

Based upon these comments, FDA has decided to increase the agency's proposed burden estimates. These revisions are reflected in the Table 2 of this document. In addition, the burden estimates for §§ 314.55(a), (b), and (c), and 601.27(a), (b), and (c), have increased because of the new requirements in the final rule to include, in addition to applications for new chemical entities and never-before-approved biologics, applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration. These estimates are based upon FDA's analysis of all marketing applications and efficacy supplements approved over the 5-year period of 1993 to 1997 and those that would likely have needed additional pediatric data had this rule been in effect by 1993 (see "Analysis of Impacts," in section VIII of this document). In addition, burden estimates have been added in Table 2 of this document for the new requirements in the final rule concerning submissions for end-of-phase 1 and end-of-phase 2 meetings under § 312.47(b)(1)(iv) and submissions for pre-NDA meetings under § 312.47(b)(2). These estimates are based on FDA's records of the number of these meetings held during 1997. Finally, burden estimates have been added for new postmarket report requirements added for biological products under § 601.37(a), (b), and (c), corresponding to § 314.81(b)(2)(i), (b)(2)(vi)(c), and (b)(2)(vii). These estimates are based upon FDA's records of the number of licensed biological products.

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

Description: This final rule includes the following reporting requirements: (1) Reports on planned pediatric studies in IND's (§ 312.23(a)(10)(iii)); (2) Reports for end-of-phase 1 and end-of-phase 2 meetings (§ 312.47(b)(1)(iv)) and reports for pre-NDA meetings (§ 312.47(b)(2)); (3) Summaries of data on pediatric safety and effectiveness in NDA's (§ 314.50(d)(7)); (4) Reports assessing the safety and effectiveness of certain drugs and biological products for pediatric use in NDA's and BLA's or in supplemental applications (§§ 314.55(a) and 601.27(a)); (5) Requests seeking deferral of required pediatric studies (§§ 314.55(b) and 601.27(b)); (6) Requests seeking waiver of required pediatric studies (§§ 314.55(c) and 601.27(c)); (7) Postmarketing reports of analyses of data on pediatric safety and effectiveness (§§ 314.81(b)(2)(vi)(c) and 601.37(a)(1)); (8) Postmarketing reports on patient exposure to certain marketed drug products (§§ 314.81(b)(2)(i) and 601.37(a)(2)); (9) Postmarketing reports on labeling changes initiated in response to new pediatric data (§§ 314.81(b)(2)(vi)(c) and 601.37(a)(3)); and (10) Postmarketing reports on the status of required postapproval studies in pediatric patients (§§ 314.81(b)(2)(vii) and 601.37). 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.

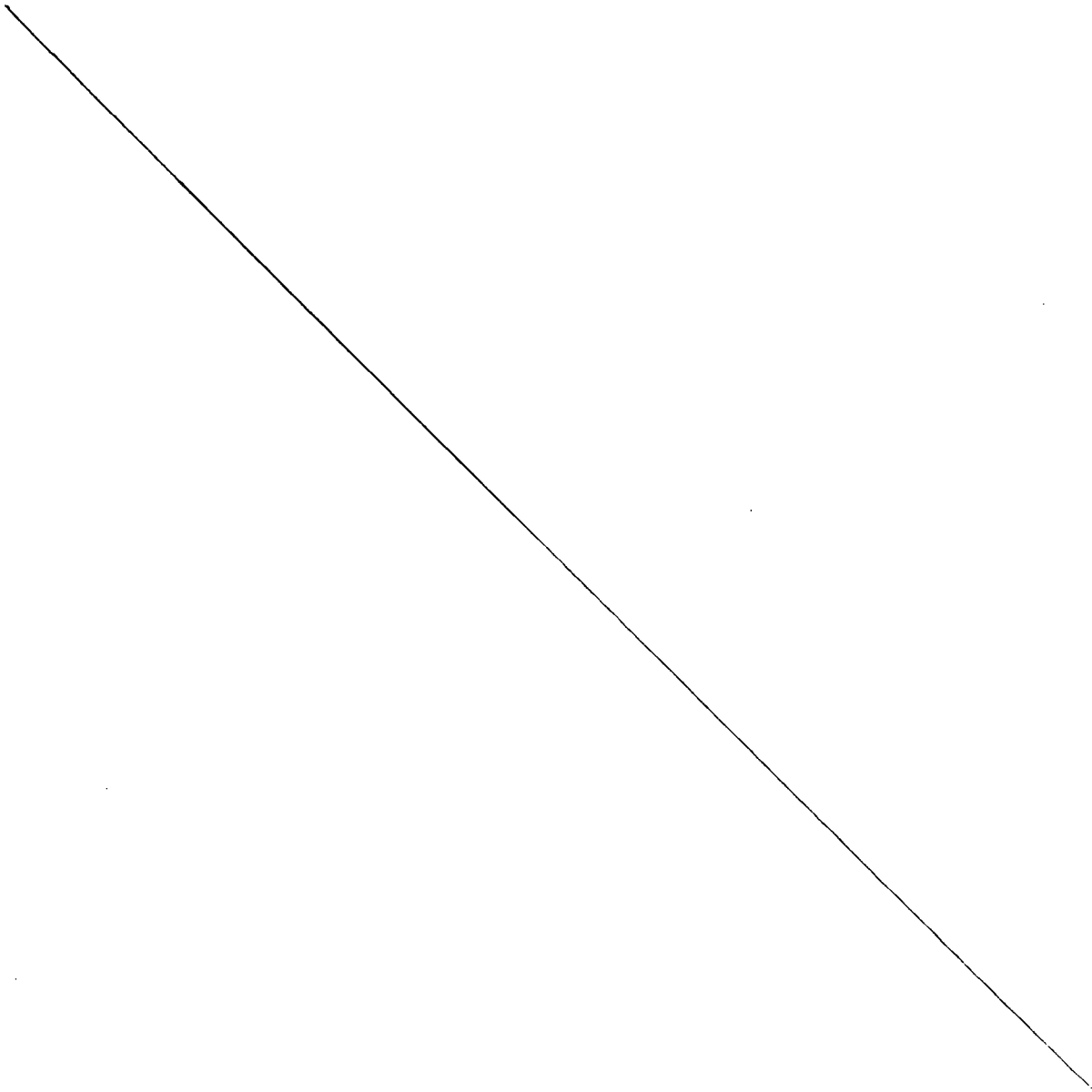


Table 2.--Estimated Annual Reporting Burden ¹					
21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
201.23	2	1	2	16	32
312.47(b) (1)(iv)	27	1.2	32	16	512
312.47(b) (2)	36	1.3	46	16	736
314.50(d) (7)	150	1	150	50	7,500
314.55(a)	88	1	88	48	4,224
314.55(b)	88	1	88	24	2,112
314.55(c)	176	1	176	8	1,408
314.81(b) (2)(i)	625	1	625	8	5,000
314.81(b) (2)(vi)(c)	625	1	625	24	15,000
314.81(b) (2)(vii)	625	1	625	1.5	937.5
601.27(a)	3	1	3	16	48
601.27(b)	3	1	3	16	48
601.27(c)	4	1	4	16	64
601.37(a)	69	1	69	8	552
601.37(b)	69	1	69	24	1,656
601.37(c)	69	1	69	1.5	103.5
Total					39,933

¹ There are no capital or operating and maintenance costs associated with this collection of information.

