory approval. Although many drug sponsors would wait until they are relatively certain that their product will be shown safe and effective for the indicated use in adults before spending substantial resources on pediatric uses, other sponsors may need to begin pediatric examinations earlier to have data included with the new drug or product licence application. It is difficult for FDA to judge how much additional pediatric research would be directed towards products that are not approvable. The agency notes, however, that because only about 65 percent of all NME's that enter phase III trials are eventually approved, the number of drugs entering phase III trials is about 54 percent greater than the number of actual approvals (100/65 = 1.54). Since some, but not all, of these unapprovable drugs would initiate some pediatric research, FDA has increased its estimate of the annual number of affected drugs and pediatric patients by 30 percent, to a projected total of 14 drugs and about 1,850 pediatric patients per year.

The agency is aware that forecasting future trends based on historical data can be imprecise. For example, over time, even in the absence of this rule, the percentage of new drugs with labels that provide adequate pediatric use information could change. At this time, however, FDA is not aware of any marked trend. Also, the above estimates ignore those pediatric studies that were promised, but not yet underway at the time of drug

approval. To the extent that these commitments are honored, the above estimates of research attributable to the regulation are overstated. Finally, the methodology implies that the standards used by FDA to judge the 1991-1995 approvals would remain unchanged. While subsequent change is possible, FDA does not anticipate that its present views would differ substantially. Thus, while acknowledging substantial uncertainty, the agency's cost estimates are based on the assumption that the proposed rule would require additional research on about 14 drugs, involving a total of 1,850 pediatric patients per year.

C. Cost of Studies

The agency finds that the cost of conducting clinical research with pediatric patients varies directly with the size, duration, and complexity of the clinical research. Although FDA has little detailed information on the cost to drug sponsors of conducting research on clinical patients, one private consulting firm reports that the costs of hiring clinical investigators to conduct phase IV pediatric drug trials ranges from $300-$500 per patient for studies on vaccines or fevers to $3,600 and $5,000 per patient for renal disease and epilepsy, respectively.[3] Similarly, a number of academic researchers have reported average costs of from $1,500 to $3,400 per patient for pediatric trials. These estimates, however, do not account for the many

[3]DataEdge, LLC, Faxed data, March 7, 1997.

administrative, monitoring, data analysis, and document preparation tasks that would be required of a drug sponsor. Since a published study suggests that a total accounting of all sponsor costs may be three times as great as investigator costs,[4] FDA has assumed that the average costs of conducting the newly required studies would range from $5,000 to $9,000 per pediatric patient. As a result, the estimated 1,850 additional pediatric patients that would need to be studied annually suggests new research costs to the pharmaceutical industry of between $9.25 million and $16.65 million per year.

In addition, the testing of a new drug in children would sometimes require the development of a new pediatric dosage form. (Typically a liquid or suspension formulation in place of a tablet or capsule.) Of the 47 drugs identified in the first category of Table 2 (therapeutically important with some potential pediatric use), 14 (30 percent) were available only in tablets or hard capsules at the time of approval. (Manufacturers of 4 of these 14 have since developed oral suspensions.) It seems reasonable, therefore, to assume that, of the 14 new drugs per year estimated to require additional pediatric research, about 4 might require new formulations. The agency solicits comment on the estimate that four new formulations would be required per year.

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[4]Thomas Hill, "Calculating the Cost of Clinical Research," Scrip Magazine, p. 29, March 1994.

The effort and cost of developing such formulations could be substantial. Drug developers and manufacturers would have to find appropriate solvents and develop additional data for demonstrating adequate product stability, bioavailability, and production process validation. While such costs would vary with the particular drug type, one industry consultant suggests that per drug laboratory costs could average from $300,000 to $500,000 and corresponding regulatory requirements could bring this figure close to $1 million. Moreover, this estimate assumes the availability of adequate preclinical data on animal toxicity and metabolic rates. Since the proposed rule permits FDA to waive the requirement for reformulation where reasonable attempts have failed, the agency assumes that the additional costs would not exceed $1 million apiece for 4 drugs, or an additional $4 million per year.

Finally, the rule will impose additional paperwork burdens related to new label content, postmarket reporting requirements, and written requests for deferred submissions and waivers. As shown above, FDA estimates that these paperwork activities will require about 4,400 hours annually. At an average compensation rate of $50 an hour, this cost amounts to about $220,000 per year.

