The Pediatric Exclusivity Provision

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January 2001 Status Report to Congress

Department of Health and Human Services
U.S. Food and Drug Administration

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Executive Summary

In 1997, as part of the Food and Drug Administration Modernization Act (FDAMA) (Pub. L. 105-115), Congress enacted a new law that provides marketing incentives to manufacturers who conduct studies of drugs in children. This law, which provides six months exclusivity in return for conducting pediatric studies, is commonly known as the pediatric exclusivity provision. The pediatric exclusivity provision has a sunset date of January 1, 2002, and includes a requirement that the Secretary report by January 1, 2001, on the experiences under the new law. This report is submitted in accordance with that requirement.

As described in this report, the *pediatric exclusivity provision* has been highly effective in generating pediatric studies on many drugs and in providing useful new information in product labeling. Some categories of drugs and some age groups remain inadequately studied, however, despite the new incentives. The Secretary has provided suggestions for modifications to the pediatric exclusivity provision that may address these gaps.

Background

Children are subject to many of the same diseases as adults, and by necessity, are often treated with the same drugs. According to the American Academy of Pediatrics only a small fraction of all drugs[1] marketed in the United States has been studied in pediatric patients, and a majority of marketed drugs are not labeled, or are insufficiently labeled, for use in pediatric patients.[2] Safety and effectiveness information for the youngest pediatric age groups is particularly difficult to find in product labeling.

The absence of pediatric testing and labeling poses significant risks for children. Inadequate dosing information exposes pediatric patients to the risk of adverse reactions that could be avoided if such information were provided in product labeling.[3] The absence of pediatric testing and labeling may also expose pediatric patients to ineffective treatment through underdosing, or may deny pediatric patients the ability to benefit from therapeutic advances because physicians choose to prescribe existing, less effective medications in the face of insufficient pediatric information about a new medication. The failure to produce drugs in dosage forms that can be used by young children (e.g., liquids or chewable tablets) can also deny them access to important medications.

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[1] For the purposes of this report, the terms *drugs, marketed drugs,* and *products* are often used interchangeably.

[2] 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.

[3] The proposed rule cited reports of injuries and deaths in children resulting from the use of drugs that had not been adequately tested in the pediatric population (62 FR 43900).

The Food and Drug Administration (FDA or Agency) implemented a number of largely voluntary measures in the early 1990s to encourage the submission of pediatric labeling information. However, these failed to produce significant increases in pediatric labeling. In August 1997, FDA proposed a regulation that for the first time would require manufacturers of new and marketed drugs and biological products to conduct pediatric studies in some circumstances.

In November 1997, Congress enacted FDAMA, which contains the provision establishing economic incentives for conducting pediatric studies. The pediatric exclusivity provision provides 6 months of exclusivity to be attached to any existing exclusivity or patent protection on a drug for which FDA has requested pediatric studies and where the manufacturer has conducted such studies in accordance with the requirements of FDAMA.

After the passage of FDAMA, FDA finalized its regulation requiring pediatric studies in some circumstances (Pediatric Rule).[4] Although FDA believed that the incentives provided by the pediatric exclusivity provision would encourage sponsors to conduct pediatric studies for many drugs, the Agency stated that the rule was still necessary to address some of the gaps left by the pediatric exclusivity provision. No studies were required to be submitted under FDA's pediatric rule before December 2, 2000.

Agency Response to Congressional Request for Specific Information

Section 505A(k) of the Federal Food, Drug, and Cosmetic Act (the Act) states that the Secretary shall conduct a study and report to Congress not later than January 1, 2001, based on the experience under the pediatric exclusivity program. The study and report are to examine all relevant issues, including 4 specific issues:

1. The effectiveness of the program in improving information about important pediatric uses for approved drugs.

The pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date. As a result of this provision, FDA has issued over 157 Written Requests, asking for 332 studies that would potentially involve well over 20,000 pediatric patients. In less than 3 years, over 58 pediatric studies have already been conducted, study reports submitted, and exclusivity granted to 25 drugs. The ultimate goal of encouraging pediatric studies is to provide needed dosing and safety information to physicians in product labeling. As a result of the pediatric exclusivity provision and FDA's filing requirement that study reports be submitted in a manner which will result in labeling information for children, critical drugs used to treat a variety of conditions (e.g., gastroesophageal reflux disease, diabetes mellitus, pain, asthma, hypertension) have or soon will have pediatric use information in their labeling.

[4] Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule (63 FR 66632; Dec 2, 1998).

The pediatric exclusivity provision has left some significant gaps in pediatric labeling information. As described in #2, below, the provision has not resulted in studies on certain important drug categories and age groups.

2. The adequacy of the incentive provided under this section.

The large number of pediatric studies proposed by the pharmaceutical industry since the provision took effect demonstrates the adequacy of the incentive provided by the pediatric exclusivity provision for many categories of products. FDA has received over 191 proposals from sponsors to conduct pediatric studies.

For some products and for some age groups, however, the incentives provided by the pediatric exclusivity provision have not produced proposals to conduct pediatric studies. The incentive is not adequate for old antibiotics and other drugs lacking market exclusivity or patent protection because these products are not eligible for any exclusivity under the current pediatric exclusivity provision. The incentive is also not adequate to produce pediatric studies in certain drugs with low sales because the value of the exclusivity decreases as sales decrease. Finally, the exclusivity is not adequate to produce pediatric studies in certain younger age groups, especially the neonatal age group for whom an appropriate trial cannot be designed until studies of older pediatric age groups have been submitted and analyzed. Although a second period of exclusivity is available in the Act it is very limited in scope and to date no sponsor has utilized this option.

Thus, while the incentive provided by the pediatric exclusivity provision has clearly been adequate for many products, it has naturally tended to produce pediatric studies on those products where the exclusivity has the greatest value. This has left some drugs of importance to children, but for which the incentive has little or no value, unstudied. For example, 10 drugs were identified in 1994 as the drugs most frequently prescribed for children that lack adequate labeling[5]. Of these, the 6 without remaining exclusivity or patent life have not been studied under the pediatric exclusivity program and remain inadequately labeled (see Appendix B, table 7).

3. The economic impact of the program on taxpayers and consumers, including the impact of the lack of lower cost generic drugs on patients, including on lower income patients.

The pediatric exclusivity granted under this program should reduce certain types of health care expenditures, but increase others. The incentives provided by the newly authorized pediatric exclusivity should lead to significant advances in pediatric medicine. Superior drug treatment information is expected to permit quicker recoveries

[5] IMS HEALTH Inc., *National Disease and Therapeutic Index®*. NDTI was used to identify the most commonly used pediatric drugs. Drugs on this list were checked against their approved labeling and from this the pediatric age range that lacked adequate labeling was identified. The top 10 most frequently prescribed drugs used in the pediatric population that lacked adequate labeling were derived from this comparison.

from childhood illnesses, with fewer attendant hospital stays, physician visits and parental work days lost. On the other hand, the pediatric exclusivity will delay the introduction of lower-priced generic drugs, which will temporarily raise the average price of prescription drugs.

The Secretary finds that the impact of the lack of lower cost generic drugs on some patients, especially those without health insurance and the elderly, may be significant. Nevertheless, the Secretary expects pediatric exclusivity costs to add less than one-half of one percent to the nation's pharmaceutical bill.

4. Any suggestions for modification that the Secretary determines to be appropriate.

a. Recommended Modifications

Based on its experience with the pediatric exclusivity provision since 1997, the Secretary believes that Congress should renew, with modifications, section 505A of the Act. The Secretary recommends the following modifications of the section to improve FDA's ability to grant exclusivity for useful pediatric studies:

- eliminate the requirement for the pediatric list;
- eliminate the second exclusivity period as currently conceived; and
- eliminate the Written Agreement.

b. Addressing Gaps in the Statute

There are still important gaps in the statute. The statute does not provide an incentive to manufacturers to conduct studies in the youngest age groups, e.g., neonates and infants, if those studies must, for scientific or ethical reasons, be delayed until the completion of studies in older age groups. Yet, sometimes the greatest need is for studies in these age groups. The statute also provides no incentive to conduct studies on drugs that no longer have patent protection or exclusivity, or that have small markets. Some drugs of great importance to children's health fall in this category. The Secretary would like Congress to consider various means to address these gaps. Ideas that might be considered in Congress' deliberations might include:

- providing an incentive for studies in younger age groups, especially neonates; and
- permitting FDA and manufacturers to focus pediatric studies on those drugs that provide the greatest health benefit to children, including those that are not eligible for the incentives in the current statute, by allowing FDA to require studies on these drugs in exchange for new incentives.

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I. Introduction

In 1997, Congress passed the Food and Drug Administration Modernization Act, amending the Act. In addition to amending numerous previously existing sections of the Act, Congress added several new provisions.

New section 505A (21 U.S.C. 355a) provides that six months of pediatric exclusivity can be added to previously earned marketing exclusivity and listed patent protection for certain drugs[6] if the sponsors of those products submit requested information to FDA relating to the use of the products in children. This section of the Act, known as the pediatric exclusivity provision, was enacted because Congress recognized that information about the effects of drug and biological products in children was lacking. It was intended to create an incentive for drug manufacturers to conduct pediatric studies. The information gained from the studies would then be included in product labeling to permit the safe and effective use of the products in children.

Congress set a sunset date for the pediatric exclusivity provision of January 1, 2002. Congress also required the Secretary to conduct a study and report on FDA's experiences under the new law by January 1, 2001. This report is intended to satisfy the statutory reporting requirement.

To obtain public input on the pediatric exclusivity program, FDA issued a *Federal Register* Notice on May 5, 2000, requesting comments on the provision. Twelve written comments were received from brand name drug manufacturers, generic drug manufacturers, trade associations, physician organizations, and organizations devoted to pediatric oncology. (For a summary of the comments submitted, see Appendix A.)

[6]The provision applies to drug and biological products approved under section 505 with patent life remaining on listed patents or for which exclusivity remains under the Drug Price Competition and Patent Term Restoration Act (Pub. L. 98-417) or the Orphan Drug Act (Pub. L. 97-414). Periods of marketing exclusivity are available to new chemical entities, drugs designated and approved for small populations, and to certain already marketed drugs for which new clinical studies are conducted, under these provisions of the Act. During the period of new chemical entity and new clinical study exclusivity generic copies of the drug may not be approved or marketed. Orphan exclusivity protects sponsors from competition by both generic and innovator drugs. Although biological products submitted under section 505 of the Act may earn pediatric exclusivity, only a handful of biological products are submitted under section 505.

This report first discusses briefly the need for more information on the use of drugs in the pediatric population and previous FDA efforts to encourage the development of more information on the effects of these products in children. The report then examines the specific issues mandated by Congress.

II. The Need for More Information about Drug Effects in Children

Children are subject to many of the same diseases as adults, and by necessity, are often treated with the same drugs and biological products. According to the American Academy of Pediatrics, however, only a small fraction of all approved drugs[7] marketed in the United States have had clinical trials performed in pediatric patients. A majority of marketed drugs are not labeled for use in pediatric patients, or are labeled for use only in specific pediatric age groups.[8] From 1973 to the present, evidence from multiple sources has shown that drugs continue to be inadequately labeled for use in pediatric patients. As shown in figure 1 below, data from 1991 to 1994 indicate that as of those dates 71 percent of the new molecular entities (NME) still were without pediatric drug labeling.[9]

Figure 1.	**A Continuum of Validation**
1973 PDR:	78% without sufficient pediatric drug labeling
1984-1989 NMEs:	80% without pediatric drug labeling
1991 PDR:	81% without disclaimers or age restrictions
1992 NMEs:	79% of potential pediatric use unapproved
1991-1994 NMEs:	71% without pediatric drug labeling

Safety and effectiveness information for some pediatric age groups is particularly uncommon in product labeling. For example, for most drug classes, there is almost no information on use in patients under 2 years of age.[10] And many of the drugs most widely used in pediatric patients carry disclaimers in their labeling stating that safety and effectiveness in pediatric patients have not been established.[11] The absence of pediatric labeling information poses significant risks for children. Inadequate dosing information exposes pediatric patients to the risk of adverse reactions, usually age-specific adverse reactions that could be avoided if such information were provided in

[7] For the purposes of this report, the terms *drugs, marketed drugs,* and *products* are often used interchangeably.
[8] 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.
[9] Wilson, John T., An Update on the Therapeutic Orphan, *Pediatrics*, 104(3); 585-590, 1999.
[10] Pina, L. M., Drugs Widely Used Off Label in Pediatrics, Report of the Pediatric Use Survey Working Group of the Pediatric Subcommittee, in *News Along the Pike*, January 1997.
[11] Cote, C. J., et.al., "Is the therapeutic orphan about to be adopted?" *Pediatrics*, 98(1); 118-123, 1996.

product labeling.[12] The absence of pediatric testing and labeling may also expose pediatric patients to ineffective treatment through underdosing, or may deny pediatric patients therapeutic advances because physicians choose to prescribe existing, less effective medications in the face of insufficient pediatric information about a new medication.

Pediatric patients also lack access to drugs that do not come in dosage forms (formulations) that children are capable of taking, such as liquids and chewable tablets. Many important drugs are not available in pediatric formulations. Failure to develop a pediatric formulation of a drug, may deny younger pediatric patients access to important new therapies, or may require pediatric patients to take a drug in extemporaneous formulations (e.g., sprinkling a crushed tablet on a child's food) that may be poorly or inconsistently bioavailable.[13]

III. Previous Efforts to Improve Pediatric Labeling Information

During the last 2 decades the medical community has expressed increased concern that drugs are used widely in children despite the fact that, in most cases, information about the effects of these products in children is absent or insufficient. In response to this concern, the Agency has undertaken a number of initiatives to address the problem of inadequate pediatric testing and inadequate pediatric use information in drug and biological product labeling.