The information collection provisions of this final rule have been submitted to OMB for review. Prior to the effective date of this final rule, FDA will publish a notice in the FEDERAL REGISTER announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) 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.

VIII. Analysis of Impacts

A. Introduction and Summary

FDA has examined the impacts of the final 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 million or more (adjusted annually for inflation).

The agency has reviewed this final rule and has determined that the rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866, and in these two statutes. Although this rule is not an economically significant regulatory action, it is still 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 agency certifies that the rule will not have a significant economic impact on a substantial number of small entities. Since the 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 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act.

FDA is requiring 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 lacks adequate pediatric information, their use in children greatly increases the risk of inappropriate dosing, unexpected adverse effects, and suboptimal therapeutic outcomes. This rule is designed to ensure that new drugs, including biological drugs, that are therapeutically important and/or likely to be used in a substantial number of children contain adequate pediatric labeling at the time of, or soon after, approval.

The agency estimated the costs to industry of the required new pediatric studies by first determining what the annual costs would have been in 1993 to 1997, had the rule become effective in 1993. The methodology included: (1) Constructing a data base of all 583 NDA's and efficacy supplements approved by the agency over that 5-year period for drugs and biologicals likely to produce health benefits in the pediatric population, (2) determining which of those applications would have been required to conduct additional pediatric studies, (3) calculating how many unapproved and already marketed drugs and biologicals would have needed additional pediatric studies, and (4) estimating the size and cost of the additional studies. The analysis indicated that, on average, this regulation would have required an

estimated 378 additional pediatric studies on about 82 drugs and biologicals per year. These studies would have involved a total of 10,860 pediatric patients, 7,408 in efficacy studies, and 3,452 in PK studies. In addition, an estimated 33 of the 82 drugs and biologicals needing new pediatric data each year may have needed new pediatric dosage forms. FDA judges that the additional studies would have cost about \$45 million and the new dosage formulations about \$33 million annually, for a total annual cost of almost \$80 million. The agency found, however, that roughly 42 percent of the costs of the studies would have been spent voluntarily had the extended pediatric exclusivity provisions of the recent FDAMA statute been in place. Adjusting for this effect lowers the agency's final cost estimate for this rule to about \$45.3 million per year.

FDA could not develop a quantifiable estimate of the benefits of this regulation, although numerous anecdotal examples illustrate the current health problem. To consider some of the potential benefits, the agency examined hospitalization rates for five serious illness (asthma, HIV/AIDS, cancer, pneumonia, and kidney infections) and found significantly higher rates for children than for middle-aged adults. Although FDA can not estimate the extent to which these differentials reflect the relative lack of pharmaceutical safety and efficacy information for pediatric compared to adult use, the agency calculated that a 25 percent reduction in these differentials would lead to

direct medical cost savings of \$228 million per year. FDA also estimates that about two-thirds of the approved applications needing pediatric studies will be addressed by the incentives established by FDAMA. If the estimated medical cost savings were adjusted by a similar ratio, the analysis suggests that a 25 percent reduction in the pediatric/adult hospitalization rate differentials would yield annual savings of \$76 million for these five illnesses.

B. Number of Affected Products and Required Studies

In the preamble to its proposal, FDA explained that neither the precise number of drugs that would require additional pediatric studies nor the cost of these studies could be predicted with certainty. To develop plausible estimates of the number of new drugs and biologicals that would be affected, the agency had 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 number of drugs that would have required additional pediatric data had the proposal been in place over that period.

Several industry comments declared that FDA's analysis of the proposal substantially underestimated the economic impact by understating both the number and size of the studies that would be required. Only two of the comments, however, included alternative estimates. One suggested that each new drug could require the testing of 300 or more pediatric patients for safety data alone. The other comment estimated that, "each new drug studied would probably require a minimum of six clinical trials (two each in Phases I, II, and III), for one indication and one formulation." This comment explained that Phase I trials would include 20 patients, Phase II trials 50 patients, and Phase III trials 100 patients. Assuming two trials for each phase, the comment projected that 34,000 pediatric patients would need to be studied each year (170 patients x 2 trials x 100 drugs).

FDA agrees that some applications will require data from a substantial number of pediatric patients. The agency believes, however, that most studies will not include large numbers of pediatric patients. For example, FDA does not necessarily require two pediatric studies for each trial phase. Moreover, FDA's 1994 final rule (59 FR 64240) explains that extrapolations from adult effectiveness data based on PK studies and other safety data can be sufficient to provide the necessary pediatric dosing information for those drugs and biologicals that work by similar mechanisms in adults and children. The agency expects

that the majority of the studies will rely, to some extent, on such extrapolations.

On the other hand, the proposal primarily addressed drugs and biologicals that contained no previously approved active moiety. The final rule requires pediatric data for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration that represent a meaningful clinical benefit over existing treatments for children, or that are likely to be widely used in children. The rule also requires pediatric studies for marketed drugs and biologicals that are already widely used among children for the claimed indications, if the absence of adequate labeling could pose significant risks; or if the drug would provide a meaningful clinical benefit over existing treatments for pediatric patients, but additional dosing or safety information is needed to permit their safe and effective use in children.

To develop a revised estimate of the number of drugs and biologicals that would require additional pediatric data, FDA constructed a data base of all 583 applications and efficacy supplements approved over the 5-year period from 1993 to 1997 for drugs and biologicals for which pediatric labeling would be likely to provide a significant health benefit. The selected

drugs and biologicals included all those for which the active moiety was listed in the priority section in the FEDERAL REGISTER of May 20, 1998 (63 FR 27733), document entitled "List of Drugs For Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population" ("List"). Mandated by FDAMA, this publication includes the agency's priority list of drugs and biologicals that would likely provide a significant benefit to the pediatric population. The selection criteria used to prepare this priority list were almost identical to those set forth in this final rule, i.e.,

- The drug product, if approved for use in the pediatric population, would be a significant improvement compared to marketed products labeled for use in the treatment, diagnosis, or prevention of a disease in the relevant pediatric population (i.e., a pediatric priority drug); or,
- The drug is widely used in the pediatric population, as measured by at least 50,000 prescription mentions per year; or,
- The drug is in a class or for an indication for which additional therapeutic options for the pediatric population are needed.

