

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

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 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. 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
- (2) assess the proportion of these costs that would be

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

²IMS, 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 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

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

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

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.

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

⁵Time, March 1997.

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 may 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 N₂O 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 CDER or 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) 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 sixth 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 adding new paragraphs (d) (7) and (g) and by redesignating paragraphs (g) through (k) as paragraphs (h) through (l) 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) 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) 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 revising paragraph (b) (2) (vii) and by adding two new sentences at the end of paragraph (b) (2) (i) and a new paragraph (b) (2) (vi)(C) 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) 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,

(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 paragraphs (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