A. 1994 Pediatric Labeling Regulation

In 1994, FDA issued a regulation requiring drug manufacturers to survey existing data and determine whether those data were sufficient to support additional pediatric use information in the labeling of their drugs.[14] If a manufacturer determined that existing data permitted modification of the label's pediatric use information, the manufacturer was required to file a supplemental new drug application to FDA seeking approval of a labeling change.

The response to the 1994 rule was disappointing and did not substantially increase the pediatric use information for marketed drugs and biological products.

[12] The proposed rule on pediatric studies issued by FDA in 1997 ("Proposed Pediatric Rule") cited reports of injuries and deaths in children resulting from the use of drugs that had not been adequately tested in the pediatric population (62 FR 43900).

[13] Bioavailability is a measure of how well a drug reaches the site in the body at which it is intended to act. Poorly or inconsistently bioavailable drugs can be both ineffective and unsafe.

[14] 21 CFR Part 201, Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling; Final Rule, December 13, 1994 (FR 59 64240).

B. Pediatric Plan

In December 1994, FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) implemented a *Pediatric Plan* designed to focus attention on and encourage voluntary development of pediatric data both during the drug development process and after marketing. These voluntary activities did not substantially increase the number of drugs with adequate pediatric labeling.

C. Pediatric Rule

The Pediatric Rule, which was proposed in 1997, finalized in 1998, and became effective on April 1, 1999, requires that manufacturers of certain new and marketed drugs and biological products conduct studies to provide adequate labeling for the use of these products in children. Under this regulation, FDA can require pediatric studies of a new drug or biological product if the product is likely to be used in a "substantial number of pediatric patients"[15] or would provide a "meaningful therapeutic benefit"[16] to pediatric patients over existing treatments. FDA can also require pediatric studies of marketed drugs if either of these conditions applies and inadequate labeling could pose significant risks.

Although the incentive provided by the pediatric exclusivity provision was expected to result in the submission of pediatric studies for many drugs, the Agency issued the final Pediatric Rule to address some of the gaps left by the pediatric exclusivity provision. No studies mandated under the Pediatric Rule were required to be submitted before December 2, 2000.

D. 1997 Pediatric Exclusivity Provision

After FDA issued the Proposed Pediatric Rule, but before that rule was finalized in 1998, Congress enacted FDAMA. Section 505A of FDAMA established economic incentives for conducting pediatric studies.

FDAMA recognized the importance of pediatric studies by providing for 6 months of exclusivity to be attached to existing exclusivity or listed patent protection for a drug whose manufacturer submits pediatric studies in compliance with section 505A.

In the sections that follow, this report discusses the FDA's implementation of the pediatric exclusivity provision during the past 3 years, addressing the issues Congress required the Secretary to address by January 1, 2001.

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[15] FDA considers the term *substantial number of patients* to mean 50,000 pediatric patients in the U.S. with the disease or condition for which the drug or biological product is indicated (63 FR 66636).

[16] The term *meaningful therapeutic benefit* is defined as 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 (314.55(c)(5)).

IV. FDA's Implementation of the Pediatric Exclusivity Provision

The Agency has implemented the pediatric exclusivity provision according to the requirements of the statute by:

- publishing a list of drugs for which pediatric information may be beneficial;
- working with sponsors to develop and issue Written Requests for pediatric studies;
- reviewing submitted studies; and
- making exclusivity determinations.

The Agency also has made organizational changes to support the implementation of the pediatric exclusivity provision, including assembling a Pediatric Team and creating a Pediatric Advisory Subcommittee. Finally, the Agency has published three guidances to facilitate the implementation of the exclusivity provision:

- *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act* (original July 1998; updated September 1999)
- *Pediatric Oncology Studies in Response to a Written Request (*Draft June 2000)[17]
- *General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (*Draft November 1998)

A. Publication of the List

Section 505A(b) of the Act required the Secretary, after consultation with experts in pediatric research, to develop, prioritize, and publish an initial list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population. FDA was required to publish the list no later than 180 days after the date of the enactment and to annually update the list.

The list was developed as required in consultation with experts in pediatric research and published on May 20, 1998. The list contained all drugs approved for use in adults for indications that occur in the pediatric population.

FDA also prioritized the list. To be included on the priority list the drug had to meet one of the following criteria:

[17] This guidance was written to address concerns raised by the pediatric oncology community that the pediatric exclusivity provision was not working to generate studies for pediatric cancer drugs. There are unique aspects in pediatric cancers that make it imperative to evaluate the safety and effectiveness of new cancer drugs in pediatric populations. The guidance provides information on a flexible regulatory approach to earning pediatric exclusivity for conducting studies on drugs to treat pediatric cancers.

- 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 priority review drug); or,

- The drug is widely used in the pediatric population, as measured by at least 50,000 projected uses per year; or

- The drug is in a class or for an indication for which additional therapeutic or diagnostic options for the pediatric population are needed.

The list has been updated annually as required in the statute. The last update was May 20, 2000. Because a drug need not appear on the priority section of the list to be eligible for pediatric exclusivity and FDA has generally issued Written Requests for pediatric studies without regard to a moiety's appearance on the list, the list has been a source of confusion for the industry.

B. Written Requests

Section 505A authorizes exclusivity for those pediatric studies submitted in response to a "Written Request" from the Secretary. A manufacturer who receives a Written Request is under no obligation to conduct a study. However, a manufacturer who submits a pediatric study is not eligible for pediatric exclusivity unless the study was submitted in response to a Written Request, and the study fairly responds to the Written Request.

To facilitate this process, FDA issued a guidance document that describes the format and contents of a Written Request (*Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*). To ensure that studies eligible for pediatric exclusivity provide meaningful safety and effectiveness information on the use of the drug in relevant pediatric age groups, a Written Request addresses, among other things, the type of studies to be performed, study design, appropriate study age groups, and clinical endpoints. To help focus scarce Agency resources on issuing Written Requests for studies that manufacturers were interested in conducting, FDA asked interested sponsors to submit a Proposed Pediatric Study Request (PPSR). In some cases, FDA has issued Written Requests to sponsors on its own initiative. As of September 1, 2000, FDA had received 191 PPSRs and issued 157 Written Requests (see Appendix B, table 1).

FDA interprets the statute as requiring the sponsor to have received the Written Request before submitting a study report to FDA. If the sponsor obtains data different from the data specified in the Written Request, the sponsor must contact the FDA to discuss whether an amendment to the Written Request is appropriate. The sponsor must obtain an amended Written Request before submitting any pediatric study reports.

C. Written Agreements

Section 505A(d)(1) permits the Secretary to enter into a Written Agreement with a sponsor for the conduct of a pediatric study. A Written Agreement may serve to clarify any points in a Written Request for which additional detail or specificity are needed to ensure that the proposed plan is clearly understood and responsive to the Written Request. However, section 505(d)(2) also provides that a pediatric study submitted pursuant to a Written Agreement must be conducted in accordance with both the Written Request and the Written Agreement. Having a Written Agreement in place does not provide any assurances that a particular study will satisfy the terms of the Written Request and thus result in exclusivity.

Because compliance with the terms of the Written Request is required for an exclusivity award, drug sponsors initially became interested in having Written Agreements to minimize the risk of loss of exclusivity through a misinterpretation of the terms of the Written Request. The addition of a Written Agreement, however, may further complicate the process for awarding exclusivity. When a Written Agreement is in place, the terms of both the Written Request and the Written Agreement must be satisfied before pediatric exclusivity can be awarded. The more details agreed to in the Written Agreement, the greater the chance that the final studies will fail to meet its terms. To date, one Written Agreement has been completed.

D. Scope of Pediatric Exclusivity

Section 505A does not expressly address a key question in the implementation of the provision. When a drug sponsor is awarded exclusivity for submitting pediatric studies, to which of the sponsor's patents and previous grants of exclusivity does six months of exclusivity attach? FDA has interpreted the provision to add the six months of exclusivity to any of the sponsor's listed patents or previous non-expired grants of exclusivity on drug products containing the *active moiety* that was studied. This is a broad interpretation of the scope of exclusivity because it may attach to patents and exclusivity on drug products other than those studied. FDA concluded, however, that this interpretation was the most consistent with the language and purpose of the pediatric exclusivity provision. As a necessary corollary of this interpretation, FDA has construed the provision to permit the Agency to include within a single Written Request pediatric studies on any drug products containing the active moiety, if such drug products have significant uses in the pediatric population.

FDA's interpretation of the scope of the pediatric exclusivity resulted in a lawsuit brought by members of the generic drug industry. The court in that case upheld FDA's interpretation of the statute.[18]

[18] National Pharmaceutical Alliance v. Henney, 47 F. Supp. 2d 37 (D.D.C. 1999)

V. Specific Issues to be Addressed Under Section 505A(k)

Section 505A(k) requires that the Secretary's report to Congress "examine all relevant issues, including-

1. the effectiveness of the program in improving information about important pediatric uses for approved drugs;

2. the adequacy of the incentive provided under this section;

3. the economic impact of the program on taxpayers and consumers, including the impact of the lack of lower cost generic drugs on patients, including on lower income patients; and

4. any suggestions for modification that the Secretary determines to be appropriate."

The remainder of this report will focus on these specific questions.

A. Effectiveness of the Pediatric Exclusivity Provision

The pediatric exclusivity provision has been highly effective for many drugs. In general, the industry's response has been vigorous and the public health benefits have been extensive.

1. Pharmaceutical Industry's Response

The response from the research based pharmaceutical industry to the pediatric exclusivity provision has been vigorous. Between the publication of the guidance in July 1998 and September 2000, drug sponsors have submitted over 191 proposed study requests and FDA has issued 157 Written Requests (see Appendix B, table 2). The Written Requests cover a broad range of diseases and conditions, including life-threatening conditions (see Appendix B, table 3). Sponsors have indicated that they have conducted or will conduct 80 percent or more of the studies that FDA has requested. Over 58 pediatric studies have already been completed, submitted and received a preliminary review, resulting in 25 grants of pediatric exclusivity (see Appendix B, table 4) as of September 2000.[19]

In contrast, before enactment of the pediatric exclusivity provision, few of the pediatric studies requested by FDA were completed. Over a 6-year period between 1991 and 1996, drug sponsors promised to complete 71 postmarketing pediatric studies. Only 11 were completed.

[19] Some sponsors had to conduct more than one study to obtain pediatric exclusivity (e.g., where more than one pediatric age group needed to be studied).

2. Public Health Benefit

The purpose of encouraging pediatric studies is to provide needed pediatric efficacy, safety and dosing information to physicians in product labeling. Implementing the requirement in section 505A(d) that pediatric studies be reported in accordance with FDA's filing requirements, the Agency requires that pediatric studies submitted for exclusivity be submitted as new drug applications or in supplemental applications to the sponsor's new drug application (NDA), with proposed labeling. Of the 25 drugs granted pediatric exclusivity 12 drugs have newly approved labeling for pediatric use. Labeling changes are expected for the remaining drugs granted exclusivity once the reviews have been completed approximately 6-12 months after the studies have been submitted. As a result of these pediatric studies critical drugs used to treat a variety of conditions (e.g., pain, asthma, juvenile rheumatoid arthritis, gastroesophageal reflux disease, hypertension, diabetes mellitus, Obsessive Compulsive Disorder) will now include information on pediatric use in their labeling.

Of the 12 drugs whose labels have already been changed (see Appendix B, table 5), 4 were new molecular entities for which pediatric labeling was available at the time of initial approval. The 8 remaining marketed products now have complete labeling in the relevant pediatric population. This is a significant response in only 2 years, taking into consideration the time necessary for FDA review of the studies, which under PDUFA goals ranges from a minimum of 6 months to a maximum of 1 year.

The important label changes made on these twelve drugs as a result of pediatric studies requested by FDA in a Written Request are as follows:

1. Extension of the age range down to 6 months of age for the over-the-counter use of **ibuprofen** products. (The active moiety by 2 different sponsors, each of whom received a Written Request, was granted pediatric exclusivity).

   Ibuprofen is one of the most commonly used drugs in infants to reduce fever and is relied upon by parents in times of illness to provide comfort to their children. Until these studies, ibuprofen products carried no dosing information for children under 2 years of age. An appropriate dose should provide symptom relief without side effects. If the dose is too low, the child will not experience relief. If the dose is too high, the child may experience an increase in side effects. Studies in thousands of young infants established a safe and effective dose in infants and young children from 6 months to 2 years.

2. Addition of pediatric dosing information for a new oral formulation of **midazolam,** a sedative**,** and identification of a subpopulation of pediatric patients at higher risk for adverse events.

   Midazolam is one of the most commonly used medicines to sedate children undergoing surgery or other procedures. Until a new oral formulation was developed, midazolam was available only by injection of the drug directly into a vein

or muscle. Any parent whose child has had to undergo surgery or other procedures, or had a needle injected to draw blood or provide fluid or medicines, is aware of the terror and distress demonstrated by young children in these situations. The studies submitted not only involved a new oral syrup for use by young children, but also identified the correct dose for use of the syrup in this young population. The studies also identified a serious adverse event in children with heart disease and pulmonary hypertension that can be prevented by administering a lower dose.

3. Provision of directions for use of **abacavir** in the treatment of HIV for pediatric patients 3 months to 12 years.

   HIV is a life-threatening disease. Many anti-HIV drugs have side effects that can make them intolerable for some people. Because side effects differ from one agent to another, it is important to have several drugs available for HIV-infected children, should a child be unable to tolerate one or more of the available drugs. Abacavir, a new anti-HIV drug, was studied in children before its approval, offering an additional option for infected children. The availability of pediatric dosing information at the time of abacavir's approval was particularly important to provide an additional potent antiretroviral agent for the treatment of a life-threatening condition in patients with limited therapeutic options.