FDA then identified each of the 583 applications that would likely have needed additional pediatric studies had this rule been in effect. The number and type of studies needed were projected based on specific decision rules derived from agency

experience in reviewing drug applications and developed strictly for the purpose of estimating the regulatory costs of this rule. Although in practice, these rules would have been subject to numerous exceptions, in the aggregate, FDA believes that they provide plausible estimates of the total number and type of pediatric studies that would have been required. The decision rules were as follows:

1. All New Chemical Entities (NCE's) and biologicals were assumed to need both an efficacy study and a PK study for each age group identified in the priority section of the "List" as needing pediatric information, although FDA believes that this assumption overstates the true number of efficacy studies that will be needed.

2. For the following categories of applications, both an efficacy and a PK study were assumed for each designated age group. Again, FDA believes that this assumption may overstate the true number of efficacy studies that will be needed:

- Neurological drugs;

- Oncology drugs;

- Nausea agents;

- Pulmonary agents;

- NSAIDs--arthritis/pain;

- AIDS/HIV agents;

- Asthma drugs;

- Anesthesia drugs;

Hormones;

Dermatological agents;

Acne agents

3. A PK study alone was assumed sufficient for each relevant age group for the following types of non-NCE applications:

Allergies;

Infectious diseases;

Cardiovascular diseases;

Imaging agents;

Hematology agents;

GI disorders;

Urologic drugs

4. If pediatric labeling was already adequate as the result of an approved application, additional applications for new dosage forms were assumed to be exempt.

5. If a second applicant sought approval for the same indication of the same drug as a previous applicant that had already satisfied the pediatric labeling requirements, the second applicant was considered exempt from the pediatric labeling requirement.

6. Because the regulation imposes requirements only on new NDA's or efficacy supplements that specifically address an indication needing pediatric data, no pediatric requirements were

assumed for an NDA supplement submitted for a new indication not identified as needing pediatric data.

7. Orphan drugs were excluded from additional research requirements.

The results of this analysis (see Table 3 of this document) show that about 44 percent, or an estimated 255, of the total 583 drug and biological applications for the products on the priority section of the "List" drugs approved over the 5-year period would have required additional pediatric studies, had the rule been in effect starting in 1993. Assuming separate studies for each pediatric age group specified in the "List," indicates that an estimated 459 efficacy studies and 713 PK studies would have been required for these applications.

These estimates understate the required research effort, however, because they omit pediatric studies for drugs that fail to gain approval. It is difficult to judge how much additional pediatric research would be directed towards nonapprovable products. The agency notes, however, that because only about 63.5 percent of all NME's that enter phase III trials are eventually approved (Ref. 18), the number of drugs entering phase III trials is about 58 percent greater than the number of actual approvals ($100/63.5 = 1.58$). Moreover, there are two additional complications. First, under the rule, FDA expects to defer for several years the conduct of pediatric studies of "me-too" drugs that do not offer a meaningful therapeutic benefit and that are

members of a drug class that already contains an adequate number of approved products with pediatric labeling. No additional pediatric studies would be expected for this group of unapproved drugs. On the other hand, applications for "lifesaving" drugs may need to begin pediatric trials by the start of Phase II. On the assumption that these two factors would roughly offset, FDA has retained the 58 percent figure as a reasonable adjustment factor to account for the number of studies conducted for drugs that fail to gain approval. Finally, each year, the agency expects to identify about two "already marketed" drugs that require additional pediatric efficacy data.

As shown in Table 4 of this document, adjusting for the "never approved" and the "already marketed" applications implies that, had this rule become effective in 1993, about 1,892 new pediatric studies would have been required over the 1993 to 1997 period. About 740 of the studies would have been efficacy studies and 1,151 PK studies. Thus, on average, each year, the rule would have required about 378 new pediatric studies for about 82 NDA's and/or NDA supplements--148 efficacy studies and 230 PK studies.

Table 3.--Approved New Drug Applications and Their Supplements From 1993 to 1997

Approval Year	Applications for "List" Drugs	Applications Needing Pediatric Studies	Efficacy Studies Required	PK Studies Required	Total Studies Required	New Dosage Forms
1993	77	43	63	122	185	12
1994	76	42	74	118	192	17
1995	107	38	69	107	176	13
1996	177	74	147	213	360	29
1997	146	58	106	153	259	19
Total	583	255	459	713	1,172	90
Average	117	51	92	143	234	18

Table 4.--All New Drug Applications and Their Supplements From 1993 to 1997						
Approval Year	Applications for "List" Drugs ²	Applications Needing Pediatric Studies	Efficacy Studies Required	PK Studies Required	Total Studies Required	New Dosage Forms
1993	124	69	102	197	299	22
1994	123	68	119	190	310	32
1995	173	61	111	173	284	24
1996	286	119	237	344	581	54
1997	236	94	171	247	418	35
Total	942	411	740	1,151	1,892	167
Average	188	82	148	230	378	33

¹ Includes estimates for "unapproved" and "already marketed" drugs.

² Adjusted for "unapproved" and "already marketed" drugs.

C. Number of Pediatric Patients

The number of pediatric patients needed varies with the particular type of drug studied. However, based on agency experience, FDA estimates that, for each pediatric age group studied, typical pediatric PK studies may involve about 15 patients and typical efficacy studies about 50 patients. For example, if 2 of the 4 age groups lack PK studies, FDA assumed that a total of 30 subjects would be needed for the studies. If 3 of the 4 age groups lack efficacy studies, a total of 150 subjects were assumed to be needed in all 3 age groups. These assumptions indicate that, had this rule become effective in 1993, each year, about 82 NDA's would have required additional pediatric studies; 7,408 pediatric patients in efficacy studies and 3,452 pediatric patients in PK studies, for an annual total of about 10,860 pediatric patients.

D. Costs of Compliance

1. Cost of Pediatric Studies

FDA's analysis of the proposal assumed that new studies would cost pharmaceutical firms from \$5,000 to \$9,000 per pediatric patient. Only one comment, that of a large U.S. pharmaceutical company, submitted actual estimates of the cost of conducting pediatric trials. This comment stated that a PK or bioavailability/bioequivalency study of 20 patients would cost at least \$100,000, a Phase II trial of 50 patients would cost a minimum of \$150,000, and a Phase III trial of 100 patients would cost \$200,000. For its revised analysis, therefore, FDA assumes that a PK study of 15 patients will cost \$100,000 per affected age group and that an efficacy study of 50 patients will cost \$150,000 per affected age group.