In sum, FDA anticipates that the annual costs of this proposed rule will total between $13.5 and $20.9 million per year.

D. Other Impacts

Other potential impacts would occur if the requirements contributed to delays in the submittal of NDA's. Extended drug development times would be associated with significant additional industry costs. FDA has attempted to minimize the likelihood of regulatory delays through plans for early consultation with drug sponsors and a willingness to consider deferred submissions for pediatric studies. However, the agency recognizes the importance of this issue and solicits public comment on the best means to obtain adequate and timely pediatric information without slowing the process for bringing new drugs to market. Also, as noted earlier in this preamble, the agency is aware that new pediatric supplements could impose additional user fees on drug sponsors and is considering means to alleviate this added burden. All user fee issues will be resolved before issuance of the final rule. Overall, therefore, compared to the hundreds of millions of dollars typically required to bring a new drug to market, FDA believes that the added regulatory impact imposed by this rule would be unlikely to threaten the economic viability of any promising research and development project.

E. Benefits

This proposed rule is aimed at addressing two problems associated with inadequate directions for pediatric uses of drugs: (1) Avoidable adverse drug reactions in children, i.e., drug reactions that occur because of the use of inadvertent drug

overdoses or other drug administration problems that could have been avoided with better information on appropriate pediatric use; and (2) undertreatment of children with a potentially safe and effective drug, because the physician either prescribed an inadequate dosage or regimen, prescribed a less effective drug, or did not prescribe a drug, due to the physician's uncertainty about whether the drug or the dose was safe and effective in children. Thus, the primary benefits expected from this proposed rule are the reductions in avoidable adverse drug reactions and undertreatments that would result from better informing physicians about whether, and in what dosages, a given drug was safe and effective for use in children.

FDA is aware of no systematic data in the literature that evaluate the magnitude of harm that results from inadequate information on the use of drugs in children, although numerous anecdotes and case examples exist. Physicians who care for HIV-

infected children, for example, have expressed frustration at their inability to treat these children with drugs known to be effective in adults, because they lack information on how to do so safely or effectively.[5] As mentioned previously in this preamble, history is replete with examples of children who have died or suffered other serious adverse effects as a result of the use of drugs that have not been tested in children and for which better, alternative treatments were available. Many of these adverse events (e.g., "gray baby syndrome" in babies treated with chloramphenicol) develop quickly and would be detected in early clinical studies.

While FDA could not develop a quantitative estimate of the potential benefits of the proposed rule, the agency attempted to gain some more systematic insight into the benefits that might accrue by examining the rate at which each of 20 NME's (approved between 1991 and 1995) were mentioned in the 1996 IMS National Drug and Therapeutics Index (an outpatient drug use data base). The drugs examined were all of those that could be analyzed in this IMS data base, lack full pediatric labeling, were considered to need further pediatric studies at the time of approval, and would have been affected by the proposed rule. FDA found that, after adjusting for the prevalence of the relevant diagnoses in

[5]Time, March 1997.

children and adults, 15 of the 20 drugs were mentioned less frequently in association with pediatric treatments than with

adult treatments for the same set of approved indications. In 11 of these 15 drugs, pediatric treatment mentions were less than half as frequent. Although it is not possible to conclude, based on these data, that children with those diagnoses are necessarily undertreated relative to adults, these data are consistent with the hypothesis that the lack of pediatric labeling leads to suboptimal treatment of children.

FDA also examined the number of adverse drug events (ADE's) reported to the agency from 1991 through 1996 for all NME's approved during that time. Of the 25 NME's associated with the highest number of ADE's in children, 8 NME's (responsible for 1,273 pediatric ADE's sufficiently severe to be reported to FDA) had no labeling for use in children at all. An additional 5 NME's (responsible for 434 pediatric ADE's) were labeled for use only in children age 12 and over. Furthermore, of these 13 NME's, 11 would probably have been required to be the subject of further pediatric studies (or of a justification for the lack of studies) under the conditions of this proposed rule if it had been in place at the time of the drug’s approval. While it is not possible to conclude that all (or even most) of these ADE's would have been avoided had these drugs been fully labeled for pediatric use, these data confirm that there is substantial pediatric use of drugs not labeled for such use; that this use is associated with ADE's, including serious ADE's; and that the improved knowledge and labeling that would result from this

proposed rule could bring significant benefits to children treated with these drugs. The agency solicits information on any available studies or data related to the incidence and costs of either undertreatment or avoidable ADE's in pediatric age groups due to the lack of information on the effects of pharmaceuticals.