4. Addition of information on the use of **ranitidine** in the neonatal population.

   Gastroesophageal reflux is experienced as heartburn in adults but is a life-threatening event when it occurs in seriously ill neonates. The anatomy of infants allows stomach contents to easily flow up the esophagus and into the lungs. Premature infants often have underdeveloped or damaged lungs and the ongoing insult of aspirating stomach contents into the lungs can be life-threatening and lead to chronic respiratory problems. Ranitidine can be used to manage reflux of stomach contents, preventing damage to the lungs of neonates. In addition, ranitidine is frequently used in the intensive care unit where neonates requiring chronic ventilation develop gastric hyperacidity leading to gastrointestinal bleeding. The studies of ranitidine in neonates provided accurate dosing information for safer and more effective use of this drug in the management of reflux and hyperacidity in seriously ill neonates.

5. Provision of directions for use of **insulin glargine** for pediatric patients 6 years and older.

   Diabetes is a life-threatening disease. Better control of diabetes means fewer organ failures and a healthier life. In addition, for children with diabetes, wide swings in blood sugar interfere with daily functioning and learning. Because learning is one of the fundamental tasks of childhood, it is critically important to stabilize blood sugar levels. The new recombinant insulin requires administration only once a day. This insulin is expected to provide better control of blood sugar in pediatric patients and patients will be able to stick themselves less frequently to check blood sugar levels. The new recombinant products are also reported to have fewer allergic reactions

and therefore are able to be used longer, an advantage for children, who will take insulin for longer periods than those with adult-onset diabetes. Pediatric information was included in the label at the time the drug was approved.

6. Provision of safety and effectiveness information for both **pemirolast** and **azelastine** for use down to the age of 3 years.

   Itchy, watery eyes are symptoms associated with the condition of allergic conjunctivitis. Drugs such as pemirolast and azelastine are administered as eye drops to relieve the symptoms of itchiness or tearing. Treatment of the condition and the relief of symptoms should prevent children from traumatizing their eyes because they itch. Watery and matted eyes can also cause a decrease in vision that can be dangerous in the active and exploring young child and may interfere with learning in the older child. Both drugs were studied in children before approval, resulting in labeled directions for pediatric use at the time of initial approval of the drugs.

7. New indication for **etodolac** for patients 6 to 16 years old.

   This was an important milestone for children with juvenile rheumatoid arthritis (JRA) because there was only one other oral drug approved to treat this frequently debilitating disease. JRA is a form of arthritis that affects approximately 100,000 children in the United States. Young children and adolescents with JRA face tremendous challenges in everyday life to cope with this painful disease. It affects school, social life, family relationships, dating, sports and almost every other aspect of their daily lives.

8. Addition of proper dosing information for **cromolyn** in children between the ages of 2 years and 6 years, as well as additional data supporting safety and compliance.

   Cromolyn is an important preventative medicine in the armamentarium of therapies for allergies. Prevention is always a better approach than treating allergy symptoms after they occur. Many of the therapies for allergies are sedating or conversely act as stimulants and potentially interfere with the important task of learning. Cromolyn has neither of these side effects.

9. Provision of appropriate pediatric dosing and long-term safety information for **fluvoxamine** in pediatric patients 8 years to 17 years.

   The obsessions (persistent and recurrent ideas, images, thoughts) or compulsions (repetitive, purposeful, and intentional behaviors, such as hand washing) in patients with obsessive compulsive disorder (OCD) cause marked distress, and interfere with the child's ability to learn and play. These behaviors often lead to taunting and rejection by their peers. Fluvoxamine is approved for the treatment of OCD in children. The studies performed indicated that the dose in adolescents may need to be increased up to the adult dose. Further, girls (8-11 years) may require a lower dose. In addition, long term safety appears to be similar to that seen in adults.

10. Provision of safety and effectiveness information down to 2 years of age for **ammonium lactate** in the treatment of ichthyosis vulgaris and xerosis.

    The conditions of ichythosis vulgaris and xerosis are manifested by dry, scaly skin. The skin becomes less flexible and rough and is prone to cracking and fissuring. Children experience itchiness of the skin that is particularly troublesome and may lead to scratching, excoriation, and ultimately to infection of the skin. In addition, these children are fussy and irritable, causing them problems with concentrating during the day and sleeping at night. Ammonium lactate is now shown to be safe and effective down to 2 years of age. The drug increases skin hydration and provides symptomatic relief to the dry, itchy skin.

As another measure of the benefit provided by the pediatric exclusivity provision, the Secretary obtained information on the extent of use of the drugs studied. Providing adequate labeling instructions for pediatric use is particularly important where children are frequently exposed to a drug. The Secretary obtained IMS HEALTH data from January 1994 through December 1999 (6 years) on how often 14 of the 25 drugs granted pediatric exclusivity were mentioned in the pediatric population requested for study (see Appendix B, table 6). IMS HEALTH data are used to project the number of times that a particular drug is used in a specified population. The greatest number of mentions in the 6-year period evaluated was for ibuprofen for children 6 months to 2 years old: an average of 1.4 million uses per year. Cromolyn sodium had an average of 396,000 mentions in children 2 to 6 years old per year. Ranitidine had an average of 247,000 mentions in neonates per year. The remaining drugs had between 2700 and 65,000 mentions per year in the specified population.

B. Adequacy of the Incentive

In general, the pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date. However, experience with the provision has revealed several categories of products and age groups for which the incentive is not adequate. Limitations on the scope and effect of the pediatric exclusivity provision have left some significant gaps in pediatric labeling. For example, because exclusivity applies only to products that have existing patent protection or exclusivity under the Drug Price Competition and Patent Term Restoration Act or the Orphan Drug Act, there is no incentive for sponsors to conduct studies on most antibiotics or on those products that no longer enjoy exclusivity or patent protection. The pediatric exclusivity provision does not provide adequate incentives to study the following products:

1. Drugs Lacking Exclusivity or Patent Protection

As noted previously the incentive for developing pediatric information under section 505A currently applies only to those products that are covered by listed patents or exclusivity under the Drug Price Competition and Patent Term Restoration Act or the

Orphan Drug Act. Sponsors of marketed products that have no remaining patent life or exclusivity have no economic incentive to study these products. Many such products, however, have important uses in children and have not been adequately studied. For example, dopamine is a very important drug used in the treatment of serious life-threatening conditions (i.e., hypotension, heart conditions). However, it will most likely not be studied due to the lack of exclusivity or patent protection. In 1994, FDA conducted a study to determine the 10 drugs most widely used in children without adequate labeling information (see Appendix B, table 7).[20] Of these 10 drugs, 6 are not covered by exclusivity or patent protection and none of the sponsors of these drugs has submitted a PPSR.

Old antibiotics — those approved under Section 507 of the Federal, Food, Drug, and Cosmetic Act, which was repealed in FDAMA — are ineligible for the pediatric exclusivity incentive, because they were never eligible for patent listing or exclusivity under the Drug Price Competition and Patent Term Restoration Act. Many of these antibiotics have the potential to provide a significant clinical benefit in the pediatric population. Studies of this group of drugs are needed to assess their use in neonates and to treat serious diseases that affect small numbers of pediatric patients. Despite the need, these antibiotics will remain unstudied under the pediatric exclusivity provision.

2. Drugs with Insufficient Sales

The exclusivity incentive is inadequate for products that do not generate sufficient sales in either the adult or pediatric population to provide a large market return for conducting pediatric studies. For example, amphotericin, which is used for serious and life-threatening fungal infections, even if covered by exclusivity or patent life, has such a small market that it is unlikely the pediatric exclusivity incentive would be adequate to produce pediatric studies.

3. Drugs for which Sequential Pediatric Studies are Necessary

Many drugs of importance to children need to be studied in more than one pediatric age group because size and maturation of body systems can affect both dosing and side effects. For some drugs, such as neurotropic drugs, heightened safety concerns about exposure of neonates, infants, and young children to the drugs have dictated that studies in these age groups be deferred until additional information is available from animal studies, studies in older children, or wider use in adults. In these settings, FDA has granted pediatric exclusivity upon completion of the studies in the older pediatric age groups.

Once pediatric exclusivity is granted for studies in older pediatric age groups, section 505A does not provide an adequate incentive to conduct later studies in the younger age groups. The opportunity to obtain a second grant of exclusivity for later studies on the same drug, in 505A(h), applies to a very limited subset of drugs (see section V. D. 2,

[20] IMS HEALTH Inc., *National Disease and Therapeutic Index*

below). This has left some age groups, especially neonates, unstudied, even where the need for the drug in those age groups is great.

C. Economic Impact of the Pediatric Exclusivity Provision

Section 505A(k) specifically asks that the Secretary examine:

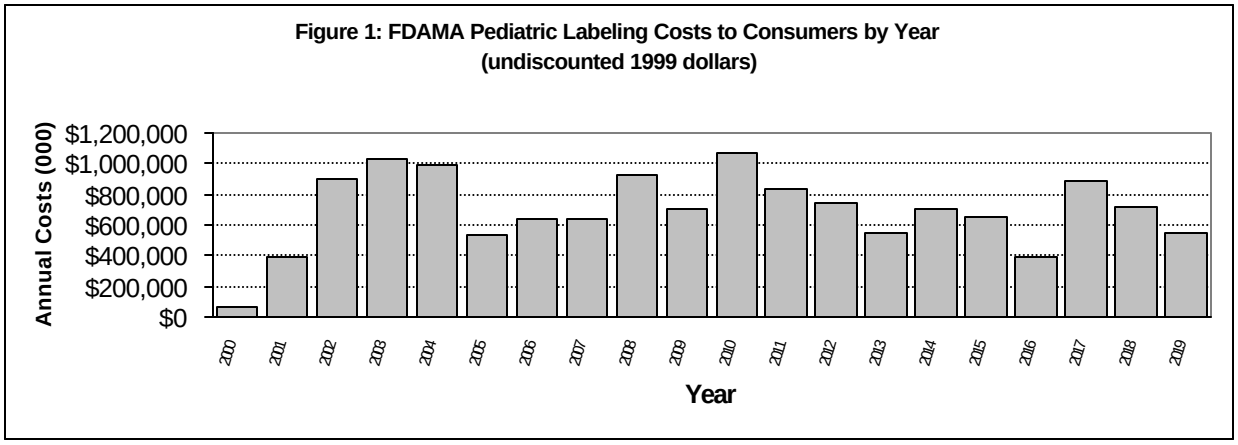
> "The economic impact of the program on taxpayers and consumers, including the impact of the lack of lower cost generic drugs on patients, including on lower income patients."

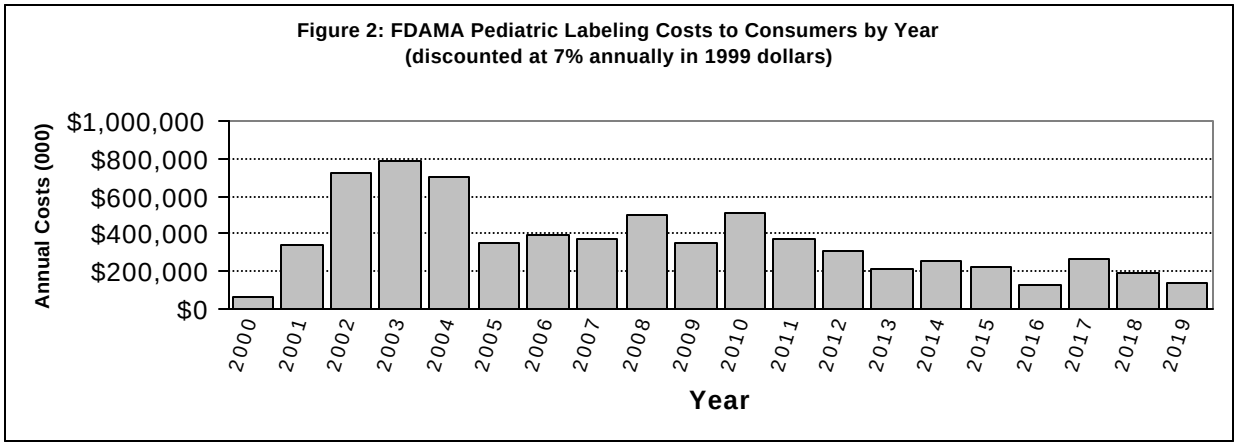
The robust incentives provided by the newly authorized pediatric exclusivity should lead to significant advances in pediatric medicine. The pediatric exclusivity granted under this program should reduce certain types of health care expenditures, but increase others. Superior drug treatment information will permit quicker recoveries from childhood illnesses, with fewer attendant hospital stays and physician visits. These improved health outcomes should produce significant health care cost savings for the United States economy.

Although FDA anticipates that these future health care cost savings will be substantial, the expected improved health outcomes have just begun to be realized. Consequently, the Agency has not attempted to develop a quantitative estimate of these savings. Nevertheless, in the preamble to the Pediatric Rule, the Agency gave several anecdotal examples that illustrate the potential cost savings that could follow the availability of expanded pediatric clinical information (63 FR 66665-66667). To consider these potential savings, the Agency examined hospitalization rates for five serious illnesses (asthma, HIV/AIDS, cancer, pneumonia, and kidney infections) and found significantly higher rates for children than for middle-aged adults. FDA hypothesized that a substantial fraction of the difference between these pediatric and adult hospitalization rates for like disease conditions may be attributable to the greater range of informed drug therapies and better data on drug dosage for adults. The Agency calculated that eliminating just 25 percent of these differentials for these five illnesses would lead to direct medical cost savings of $228 million annually. This figure does not capture the potential cost savings from the many other illnesses that are common to children, including such life-threatening conditions as hypertensive disease and renal disease.

On the other hand, pediatric exclusivity will increase the level of certain health care expenditures, because it will delay the introduction of lower-priced generic drugs, which will temporarily raise the average price of prescription drugs. The increased dollar outlays are estimated to total about $13.9 billion over the 20-year period. Sixteen of the drugs studied account for about one-half of the $13.9 billion and one product accounts for 11.1 percent. The estimated present value of these revenue/cost increases (discounted at the 7 percent rate preferred by the U.S. Office of Management and Budget) amounts to approximately $7.2 billion, or $61 million per drug over the next 20 years. (Discounting reflects the time value of money by accounting for the fact that a dollar paid or received in the future is worth less than a dollar today.) Figure 1 presents

a bar graph of the estimated undiscounted costs of the exclusivity by year for 20 years. Some years are considerably more expensive than others, but the estimated *annual* cost over the 20-year period averages $695 million. Figure 2 displays the discounted costs by year. The method used to derive these costs and the sensitivity of the results to the assumptions made may be found in Appendix C.