As FDA estimates that the regulation would have required pharmaceutical companies to annually conduct an estimated 378 additional pediatric studies for 82 NDA's, 148 efficacy studies, and 230 PK studies; the above unit cost estimates imply total industry costs of \$45 million annually. Although the industry comment that included the cost data projected clinical trial costs totaling over \$100 million per year, this estimate assumed the need for 34,000 additional pediatric patients. FDA found that had this rule been in place over the 1993 to 1997 period, it would have required additional data from about 10,860 patients per year.

2. Cost of New Formulations

In its earlier analysis of the proposal, FDA calculated that about 30 percent of all NME's were available only in tablets or hard capsules at the time of approval. Acknowledging the potential difficulties of developing new formulations for certain drugs, FDA estimated that the overall costs could average \$1 million for each new formulation developed. Several comments questioned the agency's estimates. Based on an informal survey of its members, a major industry trade association reported that the development of a pediatric formulation could take from 5 months to 4 years and cost from \$500,000 to \$3.5 million. None of these comments, however, offered an alternative methodology for projecting the aggregate value of these costs.

To develop reasonable estimates of the number of new dosage forms that would be needed, FDA again reviewed all of the 255 approved drug applications that would likely have required new pediatric studies during the 1993 to 1997 period, had this rule been in place. The agency generally assumed that those drugs identified as having a meaningful clinical pediatric benefit for the youngest three age groups, but available only in tablets or hard capsules at the time of approval, would have needed to develop an alternative dosage form. The agency also assumed that a new pediatric formulation would not be counted if a more appropriate pediatric dosage form was subsequently approved for the same drug. FDA is aware that these estimates can not be

considered precise. For example, not all liquids are adequate for pediatric populations. On the other hand, new formulations may not be needed if a drug is used primarily for children between the ages of 8 and 12 years. Nevertheless, as shown in Table 3 of this document, the results of this methodology show that about 35 percent of the approved applications needing studies, or about 18 per year, would have needed new dosage forms. Table 4 of this document raises this estimate by 83 percent, or to 33 per year, to account for the number of new dosage forms developed for drugs not subsequently approved. While FDA cannot confidently predict a typical initiation time for this effort, the calculation assumes that work on about 25 percent of all new formulations would be initiated at the start of Phase 2 trials and 75 percent by the start of Phase 3 trials. (The probability of approval was assumed to be .635 for a drug entering phase 3 trials and .31 for a drug entering phase 2 trials (Ref. 18).)

The development of some pediatric formulations will be difficult, the development of others relatively straightforward and achieved without substantial problem. The rule requires only that sponsors take all reasonable steps to develop needed new formulations. Thus, while acknowledging that the cost for particularly difficult formulations may be higher, FDA has retained its average cost estimate of \$1 million to develop each

new dosage form and projects this total industry cost at nearly \$33 million per year.

3. Cost of Added Paperwork Requirements

The rule also requires additional industry effort for new or expanded paperwork reporting. Section VI of this document describes these reporting tasks, discusses the industry comment that questioned the agency's estimate of the paperwork burden for the proposal, and presents the agencies revised estimate for this final rule. As shown in that section, FDA projects an annual burden of almost 40,000 hours per year. On the assumption that 25 percent of these hours will be for upper management staff, 50 percent for middle management staff, and 25 percent for administrative and clerical support, at respective labor costs of \$52, \$34, and \$17 per hour, FDA estimates these total paperwork costs at about \$1.4 million per year.

4. Total Costs

Table 5 of this document summarizes the agency's estimates of costs for efficacy studies, PK studies, new dosage forms, and paperwork. Because the expense of pediatric trials and dosage form development will be spread over 2 or 3 years for any given drug, the total costs to industry in any given year are unlikely to vary as much as shown in Table 5. Most importantly, however, the average \$80.1 million annual cost figure reflects only what the rule would have cost had the rule been in effect from 1993 to 1997. The incentives generated by the additional 6-month

marketing exclusivity offered by FDAMA will reduce the future costs of the regulation.

Table 5.--Estimated Industry Costs--Compliance With Pediatric Labeling (in millions)					
Year	Efficacy Studies	PK Studies	New Dosage Form Developed	Paperwork	Total
1993	\$15.3	\$19.7	\$22.3	\$1.4	\$58.6
1994	\$17.9	\$19.0	\$31.6	\$1.4	\$69.9
1995	\$16.7	\$17.3	\$24.1	\$1.4	\$59.5
1996	\$35.6	\$34.4	\$53.9	\$1.4	\$125.2
1997	\$25.7	\$24.7	\$35.3	\$1.4	\$87.0
Average Per Year	\$22.2	\$23.0	\$33.4	\$1.4	\$80.0

FDA cannot develop precise adjustments for the forthcoming effects of FDAMA, due to the complexity of the economic forecasting that would be needed. Nevertheless, the agency developed rough projections of the potential impact of this statute by comparing the estimated present value of the 6-month exclusivity gain with the estimated cost of the new pediatric studies, for each of the 85 drugs with applications approved in 1993 and 1994 that would have needed new pediatric labeling. (More recent years were not used, because the revenues of newer drugs are far below their peak values.) Where the estimated exclusivity gain exceeded the cost of all required studies, including the development of new dosage forms, FDA concluded that the studies for that drug would have been initiated voluntarily

and their cost attributable to FDAMA rather than to this regulation.

The methodology assumed that a 6-month gain of marketing exclusivity would be worth about 25 percent of a drug's annual sales revenue during the year the exclusivity is needed, less 60 percent for production, administrative, and marketing costs (Ref. 19). Costs of conducting the required studies for each of the 85 drugs were based on the cost estimates described previously (\$150,000 for each efficacy study, \$100,000 for each PK study, and \$1 million for each new dosage form. The present value of the additional revenues (at a 7 percent discount rate) were calculated from 1997 sales data published by IMS America (Ref. 20). Because 1997 sales revenues probably underestimate the sales revenues that will be realized at the time that the added exclusivity is used, this methodology likely underestimates the effects of FDAMA, hence overestimating the costs of the rule. The analysis found, however, that the necessary studies would have been conducted voluntarily for 56 out of the 85 affected applications. Adjusting estimates of all approved applications by this percentage (FDAMA was not assumed to affect studies for applications not obtaining approval), FDA projects that the annual costs attributable to this rule will be approximately \$45.3 million.