F. Small Entities

FDA believes that this proposed rule will not have a significant economic impact on a substantial number of small entities. New drug development is typically an activity completed by large multinational drug firms. FDA reviewed the size of every company that submitted the 60 new drug and biological applications that would likely have been affected by this rule between 1991 and 1995 (see the first two categories in Table 1). Over this 5-year period, only two were for products sponsored by small businesses as defined by the Small Business Administration. Because so few small firms are likely to be significantly affected in any given year, the Commissioner certifies that this rule will not have a significant economic impact on a substantial number of small entities. Therefore, no further analysis is required under the Regulatory Flexibility Act. The agency notes, however, that where pediatric use qualifies as an orphan indication, some of these added research costs could be reimbursed under the various grant and tax deduction provisions of the Orphan Drug Act.

XI. Request For Comments

Interested persons may, on or before (insert date 90 days after publication in the FEDERAL REGISTER), submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals my submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA.

XII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Committee on Drugs, American Academy of Pediatrics, Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations, Pediatrics, 95(2):286-294, 1995.

2. Pina, L. M., Drugs widely used off label in pediatrics, Report of the pediatric

use survey working group of the pediatric subcommittee. Draft.

3. Cote, C. J. et al., "Is the therapeutic orphan about to be adopted?" Pediatrics, 98(1):118-123, 1996.

4. Koren, G. et al., "Unexpected alterations in fentanyl pharmacokinetics in pediatric patients undergoing cardiac surgery: age related or disease related?" Developmental Pharmacology Therapeutics, 9:183-191, 1986.

5. Gauntlett, I. S. et al., "Pharmacokinetics of fentanyl in neonatal humans and lambs: Effects of age," Anesthesiology, 69:683-687, 1988.

6. Powell, D. A. et al., "Chloramphenicol: New perspectives on an old drug," Drug Intelligences & Clinical Pharmacy, 16:295-300, 1982.

7. Oski, F. A. et al., Principles and Practice of Pediatrics, 2d Edition, J. B. Lippincott Co., Philadelphia, p. 864, 1994.

8. Nathan, D. G. et al., Hematology of Infancy and Childhood, 4th Edition, W. B. Saunders Co., Philadelphia, p. 92, 1993.

9. Kauffman, R. E., "Fentanyl, fads, and folly: who will adopt the therapeutic orphans?" Journal of Pediatrics, 119:588-589, 1991.

10. McCloskey, J. J. et al., "Bupivacaine toxicity secondary to continuous caudal epidural infusion in pediatric patients," Anesthesia and Analgesia, 75:287-290, 1992.

11. Fisher, D. M. et al., "Neuromuscular effects of vecuronium (ORG NC45) in infants and pediatric patients during N_2O halothane anesthesia," Anesthesiology, 58:519-523, 1983.

12. Agarwal, R. et al., "Seizures occurring in pediatric patients receiving continuous infusion of bupivacaine," Anesthesia and Analgesia, 75:284-286, 1992.

13. Mevorach, D. L. et al., "Bupivacaine toxicity secondary to continuous caudal epidural infusion in pediatric patients," Anesthesia and Analgesia, 77:13005-1306, 1993.

14. Editorial: "Cystic fibrosis and colonic strictures," Journal of Clinical Gastroenterology, 21(1):2-5, 1995.

15. Olkkola, K. T. et al., "A potentially hazardous interaction between erythromycin and midazolam," Clinical Pharmacology Therapeutics, 53:298-305, 1993.

16. Hiller, A. et al., "Unconsciousness associated with midazolam and erythromycin," British Journal of Anaesthesia, 65:826-828, 1994.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, and Safety.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and Recordkeeping Requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

Therefore under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to

the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 201, 312, 314, and 601 be amended as follows:

PART 201--LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 510, 512, 530-542, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg-360ss, 371, 374, 379e); secs. 215, 301, 351, 361 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 264).

2. New § 201.23 is added to subpart A to read as follows:

§ 201.23. Required pediatric studies.