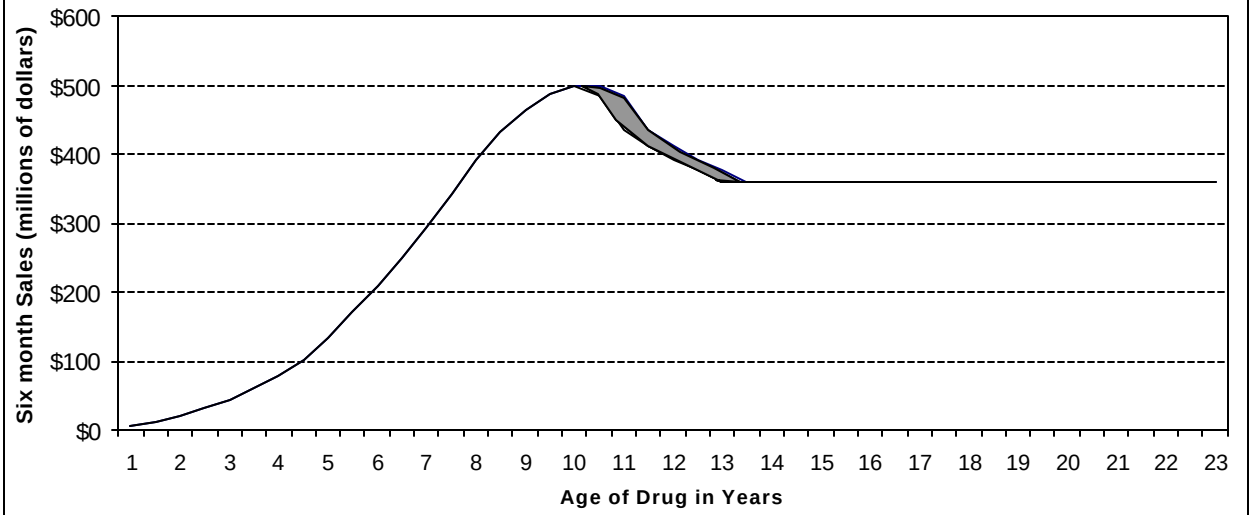


1. Consumer and Taxpayer Impacts

Section 505A(k) directs the Secretary to examine the economic impact of the program on taxpayers and consumers, including the impact on lower income patients. This analysis finds that the cost impact on consumers will be substantial due to the additional 6 months of time that innovator drugs will be marketed without competition from lower-priced generic drugs.

Figure 3 graphically demonstrates the methodology for a hypothetical drug with innovator sales reaching a peak of $500 million in a six-month period, or $1 billion a year. (Our estimates indicate that the actual average annual peak revenue for the studied drugs will be about $710 million.) During the first 10 years, innovator sales

Figure 3: Typical Sales History of Drug reaching $1 Billion per Year



revenues increase until market exclusivity expires. During the 3 years following the expiration of innovator marketing exclusivity, total drug sales revenues decline.

Finally total sales revenues are assumed to stabilize 3 years after the first generic competition enters the market. The two illustrated sales curves are identical, except that one includes an additional 6 months of innovator sales before generic competition enters the market. The shaded area, or the difference between the curves, represents the increased costs to consumers of these drugs. Beyond the 3-year period following patent/exclusivity expiration, the estimated differences disappear. It is important to recognize that these projected sales include sales for all therapeutically equivalent products containing the moiety of the innovator drug. That is, after the expiration of the drug's patent or exclusivity, generic sales are included in the sales projections.

These pediatric exclusivity awards are expected to increase the cost of drugs by an average of about $695 million per year in undiscounted dollars (see figure 1). Estimates of total national pharmaceutical spending provide a perspective for such outlays. The Health Care Financing Administration (HCFA) indicates that prescription drug spending reached just over $100 billion in 1999 and projects this figure will rise to about $185 billion by 2005.[21] The National Association of Chain Drug Stores reports that prescription drug spending already exceeded $121 billion in 1999.[22] Consequently, the

[21]Office of the Actuary, Health Care Financing Administration, "National Health Expenditures Projections: 1998-2008," Table 12a.

[22]"Pharmaceutical Marketplace Dynamics," Presentation by John Coster, Vice President, National Association of Chain Drug Stores, at the National Health Policy Forum, May 31, 2000. Data referenced to IMS HEALTH. If this information was to be updated as of November 2000, the figure would be $130.1 billion.

Secretary expects pediatric exclusivity costs to add about one half of one percent to the nation's pharmaceutical bill.

It is difficult to determine which consumer groups will ultimately bear the greatest burden, because the nation's pharmaceutical payment systems are likely to undergo significant change over the next decade. HCFA reports that public sources (Federal, State & Local, Medicare, Medicaid) accounted for about 21 percent of all pharmaceutical spending in 1999, but suggests that this percentage will rise over the next few years. Thus, government may bear at least 21 percent of the additional costs and private payers 79 percent.

2. Lower Income Patients

The greatest burden will fall on consumers with no private or public insurance support, which may disproportionately affect lower income purchasers. IMS HEALTH data indicate that the percentage of prescription drugs paid for by cash at the pharmacy has declined sharply, from slightly over 50 percent in 1993, to about 25 percent in 1998.[23] Among these purchasers, the relative burden of higher drug prices may fall disproportionately on lower income families, as the percent of consumers without drug insurance coverage varies inversely with income.[24] This burden would be moderated to the extent that prescription drug benefits are extended to the Medicare population.

3. Impacts by Sector

As detailed in Appendix C, four main groups will experience economic impacts from pediatric labeling exclusivity: consumers facing higher drug prices, generic drug firms losing sales revenues, pharmacies receiving smaller retail price markups, and drug innovator firms gaining increased sales. The revenues gained by the innovator firms will just equal the sum of the losses of the former three groups. As previously described, we expect consumers to pay $13.9 billion (undiscounted) and $7.2 billion (discounted) for higher priced drugs over the next 20 years.

The generic drug sector will forego an estimated $10.7 billion ($5.7 billion discounted) in new sales over the 20-year period. On an annual basis, this figure amounts to about $537 million, or 6.7 percent of the reported $8 billion in industry sales.[25] As the generic drug industry's net income as a percentage of sales is about 9 percent,[26] these firms could lose over $48 million per year in unrealized profits.

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[23]The National Association of Chain Drug Stores, "The Chain Pharmacy - Industry Profile," 1999, p. 46.

[24]Department of Health & Human Services, "Prescription Drug Coverage, Spending, Utilization, and Prices: Report to the President," April 2000, pp. 25-35.

[25] Generic Pharmaceutical Industry Association; accessed July 18, 2000, at: http://www.gpia.org/edu_facts.html

[26] Average of 28 largest generic drug manufacturers, "MedAdNews," November, 1998

Retail pharmacies will also lose future revenues, because the average retail markup on generic drugs exceeds that on brand name drugs. These firms may lose $4.9 billion over the 20-year period, which amounts to about $247 million per year, or 0.2 percent of the $103 billion retail pharmacy prescription drug sales reported in 1998.[27] The discounted figures imply lost pharmacy revenues of $2.6 billion over the 20-year period.

Finally, innovator drug firms will gain sales revenues estimated at approximately $29.6 billion ($15.3 billion discounted) over the 20-year period. On an annual basis, these revenues will amount to almost $1.5 billion per year. Assuming costs of production, administrative, and marketing amount to 60 percent of brand name drug sales,[28] industry profits would rise by about $592 million annually.

In summary, while the expected improved health outcomes provided by appropriate labeling of drugs used in the pediatric population will likely result in significant health care cost savings, the health benefits of the pediatric exclusivity program will not be realized until pediatric trials are completed and the findings added to the drug labels. On the other hand, pediatric exclusivity will increase the level of certain health care expenditures, because they will delay the introduction of lower-priced generic drugs, which will temporarily raise the average price of prescription drugs.

If Congress concludes that the costs of the pediatric exclusivity provision exceed its benefits, the Secretary recommends that Congress consider reducing the size of the incentive provided by the statute rather than refusing to reauthorize the entire provision.

D. Suggestions for Modification

1. Recommended Modifications

Based on its experience with the pediatric exclusivity provision since 1997, the Secretary believes that Congress should renew, with modifications, section 505A of the Act. The Secretary recommends the following modifications:

- eliminate the requirement for the pediatric list;
- eliminate the second exclusivity period; and
- eliminate the Written Agreement.

These modifications are addressed in more detail in the following paragraphs.

[27] National Association of Chain Drug Stores, "The Chain Pharmacy – Industry Profile," 1999, p.9.

[28] Office of Technology Assessment, "Pharmaceutical R&D: Costs, Risks and Rewards, Washington, DC: U.S. Government Printing Office," Appendix G, February 1993.

a. The List

Eliminate the requirement for the pediatric list.

As the pediatric exclusivity program approaches its fourth year, the Secretary believes that there is no longer a benefit in maintaining a prioritized list of drugs, as currently required under section 505A(b). The existence of the list has not facilitated the drug development process for those drugs that would produce a health benefit in the pediatric population. In addition, the continued requirement of updating the priority list is not an efficient use of FDA's resources, for the following reasons:

- Section 505A does not require that a drug be on the priority list to qualify for pediatric exclusivity. In practice, the FDA's review divisions are now considering every proposal for pediatric studies under section 505A on its individual merits, regardless of whether the product is on the priority list. New and rapid development of the science in a disease or condition frequently accelerates the need for pediatric drug development in an area and should not be constrained by its absence from the priority list.

- The resource-intensive effort to update the priority list annually diverts resources from the timely review of specific requests for pediatric studies.

- The incorrect assumption that inclusion on the priority list is necessary to obtain exclusivity has been a source of confusion to drug sponsors.

- There is little reason to believe that products that have not been studied in children after remaining on the priority list for the first 5 years of the program will later be studied as a result of their continued presence on the list.

- The relative priority of the need for pediatric information varies with the perspective of the disease-specific advocacy group, expert/professional organization, and individual health care practitioners. Because the science is evolving rapidly, it has proven more efficient to bring experts together to focus on specific drugs and drug classes as issues arise than to attempt prospectively to develop a list of highest priority drugs.

b. Second 6-Month Period of Pediatric Exclusivity

Delete the second period of pediatric exclusivity.

The Secretary believes that section 505A(h), which authorizes a second grant of exclusivity is extremely limited in scope and has little value to sponsors.[29]

[29] As currently drafted, FDA understands that section 505A(h) limits second extensions of exclusivity to a very limited set of drugs: those that have obtained 3 years of exclusivity for making a change in an already approved product, e.g., adding a new indication, if the application was supported by clinical trials.

c. Written Agreement

Delete the optional Written Agreement.

Because compliance with the terms of the Written Request is required for the exclusivity award, some drug sponsors expressed initial interest in Written Agreements to try to eliminate ambiguity in a Written Request and minimize the risk of loss of exclusivity based on a misinterpretation of the terms of the Written Request. The addition of a Written Agreement, however, complicates matters rather than clarifying them. When a Written Agreement is in place, the terms of both the Written Request and the Written Agreement must be satisfied before pediatric exclusivity can be awarded. The more details agreed to in the Written Agreement, the greater the chance that the final studies will fail to meet its terms. After initial efforts to develop Written Agreements, it became clear that to prevent any possible misinterpretation, a Written Agreement must become long and cumbersome. Because, in practice, the Agency recognized that Written Agreements make it harder rather than easier for sponsors to earn exclusivity, the Agency has negotiated fewer than five Written Agreements and completed only one.

2. Addressing Gaps in the Statute

The Secretary would also like Congress to consider addressing some of the gaps in the current statute. In its deliberations, Congress might take under consideration the following ideas:

a. Incentive for Studies in Younger Age Groups

There is currently an inadequate incentive to conduct pediatric studies in certain younger age groups when those studies must be deferred until additional information has been gathered from studies in older children or from other sources. To encourage studies in these younger age groups, especially neonates, an additional incentive could be provided. FDA believes this may be advisable because it is clear from its experience that Written Requests issued by the Agency frequently do not request studies in neonates and younger pediatric age groups for scientific, medical or ethical reasons. It is anticipated that as knowledge is obtained in older children, studies in these younger age groups will be appropriate at a future time. Studies of the younger age groups, especially the extremely vulnerable and technically challenging to study neonatal population, should be undertaken with additional caution but should not be excluded from the drug development process.

When there is a need to proceed in a sequential manner for the development of pediatric information, FDA should have the option of issuing a second Written Request for the conduct of studies in the relevant younger age group(s). For this option to be meaningful, the second Written Request, after receiving the studies to an initial Written Request and pediatric exclusivity awarded, would be linked with a meaningful incentive to sponsors. Studies submitted in response to such a request could qualify for the additional incentive.

b. Ensuring that Certain Drugs of Importance are Studied

The statute currently provides little or no incentive to conduct studies on drugs that lack patent protection or exclusivity, or that have very small markets. Some of these drugs, however, have very important uses in children. The Secretary would like Congress to consider, perhaps at a later date, ensuring that pediatric studies are conducted on all the drugs of importance to children, not simply on those for which the current incentive is most valuable. Congress should consider various ways to achieve this goal. One possible means would include the following elements:

1. Expressly codify FDA's authority to require pediatric studies on drugs of importance to children. These would include both marketed and not-yet approved drugs.