Further, although the agency has not yet evaluated the full economic impact of the FDAMA legislation, it believes that the present value of the net revenues expected from the 6 months

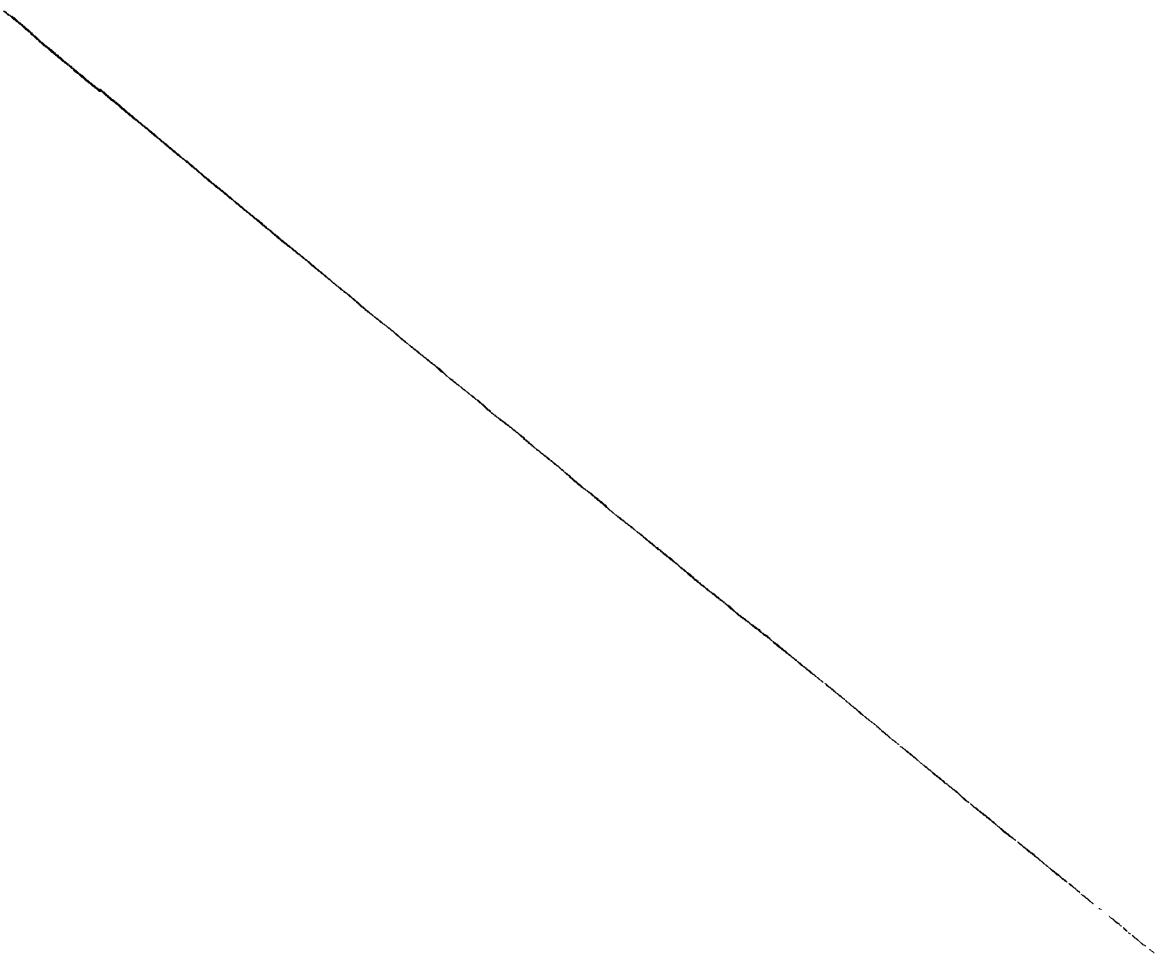
of added exclusivity granted under the new FDAMA legislation will greatly exceed the additional costs imposed by this regulation. One industry publication (MedAdNews, June 1998, p. 10) for example, reports that products currently valued at \$41 billion in annual sales will come off patent between 1998 and 2008, or an average of \$11 billion per year. Alternatively, FDA estimates that the annual revenues for NCE's coming off patent may average between \$200 and \$300 million each. If 25 NCE's lose exclusivity each year, these annual revenues would range from \$5 billion to \$7.5 billion. If only 60 percent of these NCE's become eligible for extended exclusivity, the methodology described above implies that industry net incomes will increase from \$300 to \$450 million per year. Thus, FDAMA and this rule, taken together, will provide critical pediatric information without diverting current resources from pharmaceutical innovation.

E. Benefits

The rule addresses two major problems associated with the lack of adequate information on the effects of drugs on pediatric patients: (1) Adverse drug reactions in children due to inadvertent drug overdoses or other drug administration problems that could be avoided with better information on appropriate pediatric use; and (2) under use of safe and effective drugs for children due to the prescribing of an inadequate dosage or

regimen, a less effective drug, or no drug at all because of uncertainty over the drug's effect on children or the unavailability of a pediatric formulation. By developing improved information on whether, and in what dosage, a drug is safe and effective for use in children, FDA believes that the regulation will result in fewer adverse drug reactions and fewer instances of less-than-optimal treatment of pediatric patients.

Despite numerous reports of children endangered by the absence of adequate drug labeling, FDA has found no systematic studies in the literature that evaluate the overall magnitude of



the harm that results from the incomplete labeling of drugs for use in children. In the preamble to the proposal, the agency specifically requested, "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." The comments received cited case after case of children who have died or suffered because of the inadequate testing of drugs in children, but the information was largely anecdotal and related to particular instances of drug misuse or underuse.

For example, physicians who care for HIV-infected patients expressed frustration at their inability to treat children with drugs known to be effective in adults. Pulmonary specialists described the dearth of information on risks versus benefits of new antimicrobials for pediatric patients, citing the example of ciprofloxacin, a quinolone that may be valuable in treating cystic fibrosis, although the safety and effectiveness of the drug in children has not been established. Comments received from asthma specialists reaffirmed the difficulties of administering medications, treating drug side effects, or withholding treatment for children with asthma, due to the lack of research on drug safety and effectiveness.