(a) A manufacturer of a drug product, including a biological drug product, that is widely used in pediatric patients, or that is indicated for a very significant or life threatening illness, but whose label does not provide adequate information to support its safe and effective use in pediatric populations for the claimed indications may, in compelling circumstances, be required to submit an application containing data adequate to assess whether the drug product is safe and effective in pediatric populations. The application may be required to contain adequate evidence to support dosage and administration in some or all pediatric subpopulations, including neonates, infants, children, and adolescents, depending upon the

known or appropriate use of the drug product in such subpopulations. The applicant may be required to develop a pediatric formulation for a drug product that is indicated for a very significant or life threatening illness for which a pediatric formulation is necessary, unless the manufacturer demonstrates that reasonable attempts to produce a pediatric formulation have failed.

(b) The Food and Drug Administration (FDA) may, by order issued by the Center for Drug Evaluation and Research (CDER) or Center for Biologic Evaluation and Research (CBER) Center Director, after notifying the manufacturer of its intent and offering an opportunity for a written response and a meeting, which may include an advisory committee meeting, require a manufacturer to submit an application containing the information described in paragraph (a) of this section within a time specified in the letter, if FDA finds that:

(1) The drug product is widely used in pediatric populations for the claimed indications and the absence of adequate labeling could pose significant risks to pediatric patients; or

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

(c)(1) FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant.

(2) An applicant may request a full waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) Necessary studies are impossible or highly impractical, e.g., because the number of such patients is so small or geographically dispersed; or

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

(3) An applicant may request a partial waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The drug product:

(A) Is not indicated for a very significant or life threatening illness; and

(B) Is not likely to be used in a substantial number of patients in that age group; or

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed; or

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

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

(4) The request for a waiver must provide an adequate justification.

(5) FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraph (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation.

If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(d) If a manufacturer fails to submit a supplemental application containing the evidence described in paragraph (a) of this section within the time specified by FDA, and the Center Director of CDER or CBER, under the requirements of paragraph (c) of this section, has not granted a waiver, the drug product may be considered misbranded or an unapproved new drug.

PART 312--INVESTIGATIONAL NEW DRUG APPLICATION

3. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371); sec. 351 of the Public Health Service Act (42 U.S.C. 262).

4. Section 312.23 is amended by redesignating paragraph (a)(10)(iii) as paragraph (a)(10)(iv) and adding new paragraph (a)(10)(iii) to read as follows:

§ 312.23 IND content and format.

(a) * * *

(10) * * *

(iii) Pediatric studies. If the drug is a new chemical entity, plans for assessing pediatric safety and effectiveness.

5. Section 312.47 is amended by revising paragraph (b)(1)(i) and the second sentence of paragraph (b)(2) and by adding a new sentence after the fifth sentence to paragraph (b)(1)(v) to read as follows:

* * * * *

§ 312.47 Meetings.

* * * * *

(b) * * *

(1) End-of-Phase 2 meetings--(i) Purpose. The purpose of an end-of-phase 2 meeting is to determine the safety of proceeding to phase 3, to evaluate the phase 3 plan and protocols and the adequacy of plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

* * * * *

(v) Conduct of meeting. * * * FDA will also provide its best judgment, at that time, of the pediatric studies that will be required for the drug product and their timing. * * *

(2) "Pre-NDA" meetings. * * * The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to identify current or planned studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application.* * *

* * * * *

6. Section 312.82 is amended by revising the last sentence of paragraph (a) and the second sentence of paragraph (b) to read as follows:

§ 312.82 Early consultation.

* * * * *

(a) Pre-investigational new drug (IND) meetings. * * * The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.

(b) End-of-phase 1 meetings. * * * The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the drug in pediatric patients. * * *

PART 314--APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

7. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

8. Section 314.50 is amended in subpart B by redesignating paragraphs (g) through (k) as paragraphs (h) through (l) and by adding new paragraphs (d)(7) and (g) to read as follows:

§ 314.50 Content and format of an application.

* * * * *

(d) * * *

(7) Pediatric use section. A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or

uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and

risks of the drug in pediatric populations for the claimed indications, and a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section.