   The factors for determining which marketed drugs provide the greatest health benefit would include:

   - whether the drug would provide a meaningful therapeutic benefit; or
   - whether the drug is or would be used in a substantial number of pediatric patients either for treatment of a labeled indication, or off-label; and
   - whether the absence of pediatric labeling could pose significant risks to patients.

   For marketed drugs, FDA would utilize the recommendation of an expert pediatric panel to identify drugs meeting the above criteria. Once the drugs are identified FDA would issue a written notification of requirements for pediatric studies (i.e., analogous to the Written Request), including, if appropriate, development of a pediatric formulation, and the deadline for their submission. Drug sponsors could propose additional drugs for which studies would be required.

2. For not-yet-approved drugs that represent a meaningful therapeutic benefit or are likely to be used in a substantial number of pediatric patients either for treatment of a labeled indication, or off-label, FDA would consult with the sponsor of the drug early in the drug development process and agree on a schedule for conducting pediatric studies. FDA would issue a written notification of requirements to the sponsor incorporating the elements of the pediatric drug development plan including, if appropriate, development of a pediatric formulation. FDA would not delay approval of a drug for adult use because required pediatric studies were not completed.

3. For not-yet approved or recently approved drugs, FDA could defer pediatric studies to permit the sponsor and FDA to obtain additional information about the safety of the drug in animals and/or humans.

4. A period of exclusivity or other incentive would be available to those who submitted the results of the studies that met the terms of the written notification of requirements. The results must be submitted in a new drug application or supplement that included proposed pediatric labeling changes.

   - For those drugs with existing exclusivity or listed patents, pediatric exclusivity would be awarded as under the present provision.

   - For those drugs without existing exclusivity or listed patents, an alternative incentive (although not within FDA's purview) could be considered by Congress, such as tax incentives or a period of exclusivity that could be transferred to another drug with existing exclusivity or listed patents held by the sponsor, or, if none exists, to a drug from another sponsor. A transferable exclusivity could be shorter than the six months that would have attached had the drug studied obtained pediatric exclusivity under the existing provision. In addition, such an exclusivity should not be transferable to a drug that has already received pediatric exclusivity or to a drug for which FDA has already required pediatric studies.

5. Congress would require FDA to publish a list of sponsors of approved drugs who have received written notification of required studies, the type of studies required, the timetable for submission and outcome of the studies, if completed. If a sponsor failed to conduct a required study, FDA would have the authority to impose a civil penalty or seek an injunction in federal court requiring that studies be conducted.

E. Other Relevant Issues

FDA does not currently have sufficient staff with expertise in pediatrics to respond efficiently to the tremendous number of new pediatric studies submitted by the pharmaceutical industry. The number of studies submitted is expected to continuously increase in the future. This shortage will slow initiation and review of studies and negatively impact the entire pediatric drug development program. Since FDAMA exempted these supplements from PDUFA fees, they are not self-financing, and it will be increasingly difficult for FDA to review these pediatric studies in the target time frames.

There is also a great need to address the knowledge gaps that exist in certain conditions particularly in young children and neonates. For example, treatments of many mental health conditions are difficult to study in young children because there is no agreement on how to accurately diagnose the conditions or how to assess improvement. Without additional staff to help develop valid assessment tools and study endpoints, it will be difficult to develop the scientific and regulatory framework necessary to draft Written Requests for these conditions.

VI. Conclusion

The pediatric exclusivity provision of FDAMA has been effective for obtaining pediatric studies for many drug products. An unprecedented number of pediatric studies have been or are projected to be conducted under this provision. Many of the studies have been conducted on drugs for important childhood diseases and on drugs that are used widely in children. These studies are expected to result in new pediatric labeling that will improve the medical care of children. The Agency's experience with the provision during the past 3 years has also revealed that the provision has gaps. Important categories of drugs and age groups remain unstudied because of limitations on the availability of the incentive it offers. The Secretary recommends that the pediatric exclusivity provision be renewed, with modifications to improve the efficiency of the pediatric exclusivity program and to close some of the gaps in the current legislation.

Although the pediatric exclusivity provision is expected to lead to significant advances in pediatric medicine and thereby provide great benefits, it also imposes substantial costs on consumers and taxpayers. However, its unprecedented success in generating needed pediatric studies should not be forfeited.

Appendix A

Public Comments

To obtain public input on the pediatric exclusivity program, FDA issued a *Federal Register* Notice on May 5, 2000 (Vol. 65, No.88), requesting comments on the provision. In response to the notice, 12 written comments were received from various sources including professional societies, members of the pharmaceutical industry, organizations that conduct pediatric clinical trials, and an organization devoted to pediatric oncology. The comments received looked at the 4 specific areas as outlined in section 505A(k).

1. The effectiveness of the program in improving information about important pediatric uses for approved drugs.

Many comments from manufacturers of brand name drugs and from the pediatric community agreed that the provision has been effective. Comments from other manufacturers expressed concern about the difficulties in conducting pediatric studies and about the time required to develop Written Requests and Written Agreements. Two organizations devoted to pediatric oncology did not believe that the pediatric exclusivity provision has been effective. Comments from generic drug manufacturers argued that the Pediatric Rule should be used to require pediatric studies and that the pediatric exclusivity provision should be allowed to sunset in 2002.

In addition, an unsolicited report by the Tufts Center for the Study of Drug Development published in April 2000 concluded that the intent of the law (to improve information on the effects of existing drugs on the pediatric population) is being met.[30]

2. The adequacy of the incentive provided under this section.

Comments from brand name and generic drug manufacturers, and the American Academy of Pediatrics indicated that the incentive provided by the pediatric exclusivity provision was adequate or more than adequate. An organization of researchers and health care providers in pediatric oncology stated that the incentive was not adequate for pediatric cancer agents.

3. The economic impact of the program on taxpayers and consumers, including the impact of the lack of lower cost generic drugs on patients, including on lower income patients.

Comments from the American Academy of Pediatrics stated that lack of proper pediatric information related to dosing, toxicity, adverse effects, and drug interactions can lead to medical errors and injury, which may be associated with monetary as well as emotional

[30] Impact Report, "*Drug Firms Embrace Pediatric Study Program During First 2 Years of FDAMA.*" Tufts Center for the Study of Drug Development, vol. 2, April 2000.

and physical costs. These comments stated further that economic arguments "cannot adequately provide the evidence of the effectiveness and importance of this program for children."

Generic drug manufacturers stated that the provision has a negative economic impact on patients, particularly those without insurance and the elderly. They also stated that the provision has a negative impact on the generic drug industry because last minute changes in exclusivity and patent status interfere with the industry's ability to make development and production decisions. Brand name manufacturers provided no comment on the economic impact of the pediatric exclusivity program.

4. Any suggestions for modifications that the Secretary determines to be appropriate.

Comments from the pediatric community and brand name manufacturers stated that incentives should be provided to conduct studies on drugs that are not currently covered by the provision. The American Academy of Pediatrics urged the development of different incentive levels depending on the need for information on specific drugs, to mitigate the tendency to conduct studies on those drugs with the greatest profits rather than those with the greatest need.

Comments from the American Academy Pediatrics and from generic drug manufacturers stated that exclusivity should be expressly tied to labeling changes (i.e., approval of applications or supplements).

Comments from brand name manufacturers suggested adding flexibility to the granting of exclusivity where sponsors have shown "due diligence" in their attempts to comply with Written Requests.

Comments from generic drug manufacturers urged that the pediatric exclusivity program not affect the review and approval of abbreviated new drug application (ANDA) suitability petitions. These comments also urged that exclusivity be available only when (1) a drug is for a serious and life-threatening illness, (2) the studies result in significant new pediatric labeling, and (3) the drug shows an advantage over existing therapies.

Comments from organizations devoted to pediatric oncology urged the addition of adequate incentives for pediatric cancer drugs.

5. Other Relevant Issues

Comments from PhRMA and individual drug sponsors indicate areas in the implementation program where FDA is the "rate-limiting step." The comments focus on the time required to review a Proposed Pediatric Study Request and issue a Written Request and the time required to review and respond to a sponsor's proposal to amend a Written Request. In its comments, PhRMA also stated that "for the legislation to work

optimally, the FDA needs to establish consistency among review divisions, based on the best of pediatric and pharmaceutical science." These comments urged additional resources for FDA to address these problems. Comments from the American Academy of Pediatrics and the Pediatric Pharmacology Research Units also stated that appropriate funding for additional FDA staff was needed to expeditiously implement the pediatric exclusivity provision.

Appendix B

Table 1

Proposed Pediatric Study Requests (PPSR) / Written Requests (WR) As of September 2000		
Review Division	**PPSRs Received**	**WRs Issued**
Cardiorenal	26	24
Neuropharm	25	18
Oncology	5	3
Medical Imaging	0	0
Anesthetic	14	9
Gastroenterology	11	5
Metabolic & Endocrine	25	15
Anti-Infective	3	2
Anti-Viral	20	20
Dermatology	13	7
Anti-Inflammatory	22	36
Over-the-Counter	4	3
Pulmonary	12	9
Reproductive	1	0
Special Pathogens	10	6
Total	**191**	**157**

FDA may have issued more than one Written Request for the same moiety if multiple sponsors hold NDAs for the moiety. This table does not reflect incomplete actions FDA has taken on proposals submitted by industry.

Appendix B

Table 2

Approved Active Moieties to which FDA has issued a Written Request for Pediatric Studies under Section 505A of the Federal Food, Drug, and Cosmetic Act

NOTE: This list simply identifies approved drug products (as of April 1, 1999) and active moieties (after April 1, 1999) to which FDA has issued a Written Request for pediatric studies. If a product appears on this list, it does not imply that studies have been conducted or submitted to the Agency, nor does it mean that the studies described in the Written Request will be conducted. A sponsor is NOT required to perform pediatric studies in response to a Written Request. Conducting pediatric studies in response to a Written Request is voluntary. For a list of approved products containing the active moiety by the sponsor please see http://www.fda.gov/CDER/Drug.htm and click on approved drug products.

Active Moiety	Sponsor
Abacavir	Glaxo Wellcome
Acetazolamide	Wyeth-Ayerst
Alosetron	Glaxo Wellcome
Amiodarone	Wyeth Ayerst
Amlexanox	Block Drug
Amlodipine	Pfizer, Inc.
Ammonium Lactate	Westwood Squibb
Amprenavir	Glaxo Wellcome
Atorvastatin	Warner-Lambert
Atovaquone/Proguanil	Glaxo Wellcome
Azelastine	ASTA Medica
Beclomethasone	Schering
Benazepril	Novartis
Betamethasone	Schering
Betaxolol	Lorex Pharmaceuticals
Betaxolol	Alcon
Bisoprolol	Wyeth-Ayerst
Brimonidine	Allergan
Brinzolamide	Alcon
Budesonide	Astra Zeneca

Buproprion	Glaxo Wellcome
Buspirone	Bristol-Myers Squibb
Busulfan	Orphan Medical
Calcitriol	Abbott
Candesartan	Astra Pharmaceuticals
Carteolol	CIBA
Carvedilol	SmithKline Beecham
Celecoxib	Searle
Cerivastatin	Bayer
Cetirizine	Pfizer
Ciprofloxacin	Bayer
Ciprofloxacin	Alcon
Cisatracurium	Glaxo Wellcome
Citalopram	Forest Laboratories
Cromolyn Sodium	Pharmacia & UpJohn
Cromolyn Sodium	Bausch & Lomb
Cytarabine	SkyePharma Inc.
Dichlorphenamide	Merck
Didanosine	Bristol-Myers Squibb
Dorzolamide	Merck
Efavirenz	DuPont
Enalapril Maleate	Merck
Esmolol	Baxter Pharmaceutical
Etodolac	Wyeth-Ayerst
Famotidine	Merck
Felodipine	Astra Pharmaceutical
Fenoldopam	Elan Pharmaceutical
Fentanyl	Janssen
Fexofenadine	Aventis
Fluvoxamine	Solvay Pharmaceutical
Fluoxetine	Lilly
Fluticasone	Glaxo Wellcome, Inc.

Fosinopril	Bristol-Myers Squibb
Fosphenytoin	Parke-Davis
Gabapentin	Parke-Davis
Gentamicin	Schering
Glatiramer Acetate	Teva
Ibuprofen	McNeil
Ibuprofen	Whitehall-Robbins
Indinavir	Merck
Insulin aspart [rDNA origin]	Novo Nordisk
Insulin glargine	Aventis
Irbesartan	Bristol-Myers Squibb
Isotretinoin	Hoffman-LaRoche
Itraconazole	Janssen
Ketoconazole	Janssen
Ketorolac	Allergan
Labetalol	Schering
Lamivudine	Glaxo Wellcome, Inc.
Lamotrigine	Glaxo Wellcome, Inc.
Lansoprazole	TAP Holdings, Inc.
Leflunomide	Hoechst Marion Roussel
Levobetaxolol	Alcon
Levobunolol	Allergan
Linezolid	Pharmacia & UpJohn
Lisinopril	Zeneca Pharmaceutical
Lisinopril	Merck
Loratadine	Schering
Losartan	Merck
Lovastatin	Merck
Metformin	Bristol-Myers Squibb
Methazolamide	Wyeth-Ayerst
Metipranolol	Bausch & Lomb
Metoprolol	Astra Zeneca

Midazolam	Hoffmann-La Roche
Milrinone	Sanofi Synthelabo
Mirtazepine	Organon Inc.
Moexipril	Schwarz Pharma
Mometasone	Schering
Montelukast	Merck
Nabumetone	SmithKline Beecham
Nefazodone	Bristol-Myers Squibb
Nelfinavir	Agouron
Nevirapine	Boehringer Ingelheim
Nicotine	SmithKline Beecham
Norfloxacin	Merck
Ofloxacin	Allergan
Omeprazole	Astra Zeneca
Oseltamivir	Roche
Oxcarbazepine	Novartis
Oxaprozin	Searle
Oxycodone	Purdue Pharma L.P.
Paroxetine	SmithKline Beecham
Pemirolast	Santen
Pravastatin	Bristol-Myers Squibb
Propofol	Zeneca Pharmaceutical
Quinapril	Parke-Davis
Ranitidine	GlaxoWellcome
Remifentanil	Glaxo Wellcome
Repaglinide	Novo Nordisk
Ribavirin in combination with Interferon alfa-2B, recombinant	Schering
Rifapentine	Hoechst-Marion Roussel
Ritonavir	Abbott Laboratories
Ropivacaine	Astra Zeneca
Rosiglitazone	SmithKline Beecham
Salmeterol	Glaxo Wellcome, Inc.