In both written comments and in commentary at the public hearing in October 1997, concerns were raised about the costs of not implementing a requirement for pediatric labeling. Avoidable

adverse outcomes, cited in relation to pediatric dosage problems, included opportunistic infections from too much immunosuppression, and loss of grafts in pediatric renal transplant patients with too little immunosuppression. Comments also cited added health care, including increased hospitalizations, required as a result of less effective treatment for pediatric patients. One comment estimated the cost of delayed access in terms of infant deaths, attributing an additional 2,000 unnecessary infant deaths over a 2-year period to the delay in access to AZT for HIV-exposed infants. Another suggested using the Vaccine Injury Compensation program figure of \$250,000 per child as the value of an avoided death resulting from an ADR. Other comments confirmed that many adverse outcomes develop quickly and would be detected in early clinical studies (e.g., "gray syndrome" in babies treated with chloramphenicol).

While clearly demonstrating the critical need for improved pediatric information, these comments do not suggest a practical methodology for quantifying the aggregate benefits of this rule. FDA, also, has been unable to develop a precise assessment of the probable regulatory benefits. The agency's approach to estimating regulatory benefits therefore is framed in terms of the following two questions: (1) Are data available to assess current differences in the safety of drug therapy for adults versus children with the same condition? and (2) Are data

available to assess current differences in the effectiveness of drug therapy for adults versus children with the same condition?

FDA first attempted to assess the safety of drug therapy by looking for differences in the frequency and severity of ADR's for adults versus children treated for the same condition. The available clinical and health survey data, however, did not provide a reliable estimate of the contribution of ADR's to pediatric as compared to adult rates of mortality and morbidity. ADR-related data are limited by the lack of a general requirement and a ready mechanism for the comprehensive reporting of incidents directly attributable to ADR's (Ref. 21). Moreover, most available studies have not addressed ADR rates and associated death rates by age group within a treated condition (Refs. 22, 23, and 24). For example, one study of pediatric patients shows an ADR-related admission rate in the range of only 2.0 to 3.2 percent, well below the average for adult and pediatric studies combined. Pediatric cancer patients, however, experienced a 22 percent ADR-admission rate (Ref. 25), suggesting that pediatric risks may be significantly greater within condition-defined subpopulations. In addition, potential concerns about negative public attention (Ref. 26) or liability inhibit reporting of ADR's. Finally, for many seriously ill patients, it is very difficult to attribute a specific medical outcome to a particular medication, as opposed to some other complication in the patient's condition, or misadventure in the

patient's care. The agency found therefore that it could not rely on available ADR studies to derive an assessment of the potential benefits of this rule.

Data to assess the effectiveness of drug therapy would indicate differences in clinical outcomes, or in other health care utilization concomitant with drug therapy. If drug therapies for children were less effective than that for adults with the same condition, one might see longer recovery times, or lower recovery rates, together with increased health services use, assuming a similar prognosis and course of illness. A limitation to this approach is that the prognosis and course of illness may not be the same in children and adults with the same serious health condition, even if the same drugs were included in best-practice treatment. Moreover, differential patterns of health care utilization may reflect variations in physician practice patterns, insurance benefits, or patient and family behavior and preferences, rather than measures of drug effectiveness. Notwithstanding such limitations, comparisons of health care resource use for one therapeutic approach compared to another are commonly used in evaluations of therapy effectiveness in the field of pharmacoeconomics. In this instance, FDA finds that health care utilization data may provide at least an indirect indication of potential benefits. Hospitalization rates, in particular, are the most extensively studied measure of morbidity related to adverse drug reactions and of quality of

care for a number of chronic (e.g., asthma) and acute conditions (e.g., pneumonia) (Refs. 27 and 28). While hospitalizations due to adverse drug reactions or drug therapy undertreatment are not always recognized, these admissions are routinely classified with a primary diagnosis of the underlying disease. FDA therefore has relied on diagnosis-related hospitalization rates to develop an order-of-magnitude assessment of the potential benefits of this rule.

For this assessment, the agency compared rates of hospitalization of pediatric patients to rates of hospitalization of adult patients for several important disease conditions. Next, the agency examined the potential direct and indirect cost savings that would be realized by diminishing any age-related disparities. The pediatric population was defined to be all persons under the age of 15 and the comparison group to be those adults between the ages of 15 and 44. (The exclusion of older adult patients minimizes the confounding effect of the age-related increased morbidity and mortality.) Comparisons were limited to asthma, HIV/AIDS, cancer, pneumonia, and kidney infection, as these conditions are life threatening, occur in both adults and children, and comparable data are available for adult and pediatric patients. Moreover, reports received in the FDA Spontaneous Reporting System (SRS) in 1993 indicated that the therapeutic areas for which the highest number of ADR's were reported for patients under age 15, relative to the number

reported for patients 15 to 44, included those for anti-infectives, pulmonary drugs and oncology drugs.

Direct costs were based on the estimated number of cases, hospitalization rates, and length of stay for each of the selected conditions. The number of cases reported were based on national health survey (Ref. 29) and public surveillance data (Refs. 30, 31, and 32). In 1994, the total number of cases for these 5 conditions, in patients under age 15, was approximately 6.65 million. The total number of cases for patients ages 15 to 44 was approximately 8.3 million. The number of hospitalizations per year for which the selected condition was the primary diagnosis was obtained from the National Hospital Discharge Survey (Ref. 33). As shown in Table 6 of this document, the pediatric hospitalization rate exceeded the adult rate for all five conditions.

Table 6.--Hospitalization Rates per Patient per Year		
Primary Diagnosis	Rate Under Age 15	Rate for Ages 15-44
Asthma	.045	.024
HIV/AIDS	.533	.233
Cancer	4.247	3.903
Pneumonia	.147	.129
Kidney Infection	.191	.073

The average length of hospital stay (ALOS) for patients with the selected condition as the primary diagnosis (based on ICD-9 code) was obtained from recent hospital survey data (Ref. 34),

the average cost per day of inpatient hospital care for each of the selected conditions was based on hospital charge data reported in the survey (Ref. 35), and the cost of physician services associated with each episode of hospitalization was based on physician charge data (Ref. 36). Each episode of care was assumed to include physician charges for emergency room service, daily inpatient visits, and a postdischarge office visit. For cancer hospitalizations, daily inpatient visits and a followup office visit were included. The calculation of indirect costs assumed 8 hours of parental time away from work for each episode of hospitalization and income and productivity losses based on average employee compensation, as reported in the 1997 *U.S. Statistical Abstract*. A detailed description of all assumptions, calculations, and data sources is included in the full agency report (Ref. 37).