* * * * *

(g) Pediatric use information--(1) General requirements. Except as provided in paragraphs (d)(2) and (d)(3) of this section, each application for a new chemical entity shall contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in pediatric populations, including neonates, infants, children, and adolescents, and to support dosing and administration information for each pediatric subpopulation for which the drug is safe and effective. Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults based on other information, such as pharmacokinetic studies. Studies may not have to be carried out in each pediatric age group, if data from one age group can be extrapolated to others. Assessments of safety and effectiveness required under this section for a drug product that represents a meaningful therapeutic benefit over existing treatments for pediatric patients must be carried out using appropriate formulations for each age group(s) for which the assessment is required.

(2) Deferred submission. FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (g)(1) of this section until after approval of the drug product

for use in adults. If an applicant requests deferred submission, the request must provide a certification from the applicant of the grounds for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time. If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the drug product may be approved for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(3) Waivers--(i) FDA may grant a full or partial waiver of the requirements of paragraph (g)(1) of this section on its own initiative or at the request of an applicant.

(ii) An applicant may request a full waiver of the requirements of paragraph (g)(1) of this section if the applicant certifies that:

(A) The drug product:

(1) Does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients; and

(2) Is not likely to be used in a substantial number of pediatric patients; or

(B) Necessary studies are impossible or highly impractical, e.g., because the number of such patients is so small or geographically dispersed; or

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

(iii) An applicant may request a partial waiver of the requirements of paragraph (g)(1) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(A) The drug product:

(1) Does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients in that age group; and

(2) Is not likely to be used in a substantial number of patients in that age group; or

(B) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed; or

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

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

(iv) The request for a waiver must provide an adequate justification.

(v) FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver

specified in paragraph (g)(2) or (g)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

* * * * *

9. Section 314.81 is amended by adding two new sentences at the end of paragraph (b)(2)(i) and a new paragraph (b)(2)(vi)(c) and by revising paragraph (b)(2)(vii) to read as follows:

§ 314.81 Other postmarketing reports.

* * * * *

(b) * * *

(2) * * *

(i) Summary. * * * The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) should be provided, including dosage form.

* * * * *

(vi) * * *

(c) Analysis of available safety and efficacy data conducted or obtained by the applicant in the pediatric population and changes proposed in the label based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population should be included.

(vii) Status reports. A statement on the current status of any postmarketing studies performed by, or on behalf of, the applicant. The statement shall include the status of postmarketing clinical studies in pediatric populations required or agreed to, e.g., to be initiated, ongoing (with projected completion date), completed (including date), completed and results submitted to the NDA (including date). To facilitate communications between FDA and the applicant, the report may, at the applicant's discretion, also contain a list of any open regulatory business with FDA concerning the drug product subject to the application.

* * * * *

PART 601--LICENSING

10. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 513-516, 518-520, 701, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 374, 379e, 381); secs. 215, 301, 351, 352 of the

Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2-12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451-1461).

11. New § 601.27 is added to subpart C to read as follows:

§ 601.27 Pediatric studies.

(a) General requirements. Except as provided in paragraphs (b) and (c) of this section, each application for a new biological product for which the applicant has not previously obtained approval shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in pediatric populations, including neonates, infants, children, and adolescents, and to support dosing and administration information for each pediatric subpopulation for which the product is safe and effective. Where the course of the disease and the effects of the product are similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled effectiveness studies in adults, based on other information, such as pharmacokinetic studies. In addition, studies may not have to be carried out in each pediatric age group, if data from one age group can be extrapolated to others. 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.

(b) Deferred submission. FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (a) of this section until after licensing of the product for use in adults. If an applicant requests deferred submission, the request must provide an adequate justification for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time. If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the product may be licensed for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(c) Waivers. (1) FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant.

(2) An applicant may request a full waiver of the requirements of paragraph (a) of this section if:

(i) The product:

(A) Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and

(B) Is not likely to be used in a substantial number of pediatric patients; or

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

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

(3) An applicant may request a partial waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if:

(i) The product:

(A) Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and

(B) Is not likely to be used in a substantial number of patients in that age group; or

(ii) Necessary studies are impossible or highly impractical, e.g., because the number of patients in that age group is so small or geographically dispersed; or

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

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

(4) The request for a waiver must provide an adequate justification.

(5) FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraph (c)(2) or (3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is

granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product’s labeling.

Dated: _____.

_____
Michael A. Friedman
Lead Deputy Commissioner for the
Food and Drug Administration

_____
Donna E. Shalala
Secretary of Health and Human Services

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