Saquinavir	Hoffman-La Roche Inc.
Sertraline	Pfizer Pharmaceutical
Sevoflurane	Abbott
Sibutramine	Knoll Pharmaceutical
Simvastatin	Merck
Sirolimus	Wyeth-Ayerst
Somatropin [rDNA origin]	Serono Laboratories
Sotolol	Berlex Laboratories
Stavudine	Bristol-Myers Squibb
Sumatriptan	Glaxo Wellcome
Tamoxifen	Astra Zeneca
Timolol	Merck
Timolol	Falcon Pharmaceutical
Timolol	Santen
Tobramycin	Falcon Pharmaceutical
Topotecan HCl	SmithKline Beecham
Tramadol	R.W. Johnson
Venlafaxine	Wyeth-Ayerst
Verapamil	Elan Pharmaceuticals
Zafirlukast	Zeneca Pharmaceutical
Zanamivir	Glaxo Wellcome
Zolmitriptan	Zeneca Pharmaceutical

Spectrum of Diseases/Conditions for Which FDA Has Issued Written Requests

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Table 3

Cardiovascular	**Endocrine**
Hypertension	Familial Hypercholesterolemia
Pre-op Hypertension	Type 1 Diabetes
Controlled Hypotension	Type 2 Diabetes
Congestive Heart Failure	Renal Failure 2º Hyperparathyroidism
Tachyarrhythmia	Obesity
	McCune-Albright Syndrome
Neurology	
Depression	**Infections (not viral)**
Partial Seizures	Complicated Urinary Tract Infection
Generalized Seizures	Tuberculosis
Migraine	Malaria
Obsessive Compulsive Disorder	Candidiasis
General Anxiety Disorder	Skin and Skin Structure
Multiple Sclerosis	Bacterial Meningitis
	CSF Shunt Infections
Analgesics and Anesthetics	
Mild Pain	**Antivirals**
Moderate – Severe Pain	HIV
Chronic Pain	Hepatitis B
Anesthesia	Hepatitis C
Sedation	Influenza A & B
Gastroenterology	**Ophthalmologic**
Reflux	Increased Intraocular Pressure
Irritable Bowel Syndrome	Neonatal Conjunctivitis
	Allergic Conjunctivitis
Dermatology	
Oral mucositis	**Pulmonary/Allergy**
Aphthous ulcers	Allergic Rhinitis
Cutaneous candidiasis	Asthma
Atopic Dermatitis	Chronic idiopathic urticaria
Ichthyosis vulgaris	
Tinea cruris	**Immunomodulators**
Tinea pedis	Renal Transplant
Steroid-responsive Dermatosis	Immune Suppression
Xerosis	
	Other
Oncology	Symptoms associated with common cold and influenza
Refractory or Relapsed CNS Leukemia and Lymphoma	Smoking Cessation
Refractory or Relapsed Pediatric Malignancies	Juvenile Rheumatoid Arthritis
Allogeneic bone marrow transplants	

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Table 4

Pediatric Exclusivity Granted (as of September 2000)				
	Granted	**Moiety**	**Sponsor**	**Indication**
1	7/1/98	Ibuprofen	McNeil	Fever, Aches/Pains, Cold Symptoms
2	7/1/98	Ibuprofen	Whitehall	" "
3	9/18/98	Midazolam	Roche	Sedation/Anxiolysis/Amnesia
4	12/14/98	Abacavir	Glaxo	HIV
5	1/19/99	Ranitidine	Glaxo	Gastro-esophageal reflux
6	7/12/99	Insulin glargine	Aventis	Diabetes Mellitus
7	8/11/99	Pemirolast	Santen	Allergic conjunctivitis
8	8/11/99	Propofol	Zeneca	Anesthetic
9	8/11/99	Azelastine	Astra	Itching associated with allergic conjunctivitis
10	10/1/99	Ammonium lactate	Westwood-Squibb	Ichthyosis Vulgaris/xerosis
11	11/2/99	Cromolyn sodium	Pharmacia & UpJohn	Allergic Rhinitis
12	12/6/99	Etodolac	Wyeth Ayerst	Juvenile Rheumatoid Arthritis
13	12/6/99	Oxaprozin	Searle	Juvenile Rheumatoid Arthritis
14	1/3/00	Fluvoxamine	Solvay	Obsessive Compulsive Disorder
15	1/6/00	Sotalol	Berlex Lab	Arrhythmias
16	2/2/00	Gabapentin	Parke Davis	Epilepsy
17	2/2/00	Enalapril	Merck	Hypertension
18	3/15/00	Remifentanil	Abbott	Analgesic
19	3/15/00	Metformin	Bristol-Myers	Diabetes Mellitus
20	4/19/00	Tramadol	R.W. Johnson	Analgesic
21	4/19/00	Bisoprolol/HCTZ	Wyeth-Ayerst	Hypertension
22	5/22/00	Buspirone	Bristol-Myers	Generalized Anxiety Disorder
23	8/2/00	Sevoflurane	Abbott	Anesthetic
24	8/14/00	Loratadine	Schering	Seasonal allergic rhinitis & chronic idiopathic urticaria
25	9/22/00	Lamivudine	Glaxo	HIV

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Table 5

Labeling Changes as of September 2000		
Product	**Indication**	**Label Changes**
Ibuprofen - Motrin	Fever, minor aches & pain, cold symptoms	Extended age range to include 6 months - 2 years
Ibuprofen - Advil	Fever, minor aches & pain, cold symptoms	Extended age range to include 6 months - 2 years
Midazolam - Versed	Sedation/anxiolysis/amnesia	- Specified the effective dose, effective dose range, and time of onset - Defined volume of distribution and similarity to adult protein binding and elimination - Additional information on AEs and warnings about concomitant medications - Identified a subpopulation (children with congenital heart disease and pulmonary hypertension) at higher risk for AEs
Abacavir - Ziagen	HIV infection	Labeling for 3 months - 12 years
Ranitidine - Zantac	Gastroesophageal Reflux	Extended age range to include 0 to 1 month, characterized PK in single and continuous infusions
Pemirolast-Alamast	Allergic Conjunctivitis	Safety and effectiveness established down to 3 years
Insulin glargine-Lantus	Type 1 Diabetes	Safety and effectiveness established down to 6 years
Azelastine-Optivar	Itching associated with Allergic Conjunctivitis	Safety and effectiveness established down to 3 years
Cromolyn-Nasalcrom	Prevention and relief of nasal symptoms of hay fever and other nasal allergies	Established proper dose in 2 year – 6 year olds and provided additional safety and compliance data for this age group
Etodolac-Lodine	Signs and symptoms of Juvenile Rheumatoid Arthritis	New indication in 6 years –16 years
Fluvoxamine - Luvox	Treatment of obsessions and compulsions in patients with OCD	Determined that a dose adjustment (increased dose) may be necessary in adolescents and girls 8-11 years of age may require lower doses
Ammonium lactate-Lachydrin	Xerosis, ichthyosis	Safe and effective down to 2 years

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Table 6

IMS HEALTH Data (Outpatient Data) National Disease and Therapeutic Index™ 1994 through 1999		
Drug	**Age Range**	**# of Drug Mentions**
Bisoprolol	0 - 16 years	27,000
Cromolyn Sodium	2 years - 6 years	2,375,000
Enalapril	0 - 16 years	366,000
Etodolac	6 years - 16 years	277,000
Fluvoxamine	7 years - 17 years	390,000
Gabapentin	0 - 12 years	126,000
Ibuprofen	6 months - 2 years	8,576,000
Metformin	8 years - 16 years	46,000
Midazolam	6 months - 16 years	568,000
Oxaprozin	6 years - 16 years	274,000
Propofol*	0 - 16 years	24,000
Ranitidine	0 - 1 month	1,483,000
Sotalol*	0 - 16 years	16,000
Tramadol	0 - 16 years	135,000

This table represents IMS HEALTH data on 14 of the 25 drugs granted pediatric exclusivity under the FDAMA provision. The National Disease and Therapeutic Index™ (NDTI) database is a compilation of statistical and demographic information about the patterns and treatment of disease encountered in office-based practice. These data reflect the projected number of drug uses for the product groups and age ranges identified during a patient (diagnostic) visit. These data are not the projected number of prescriptions dispensed. These data are from the time period 1994 through 1999.

*Generally used only in a hospital setting or initiated in a hospital based program.

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Table 7

10 Drugs most widely prescribed in pediatric age groups in 1994 for which the label carried no directions for use

Drug	Treatment Use	Number of uses	Study proposal submitted by sponsor	Exclusivity or patent life
Albuterol Inhalation solution	asthma	1,626,000 times to pediatric patients under 12	No (currently labeled for patients > 2)	No
Phenergan	allergic reactions	663,000 times to pediatric patients under 2	No	No
Ampicillin Injection	infection	639,000 times to pediatric patients under 12	No	No
Auralgan otic solution	ear pain	600,000 times to pediatric patients under 16	No	No
Lotrisone cream	topical infections	325,000 times to pediatric patients under 12	Yes	Yes
Prozac	depression and obsessive compulsive disorder	349,000 times to pediatric patients under 16	Yes	Yes
Intal	asthma	solution prescribed 109,000 times to pediatric patients under 2; aerosol prescribed 399,000 times to pediatric patients under 5	Yes	Yes
Zoloft	depression	248,000 times to pediatric patients under 16	Yes	Yes
Ritalin	attention deficit disorder and narcolepsy	226,000 times to pediatric patients under 6	No	No
Alupent	asthma	84,000 times to pediatric patients under 6	No	No

IMS HEALTH Inc., *National Disease and Therapeutic Index ä*

Appendix C

Economic Impacts Methodology

Congress specifically asked that FDA examine:

> "the economic impact of the program on taxpayers and consumers, including the impact of the lack of lower cost generic drugs on patients, including on lower income patients"...

Overview

In determining the economic impact of allowing an extra 6 months of marketing exclusivity in exchange for the conduct of studies designed to determine efficacy in pediatric populations, FDA looked at the difference in sales revenue for each drug (or moiety) granted pediatric exclusivity compared with sales revenue had the drug not been granted pediatric exclusivity.

Estimating these differences was accomplished for each identified drug in three primary steps:

1) estimating sales revenue during the year of patent/exclusivity expiration,

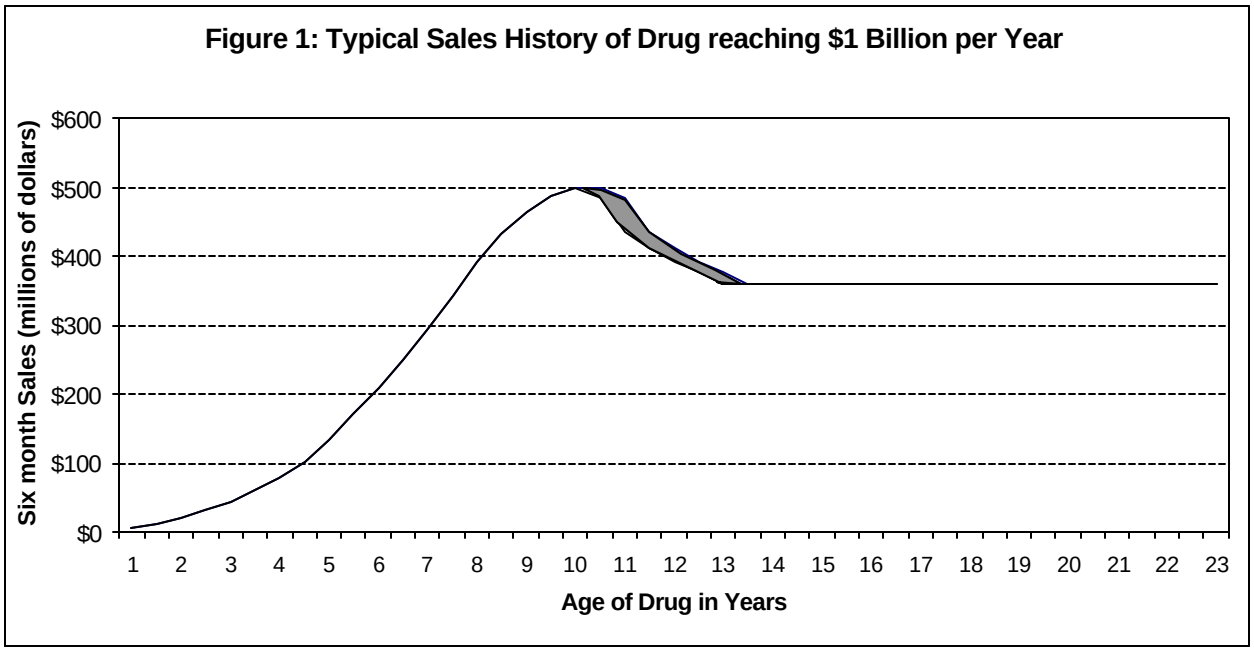
2) estimating sales revenues following patent/exclusivity expiration, and

3) comparing the sales revenues of all products containing the identified moiety with and without a 6-month period of additional exclusivity added to the innovator's patent/exclusivity expiration.

Generally, once a new drug product commences marketing, its sales revenues increase until generic competition enters the market place at some point in the future – usually determined by patent expiration or some other exclusive marketing rights granted by Hatch Waxman legislation or the Orphan Drug Act. These future dates are readily available for almost all drugs in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).