The assumed hypothesis is that a substantial fraction of the difference between pediatric and adult hospitalization rates for like disease conditions are attributable to the greater range of drug therapies and better information on drug dosages for adults. FDA cannot estimate the precise magnitude of the relevant fraction. Nevertheless, if the differentials between pediatric and adult hospitalization rates were reduced by 25 percent, the resulting direct cost savings would be \$228 million, with indirect cost savings of \$5.3 million per year. If the

differentials were reduced by as much as 50 percent, the direct cost savings would be \$456 million per year, with indirect savings of \$10.6 million. Even if the differentials were as low as 10 percent, the resulting reductions in hospitalization would lead to direct cost savings of \$91.2 million, with indirect savings of \$2.1 million per year.

The timing of the benefit after the rule's implementation is uncertain. The previous values represent the potential benefit over time as the safety and effectiveness of drugs are more extensively tested, new and already marketed drugs become labeled for use in children, and new formulations and dosage forms are developed to facilitate therapy for children. The figures may overestimate the impact for the selected conditions over the next few years, but may underestimate the potential benefits for these patients in the longer term if there is an increasing prevalence of asthma, cancer, and respiratory and other infectious diseases in the pediatric population. Thus, the lower reduction estimate may be more realistic in the near-term, with the reduction estimates offering a better indication of longer-term benefit.

As discussed previously, FDA believes that the new FDAMA statute will cause some of these pediatric studies to be conducted voluntarily. In its assessment of costs, the agency

found that about two-thirds of the applications for approved drugs needing pediatric studies may be undertaken voluntarily due to the incentives established by FDAMA. Adjusting the previous medical cost savings by a similar ratio suggests that if all of the new pediatric studies achieved a 25 percent reduction in the pediatric/adult hospitalization differentials, the additional studies prompted by this rule would yield annual savings of \$76 million for just those five diseases. This estimate may represent a lower bound on the benefits to pediatric patients, however, because a number of other disease conditions are also common to children and adults, including such life-threatening conditions as hypertensive disease and renal disease. These pediatric populations also would experience significant benefits from increased safety and access to drug treatments currently available only to adult patients.

F. Small Entities

The rule will impose a burden on relatively few small entities, because new drug development is typically an activity completed by large multinational firms. Only one industry comment questioned the agency's determination that the rule would not have a significant effect on a substantial number of small entities. That comment indicated that about 1,500 small entities are conducting diagnostic and therapeutic R&D in the United States and that "[c]ontributions to new drug approvals by the 'biotech' and 'small pharma' sector are increasing year by year, and the pace of change will--almost certainly--continue."

FDA agrees that small firms contribute substantially to the early development of many new drugs and biologicals.

Nevertheless, because of the considerable resources needed for clinical testing and marketing, the agency finds that very few of these small firms retain ownership and control through the large-scale clinical testing and approval stages. Moreover, many of the products that are sponsored by small companies are eligible for orphan designation and therefore exempted from this rule. To approximate the number of small firms that might be significantly affected, FDA determined the sponsor company size for all of the approved applications that may have required additional pediatric studies had this rule been in place over the years from 1993 to 1997. The agency found that, on average, based on the Small Business Administration's definition of a small firm, only three applications per year were submitted by small companies.

.. Multiplying by the previously described 1.58 factor to account for unapproved applications increases this estimate of the number of small entities that may have been significantly affected by this rule to just five small firms per year. Because the agency has certified that the rule will not impose a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act does not require the agency to prepare a Regulatory Flexibility Analysis. Moreover, the agency further points out that the required new studies will comprise a very small part of the total cost of developing new drugs or

biologics, which is generally estimated in the hundreds of millions of dollars for each new drug.

G. Regulatory Alternatives

The agency carefully examined two major alternatives to the final rule. The first alternative considered was the initial proposal, which covered only NCE's. The estimated cost of this alternative, excluding the FDAMA adjustment, would be about \$40 million, or roughly 50 percent of the cost of the final rule. The agency rejected this alternative because of the predominant view of the medical community that additional pediatric data were needed for all of the drugs and biologicals that may be therapeutically significant in pediatric populations, not just for the new chemical entities.

The other major alternative considered was to delay implementation of the rule until the effects of the new FDAMA statute were reviewed. FDA fully expects the FDAMA exclusivity provisions to provide a substantial incentive to conduct large numbers of pediatric studies. Nevertheless, the agency finds that relying on these incentives, alone, would leave numerous gaps in many important areas of pediatric labeling. For example, as described earlier in this preamble, voluntary research may overlook studies for many important drugs, especially where such studies require the development of new pediatric dosage forms. Thus, notwithstanding FDAMA incentives, FDA has determined that

this regulation is necessary to protect the pediatric population and that further delay is not warranted.

IX. References

The following references have been placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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15. Tejeda, H. et al., "Representation of African-Americans, Hispanics, and Whites in National Cancer Institute Cancer Treatment Trials," Journal of the National Cancer Institute, 88(12):812-816, 1996.

16. Center for Drug Evaluation and Research, Manual of Policies and Procedures, Priority Review Policy, MAPP 6020.3, April 22, 1996.

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18. DiMasi et al., "Cost of Innovation in the Pharmaceutical Industry," Journal of Health Economics, p. 127, 10:1991.

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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, 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, 21 CFR parts 201, 312, 314, and 601 are amended as follows:

PART 201--LABELING

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

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

2. Section 201.23 is added to subpart A to read as follows:
§ 201.23 Required pediatric studies.

(a) A manufacturer of a marketed drug product, including a biological drug product, that is used in a substantial number of pediatric patients, or that provides a meaningful therapeutic benefit over existing treatments for pediatric patients, as defined in §§ 314.55(c)(5) and 601.27(c)(5) of this chapter, but whose label does not provide adequate information to support its safe and effective use in pediatric populations for the approved indications may 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 also be required to develop a pediatric formulation for a drug product that represents a meaningful therapeutic benefit over existing therapies for pediatric populations for whom 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, in the form of a letter, after notifying the manufacturer of its intent to require an assessment of pediatric safety and effectiveness of a pediatric formulation, and after 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 or request for approval of a pediatric formulation described in paragraph (a) of this section within a time specified in the order, if FDA finds that:

(1) The drug product is used in a substantial number of pediatric patients for the labeled indications and the absence of adequate labeling could pose significant risks to pediatric patients; or

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

(c) If a manufacturer fails to submit a supplemental application containing the information or request for approval of a pediatric formulation described in paragraph (a) of this section within the time specified by FDA, the drug product may be considered misbranded or an unapproved new drug or unlicensed biologic.

PART 312--INVESTIGATIONAL NEW DRUG APPLICATION

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

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 371; 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. Plans for assessing pediatric safety and effectiveness.