Once generic competition enters the market, total drug sales revenue (the sum of the revenue from innovator and generic sales) gradually declines due to the lower prices of generic products and the entry of a growing number of generic competitors. FDA estimates assume that stabilization occurs 3 years after generic competition first enters the market.

Figure 1 graphically demonstrates the methodology for a hypothetical drug with innovator sales reaching a peak of $500 million in a 6-month period, or $1 billion a year. During the first 10 years, innovator sales revenues increase until market exclusivity



expires. During the 3 years following the expiration of innovator marketing exclusivity, total drug sales revenues decline.

Finally total sales revenues stabilize 3 years after the first generic competition enters the market. The two illustrated sales curves are identical, except that one includes an additional 6 months of innovator sales before generic competition enters the market. The shaded area, or the difference between the curves, represents the increased costs to consumers of these drugs. Beyond the 3-year period following patent/exclusivity expiration, the estimated differences disappear. It is important to recognize that these projected sales include sales for all therapeutically equivalent products containing the moiety of the innovator drug. That is, after the expiration of the drug's patent or exclusivity, generic sales are included in the sales projections.

In the hypothetical example illustrated by Figure 1, the additional consumer costs accrue in years 11, 12 and 13, and total about $165 million. If this were a new drug in 1999, the present value of the additional costs, or the "discounted" total would equal about $78 million. Discounting adjusts the costs downward to account for the fact that a dollar received/spent in the future is worth less than a dollar received/spent today. Consequently, it considers the time between the present and the years that the increased revenues will be realized. Discounting has the largest effect on cost estimates for drugs whose exclusivity expires far in the future (e.g., a 7% discount rate approximately halves the costs where exclusivity expires in 2007, but has a much smaller effect on those exclusivities expiring in the next couple of years).

It is important to note that the only variables affecting the undiscounted costs are the eventual stabilized loss of the innovator market share and the final generic price as a proportion of the innovator price. The length of the phase-in period for either the market penetration or the price variation becomes irrelevant to the calculation, because the two

total revenue streams are identical except for the one period shift. Thus, the time needed to achieve the stabilized generic penetration or eventual price reduction affects the discounted, but not the undiscounted cost estimates.[31]

Estimating Average Sales at the Year of Patent/Exclusivity Expiration:

Pediatric exclusivity attaches to all products with listed patents or exclusivity that contain the same active moiety as the product or products studied. An innovator may receive 6 months of exclusivity for several products by virtue of conducting studies on a single active moiety. Sometimes, these products may have differing dates of exclusivity expiration. For this analysis, products were generally treated as one drug if their exclusivity expiration dates were identical and as separate drugs if an innovator's product had two or more operating exclusivities. Such multiple product cases were infrequent, however, and had only a slight effect on the "per drug" cost estimates and no effect on the overall program costs.

Using IMS HEALTH data,[32] FDA developed complete sales histories for each of the 119 drug products (including 102 moieties) for which a sponsor had indicated, by March 1, 2000, the intent to submit pediatric studies. These sales histories ran from the year each drug is first marketed through the 1999 calendar year and ranged from 1 year to more than 18 years.

Next, based on these sales history data, FDA constructed an average sales profile using:

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[31] Let:
Annual sales of innovator drug at exclusivity expiration = P
Discount on generic drug in period i = d_i $\{d_1, d_2, \ldots d_n\}$
Fraction of market captured by generics in period i = fi $\{f_1, f_2, \ldots f_n\}$

Then,
Innovator sales w/o additional exclusivity = $P + (1-f_1)*P + (1-f_2)*P + \ldots + (1-f_n)*P$ {1}
Innovator sales with additional exclusivity = $P + P + (1-f_1)*P + (1-f_2)*P + \ldots + (1-f_{n-1})*P$ {2}
Generic sales w/o additional exclusivity = $P*f_1*d_1 + P*f_2*d_2 + \ldots + P*f_n*d_n$ {3}
Generic sales with additional exclusivity = $0+ P*f_1*d_1 + P*f_2*d_2 + \ldots + P*f_{n-1}*d_{n-1}$ {4}

So,
The difference in innovator sales = {2}–{1} = $P – (1-f_n)*P = P*f_n$ {5}
The difference in generic sales = {4}-{3} = $-P*f_n*d_n$ {6}

Finally, the costs to consumers = {5} + {6} = $P*f_n – P*f_n*d_n = P*f_n*(1-d_n)$

[32] IMS HEALTH Inc., *Retail Perspective and Provider Prospective Combined Purchases*

1) the average sales in the first full calendar year ($124 million) for all 102 products with at least 1 full calendar year of sales data, and

2) the percentage change in sales from one year to the next for all years after the first full year of marketing.

FDA derived the average weighted percentage change for each market year's sales by summing the percentage changes for each drug and weighting these changes by each drug's previous year sales. This weighting assures that the largest selling drugs (those that contribute the most to the costs of the pediatric labeling program) have a proportionately large effect on the percentage change estimates. As shown in Figure 2, which displays the estimated weighted percentage sales changes for years 3 through 17, the "average" annual percentage changes rise steadily through year 11 and then gradually level off though year 14. The change was erratic after year 14, but is based on only three or fewer drugs. For this analysis, FDA assumes that sales after year 14 remain constant at the year 14 level.

Figure 2: Average annual Percentage Increase in Sales (Weighted by Sales in Previous Year)

Market Yr	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Change	58%	35%	34%	20%	15%	13%	11%	12%	8%	0%	3%	0%	0%	0%	0%
Drugs used	88	77	62	50	42	37	28	19	18	15	13	7	NA	NA	NA

FDA used the average percentage changes to construct an "average sales curve," based on the first full calendar year sales of the 102 drugs, inflated to 1999 dollars. The "average sales curve" data, as shown in Figure 3, were then used to project sales for two sets of drugs – those which had at least one full calendar year of data (the 102 drugs), and the remaining 17 drugs (5 having a partial year of data in 1999, and 12 that were not yet marketed). For each drug in the first set (the 102 drugs), FDA projected sales at the year of patent/exclusivity expiration using their 1999 sales, their market age in 1999, their expected patent/exclusivity expiration, and the percentage changes displayed in Figure 3.

Figure 3: Projected Sales for Average Drug

Market Yr	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Change	N/A	58%	35%	34%	20%	15%	13%	11%	12%	8%	0%	3%	0%	0%	0%	0%
Annual Sales **($ millions)**	$124	$197	$265	$356	$428	$490	$554	$616	$689	$743	$740	$764	$762	$762	$762	$762
Drugs used	102	88	77	62	50	42	37	28	19	18	15	13	7	NA	NA	NA

FDA also used the "average sales curve" to project sales during the year of patent/exclusivity expiration for all drugs in the second data set; i.e., those data that had not completed a full year of marketing by the end of 1999 (the 17 drugs). In other words, FDA assumed average future sales for these 17 drugs based on the sales of the

drugs for which we had sales data for more than 1 year. For five of these drugs, we had an initial marketing date and a patent or exclusivity expiration date. In these cases, FDA used these dates and the "average sales curve" to project future sales. In four additional cases, the drugs had been approved, although not yet marketed, and we knew the drugs' patent expiration dates. In these cases, FDA assumed marketing would begin in the year 2000 and again used the "average sales curve" to project future sales. In the final eight cases, the drugs had either just been approved, approvable, or not yet approved, and FDA did not know the year of patent or exclusivity expiration. Here, FDA assumed the first year of marketing would be 2000 or 2001, depending on its current status, and assumed an average market life until patent expiration (equal to 13 years based on the other drugs in our data set). Using our "average sales curve," FDA estimated that each of these eight drugs would reach peak sales of $764 million by 13 years after initial marketing.

This methodology provides an estimate of each drug's expected sales revenues during the year of exclusivity expiration. On average, this estimating approach predicts that the average annual sales revenue at patent/exclusivity expiration (inflation adjusted to 1999 dollars) for all 119 drugs will peak at about $710 million per drug about 13 years following market entry. The estimate appears quite reasonable when compared to the average 1999 sales of $394 million for those 102 drugs on which the model is based. In 1999, on average, these 102 drugs had been on the market for approximately 6 years.

Estimating Average Sales after Patent/Exclusivity Expiration:

To estimate industry sales revenues following patent/exclusivity expiration, FDA relied on its own review of industry sales following the patent expiration of eight large selling drugs and on data presented in a recent study prepared by the Congressional Budget Office (CBO).[33] The eight particular drugs FDA reviewed (alprazolam, ranitidine, clonazepam, piroxicam, naproxen, acyclovir, cimetidine, and captopril) were chosen because each was regarded as a "blockbuster" drug and each encountered its first generic competition relatively recently (between 1992 and 1997). This analysis of industry sales data[34] found that within 3 years, generic penetration had reduced innovator revenues, on average, by 84 percent (with individual rates ranging from 68.6% to 89.7%) of sales prior to patent expiration. Assuming that brand name prices change little upon the introduction of generic competition, these percentages also hold for unit sales. Alternatively, the CBO study relied on somewhat older data to project a 60 percent loss of unit market share after 3 years of generic competition. Because both estimates are uncertain predictors of the future, FDA has assumed that the innovator market share (both units and revenues) will decline by 70 percent within 3 years of generic competition.

FDA's analysis of the eight "blockbuster" drugs also confirms previous findings that the quantity of prescriptions sold for a particular drug remains relatively constant following

[33] The Congress of the United States, Congressional Budget Office, *How Increased Competition from Generic Drugs has Affected Prices and returns in the Pharmaceutical Industry*, July 1998.
[34] IMS HEALTH Inc., *National Prescription Audit*

generic competition. On average, prescription volume for these eight drugs was 99.5 percent of the previous innovator volume after 1 year of competition, 98.2 percent after 2 years, and 104.4 percent after 3 years. However, there was considerable variation among the eight drugs at the end of the third year following patent expiration. The highest volume reached 146 percent and the lowest 65 percent.

Effects on Various Sectors

There are four main groups that share the economic consequences of the pediatric labeling exclusivity – innovator companies that gain additional sales revenues, consumers who face higher drug prices, and generic drug firms and retail marketers that lose sales revenues. The revenue gain to the innovator companies will equal the sum of the losses of the latter three groups.

Innovator Sector:

The innovator drug industry will gain sales revenues estimated at approximately $29.6 billion over affected 20-year period (119 drugs x average peak year sales of $710 million/drug x 70% avoided lost market share x 0.5 years). The agency's actual calculations assume that innovator market share falls to 80 percent during the first 6 months of generic competition, 60 percent during the second 6 months, 52.5 percent during the third 6 months, 45 percent during the fourth 6 months, 37.5 percent during the fifth 6 months, and 30 percent thereafter. On an annual basis, these new revenues amount to almost $1.5 billion per year undiscounted. As explained earlier, the pace of this market penetration does not influence the undiscounted costs, although it does affect the discounted totals, which are $15.3 billion

Costs to Consumers:

The undiscounted cost of the pediatric exclusivity program to consumers is determined by both the unit market share ultimately gained by the generic industry (assumed to be 70%) and the relative price of the generic drug compared to the brand name drug. Based on retail pharmacy data, the CBO study found that the average generic retail price is about 53 percent of the innovator price at the end of 3 years. FDA has no better estimate.

Using these values, FDA projected complete sales histories (using 1999 sales and marketing age of each product in 1999) for each drug to a point several years beyond exclusivity expiration. Finally, we projected the same sales histories plus an additional 6 months (added for pediatric exclusivity) and compared the two histories for each product. The difference in these two projections measures the transfer of income from drug consumers to the pharmaceutical industry, owing to the pediatric exclusivity extension.

As noted above, the agency's actual calculations assume that the innovator market share falls to 80 percent during the first 6 months of generic competition, 60 percent

during the second 6 months, 52.5 percent during the third 6 months, 45 percent during the fourth 6 months, 37.5 percent during the fifth 6 months and 30 percent thereafter. We assumed generic prices would be about 84 percent of innovator prices during the first 6 months following exclusivity expiration, 69 percent during the second 6 months, 61 percent during the third, 57 percent during the fourth, 55 percent during the fifth and 53 percent thereafter. We also assumed that consumer demand for each drug remains constant following patent expiration (consistent with the eight-drug analysis described above) and that the price of the innovator drugs remains unchanged after adjusting for inflation.

As a result, following generic entry, innovator firms are assumed to lose 70 percent of the drug's total revenue and other industry sectors (generally generic firms and retail pharmacies) are assumed to gain 53 percent of the 70 percent, or about 37 percent. Consequently, over the 3-year period, consumer expenditures for a typical drug fall by about 33 percent (70% - 37%). Total projected peak year sales revenues amount to $84.5 billion (119 drugs x $710 million). Thus, pediatric exclusivities are predicted to increase consumer expenditures by about $13.9 billion ($84.5 billion x ½ year x 33%) over the affected 20-year period. The annual cost to consumers, therefore, is $695 million undiscounted. On a discounted basis, these expenditures rise by $7.2 billion.

Costs to Generic Drug Manufacturers:

Manufacturers of generic drugs will experience lost revenues. Projecting these losses requires an estimate of the ratio of brand name prices to generic drug prices at the manufacturing level. Although retail prices for generic drugs were assumed to stabilize at 53 percent of the brand name price, the ratio of generic to brand name prices will be still smaller at the manufacturing level.