* * * * *

5. Section 312.47 is amended by revising paragraph (b)(1)(i) and the first sentence of paragraph (b)(1)(iv), by removing the fifth sentence of paragraph (b)(1)(v) and adding two sentences in its place, by revising the heading of paragraph (b)(2) and the second and last sentences of the introductory text of paragraph (b)(2), and by redesignating paragraph (b)(2)(iii) as paragraph (b)(2)(iv) and by adding new paragraph (b)(2)(iii) 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 current studies and plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

* * * * *

(iv) Advance information. At least 1 month in advance of an end-of-Phase 2 meeting, the sponsor should submit background information on the sponsor's plan for Phase 3, including summaries of the Phase 1 and 2 investigations, the specific

protocols for Phase 3 clinical studies, plans for any additional nonclinical studies, plans for pediatric studies, including a time line for protocol finalization, enrollment, completion, and data analysis, or information to support any planned request for waiver or deferral of pediatric studies, and, if available, tentative labeling for the drug. * * *

(v) Conduct of meeting. * * * The adequacy of the technical information to support Phase 3 studies and/or a marketing application may also be discussed. FDA will also provide its best judgment, at that time, of the pediatric studies that will be required for the drug product and whether their submission will be deferred until after approval. * * *

(2) "Pre-NDA" and "pre-BLA" 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 the status of ongoing or needed 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. * * * To permit FDA to provide the sponsor with the most useful advice on preparing a marketing application, the sponsor should

submit to FDA's reviewing division at least 1 month in advance of the meeting the following information:

* * * * *

(iii) Information on the status of needed or ongoing pediatric studies.

* * * * *

6. Section 312.82 is amended by revising the last sentence of paragraph (a) and by removing the second sentence of paragraph (b) and adding two sentences in its place 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. For drugs for life-threatening diseases, FDA will provide its best judgment, at that time, whether pediatric

studies will be required and whether their submission will be deferred until after approval. * * *

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: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 371, 374, 379e.

8. Section 314.50 is amended by adding paragraph (d)(7) 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, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under § 314.55.

* * * * *

9. Section 314.55 is added to subpart B to read as follows:

§ 314.55 Pediatric use information.

(a) Required assessment. Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. 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 usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. 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.

(b) Deferred submission. (1) 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 approval of the drug product for use in adults. Deferral may be granted if, among other reasons, the drug is ready for approval in adults before studies in pediatric patients are complete, or pediatric studies should be delayed until additional safety or effectiveness data have been collected. 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.

(2) 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. FDA may require, in appropriate cases, that drugs for which the submission of assessments of pediatric safety and effectiveness have been deferred carry labeling

statements recommending preferential use in pediatric patients of products that are adequately labeled.

(c) Waivers--(1) General. 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. A request for a waiver must provide an adequate justification.

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

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

(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 drug product would be ineffective or unsafe in all pediatric age groups.

(3) Partial waiver. An applicant may request a 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 does not represent a meaningful therapeutic benefit over existing treatments for pediatric

patients in that age group, and is not likely to be used in a substantial number of patients in that age group;

(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;

(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) FDA action on waiver. 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 (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.

(5) Definition of "meaningful therapeutic benefit". For purposes of this section and § 201.23 of this chapter, a drug will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that:

(i) If approved, the drug would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population. Examples of how improvement might be demonstrated include, for example, evidence of increased effectiveness in treatment, prevention, or diagnosis of disease, elimination or substantial reduction of a treatment-limiting drug reaction, documented enhancement of compliance, or evidence of safety and effectiveness in a new subpopulation; or

(ii) The drug is in a class of drugs or for an indication for which there is a need for additional therapeutic options.

(d) Exemption for orphan drugs. This section does not apply to any drug for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.

10. Section 314.81 is amended by revising paragraph (b) (2) (i) and (b) (2) (vii), and by adding paragraph (b) (2) (vi) (c) to read as follows:

§ 314.81 Other postmarketing reports.

* * * * *

(b) * * *

(2) * * *

(i) Summary. A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is

also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study. 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) shall be provided, including dosage form.

* * * * *

(vi) * * *

(c) Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall 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 whether postmarketing clinical studies in pediatric populations were required or agreed to, and if so, the status of these studies, 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

11. The authority citation for 21 CFR part 601 is revised to read as follows:

AUTHORITY: 15 U.S.C. 1451-1461; 21 U.S.C. 321, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263.

12. Section 601.27 is added to subpart C to read as follows:

§ 601.27 Pediatric studies.

(a) Required assessment. Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration 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, usually supplemented with other information in pediatric patients, such as pharmacokinetic studies. In addition, studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. 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. (1) 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. Deferral may be granted if, among other reasons, the product is ready for approval in adults before studies in pediatric patients are complete, pediatric studies should be delayed until additional safety or effectiveness data have been collected. 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.

(2) 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. FDA may require, in appropriate cases, that products for which the submission of assessments of pediatric safety and effectiveness have been deferred carry labeling statements recommending preferential use in pediatric patients of products that are adequately labeled.

(c) Waivers--(1) General. 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. A request for a waiver must provide an adequate justification.

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

(i) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(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) Partial waiver. An applicant may request a 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 product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group;

(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;

(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) FDA action on waiver. 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 (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.

(5) Definition of "meaningful therapeutic benefit". For purposes of this section, a product will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that:

(i) If approved, the product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population. Examples of how improvement might be demonstrated include, e.g., evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; elimination or substantial reduction of a treatment-limiting drug reaction; documented enhancement of compliance; or evidence of safety and effectiveness in a new subpopulation; or

(ii) The product is in a class of products or for an indication for which there is a need for additional therapeutic options.

(d) Exemption for orphan drugs. This section does not apply to any product for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.

13. Section 601.37 is added to subpart D to read as follows:

§ 601.37 Annual reports of postmarketing pediatric studies.

Sponsors of licensed biological products shall submit the following information each year within 60 days of the anniversary date of approval of the license, to the Director, Center for Biologics Evaluation and Research:

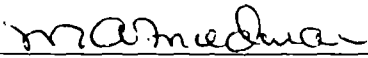
(a) Summary. A brief summary stating whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product,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

(b) Clinical data. Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(c) Status reports. A statement on the current status of any postmarketing studies in the pediatric population performed by, or on behalf of, the applicant. The statement shall include whether postmarketing clinical studies in pediatric populations were required or agreed to, and if so, the status of these

studies, e.g., to be initiated, ongoing (with projected completion date), completed (including date), completed and results submitted to the BLA (including date).

Dated: _____



Michael A. Friedman,
Acting Commissioner of Food and Drugs.

Donna E. Shalala,
Secretary of Health and Human Services.