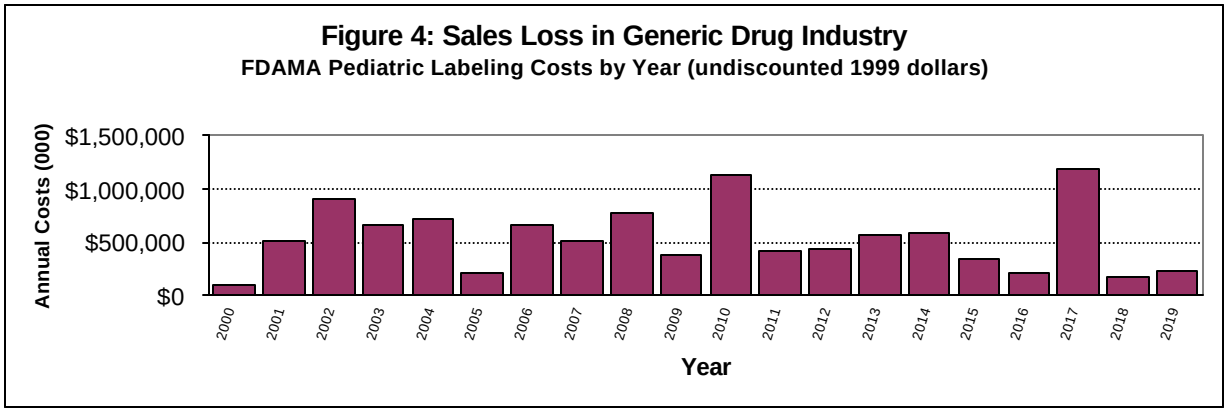
Unfortunately, few sources were available to provide accurate estimates of the needed generic to brand name price relationship. The agency therefore relied on a study conducted by Grabowski and Vernon[35] and the CBO report referenced above to derive an estimated generic-to-brand name price ratio of 36.3 percent at the manufacturer level. Grabowski and Vernon found that at 1 year after market entry, the generic to brand name price ratio at the wholesale level (actually the "exit manufacturer" level) was about 68.5 percent of the generic to brand name price ratio at the retail level. The CBO report found that generic prices were 53 percent of brand name prices 3 years after the onset of generic competition. Thus, if we assume no change in the generic to innovator mark-up ratio between year 1 and year 3 of generic competition, the generic price as a percentage of the innovator price at the manufacturer level would be 36.3 percent at year 3 of generic competition (68.5% x 53%).

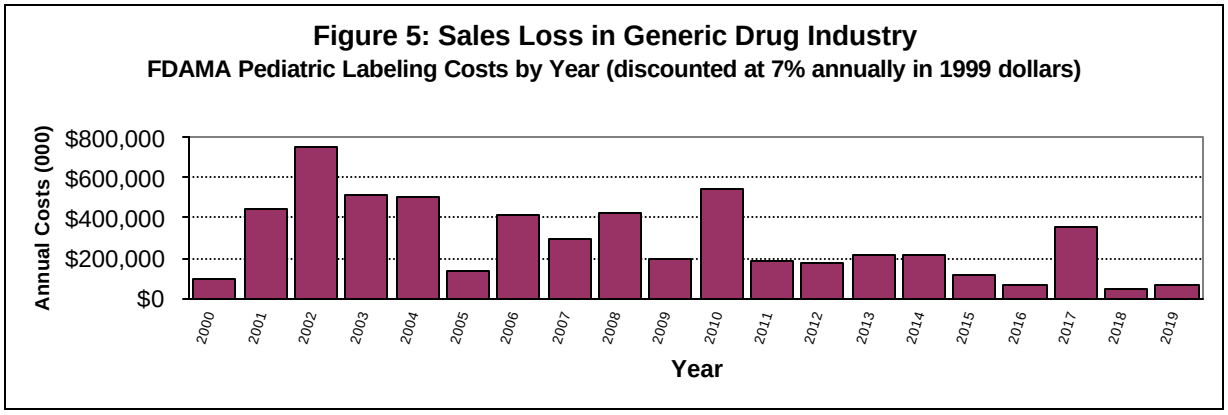
The 36.3 percent generic-to-brand name price ratio estimate may be imprecise for several reasons. First, the data sources are from different time periods. Second, it

[35] Longer Patents for Increased Generic Competition in the US; PharmacoEconomics 1996; Suppl 10, 2: 110-23

assumes a constant relationship between retail and manufacturer mark-ups between year 1 and year 3 of generic competition, although generic prices will decline over the period. Nevertheless, there is no obvious reason to expect the ratio of mark-ups to change over that time.

These assumptions indicate that the generic drug industry will forego significant increases in product sales, losing an estimated $10.7 billion (undiscounted) over the next two decades ($710 million average peak year sales x 119 drugs x 70% market share x 0.363 price ratio x 0.5 for ½ year). Figure 4 presents the projected timing of the estimated average annual sales shortfall. The average annual loss is about $537 million per year (undiscounted). Figure 5 indicates that if these figures are discounted at a 7 percent rate, the estimated total sales shortfall over the next 20 years is about $5.7 billion.



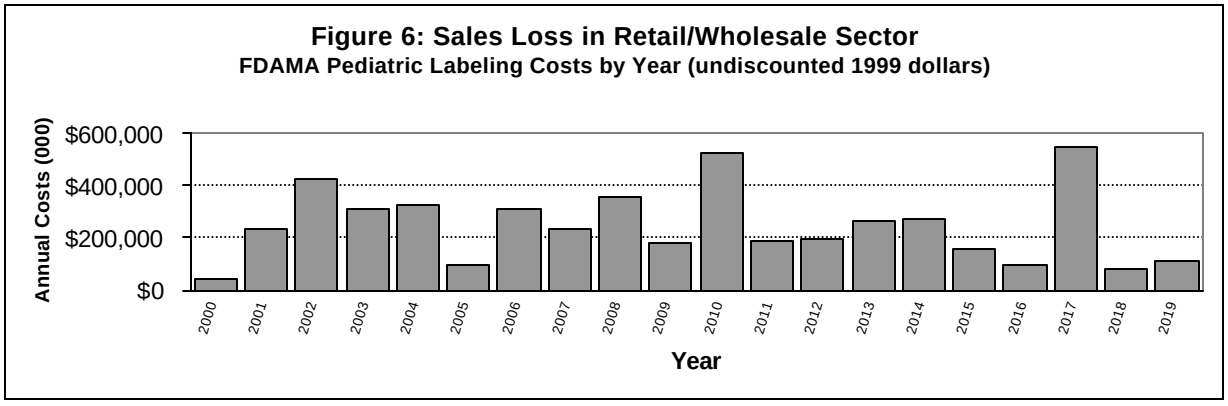


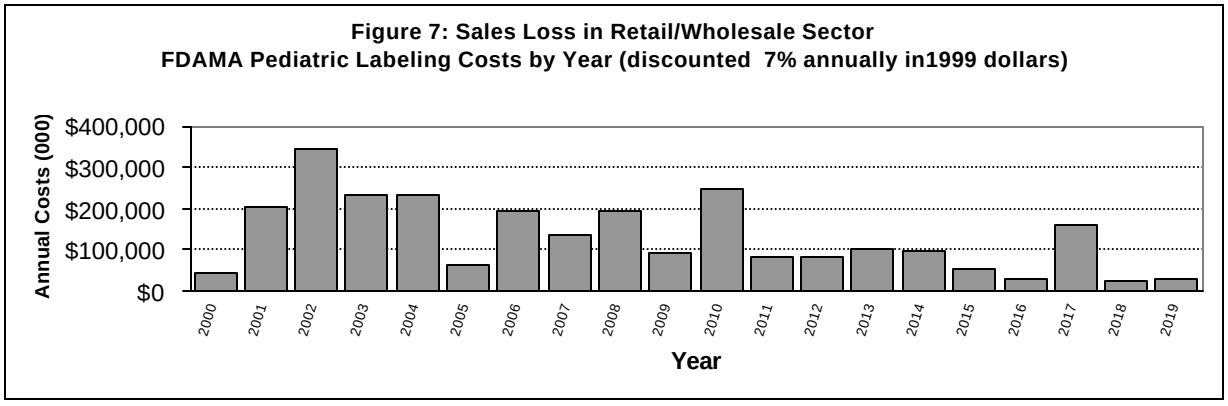
Costs to Retailers:

Similarly, pharmaceutical distributors, particularly at the retail pharmacy level, are estimated to forego future sales revenues, because generic drugs are assumed to have a higher price markup than brand name drugs. We estimated above that innovator revenues will increase by $29.6 billion over the 20-year period. Increased consumer

costs of $13.9 billion and generic industry sales shortfalls of $10.7 billion will contribute to these gains. The remaining revenue losses of $4.9 billion (i.e., $29.6 billion – ($13.9 billion + $10.7 billion)[36] will be experienced by the drug distribution sector.

An alternative means of reaching this same result is to note that the generic drug industry accounts for about 68.5 percent (36.3% ÷ 53.0%) of the price differentials at the retail level and the drug distribution system accounts for the remainder, or 16.7 percent (i.e., 53.0% - 36.3%). This calculation also implies that drug distributors will lose an estimated $4.9 billion (undiscounted) over the next two decades ($710 million average peak year sales x 119 drugs x 70% market share x 0.167 price ratio x 0.5 for ½ year). Figure 6 presents the projected timing of the estimated average annual sales shortfall. On average, this loss amounts to about $245 million annually. Figure 7 indicates that if these figures are discounted at a 7 percent rate, the estimated total sales shortfall over the next 20 years is about $2.6 billion.





Estimation Uncertainties

These projections may provide only a rough approximation of future events, because they are based on a variety of plausible but uncertain assumptions. For example, FDA

[36] Discrepancy due to rounding

relied on patent or exclusivity termination dates presented in the agency's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), but these dates are frequently subject to litigation by both innovator and generic firms, which can affect the timing of generic entry. Also, drugs are sometimes discontinued for safety reasons. The above estimates do not account for such events. Further, the agency's drug revenue projections are based on historical growth patterns, but recent changes within the pharmaceutical industry could alter these trends. Similarly, the number of affected drugs is uncertain. This analysis assumes that 119 will gain added exclusivity, but this number may be low if additional study requests are issued. Alternatively, the number may be high, because not all sponsors will complete acceptable studies. (FDA estimates that approximately 85% of the expected sponsors will respond and 90 to 95% of those responding will be granted exclusivity.) Moreover, different projection methodologies could provide different results. For example, if either the innovator share or generic prices fall by an amount greater than assumed, the impact of the pediatric exclusivity program on consumers and taxpayers will be larger than estimated. Conversely, if either the innovator share or generic prices fall by an amount smaller than assumed, the impact will be less. Finally, the use of varying discount rates would modify the present value cost projections. We now present sensitivity analyses that illustrate the impact of a number of alternative assumptions.

Sensitivity Analyses

Total Program Costs (costs to consumers)

To assess the range of plausible cost values, we determined the sensitivity of our cost estimates to several of the respective variables. We primarily looked at alternative weighting methods, and changes in the final generic penetration rate, the relative price of generic and innovator products, and the discount rate. The first row of Table 1 shows that our "best" estimate of the discounted costs over the affected 20-year period is $7.2 billion. The results of the alternative assumptions are provided in the following rows.

Our methodology considered three different methods of weighting the annual percentage increases used to project future sales. We selected "prior" year sales weighting as our "best" estimate (the percentage increases shown in Figure 2 above). If the annual percentage changes are *not* weighted (annual percentage sales increases are considered equally for all 102 drugs in our data set), the total discounted program costs would be about $8.0 billion. If the annual percentage changes were weighted by following year sales (sales during the year following the calculated percentage change), the total discounted program costs would be about $8.1 billion.

Table 1: Sensitivity Analyses - Discounted Costs to Consumers ("Best" Estimate in Bold)

Generic Market Share	Wt	Discount Rate	Generic Price	Total Costs (billions)
70%	P	7%	0.53	**$7.2**
70%	N	7%	0.53	$8.0
70%	F	7%	0.53	$8.1
60%	P	7%	0.53	$6.2
80%	P	7%	0.53	$8.2
70%	P	7%	0.40	$9.2
70%	P	7%	0.60	$6.1
70%	P	3%	0.53	$10.3
70%	P	10%	0.53	$5.7

Our "best" estimate of the eventual stabilized generic market share assumed that generic products would ultimately account for 70 percent of the quantity (prescriptions) of the moiety sold. We also assessed the costs using market penetration rates of 60 percent and 80 percent, while holding the values of other variables constant. If generic penetration stabilizes at 60 percent, the estimated discounted costs are about $6.2 billion, or about $1 billion less than our "best" estimate. If generics eventually capture 80 percent of the market, the total estimated discounted costs are about $8.2 billion, or about $1 billion more than our "best" estimate.

The data reviewed by the CBO found that generic prices stabilized at about 53 percent of innovator prices. We used this value, but also looked at the effects of assuming 40 percent and 60 percent. If the average generic price stabilizes at 40 percent of the innovator price, the total estimated costs are $9.2 billion, or an increase of $2 billion above our "best" estimate. If the average generic price stabilizes at 60 percent of the innovator price, the total estimated costs are $6.1 billion, or a decrease of $1.1 billion compared to our "best" estimate.

Discounting the value of future costs has the greatest effect on dollars spent well into the future. We used a discount rate of 7 percent for our primary analysis. We also assessed total costs using rates of 3 percent and 10 percent. Total costs were estimated to be about $10.3 billion, using a rate of 3 percent, or an increase of about $3.1 billion over our "best" estimate. If a rate of 10 percent were used, total costs fall to about $5.7 billion or about $1.5 billion less than our "best" estimate.

Comparing the sensitivity analyses described above, we found that these one-at-a-time changes resulted in a high discounted cost estimate of $10.3 billion and a low discounted cost estimate of $5.7 billion.

Lost New Sales for Generic Drug Industry

We also looked at the effect of our assumptions on our estimate of lost future sales for the generic drug industry. Table 2 presents these estimated effects. We compared our base 70 percent estimate against the alternative rates of 60 percent and 80 percent for generic drug market penetration; our base 0.53 figure against values of 0.40 and 0.60 for the relative price of generics to brand name products; and our base 7 percent to values of 3 percent and 10 percent for annual discount rates. Total discounted sales loss over the affected 20-year period using our "best" assumptions was $5.7 billion. Changing these assumptions caused the estimated sales loss to the generic industry to vary between $4.4 billion and $8.0 billion.

Table 2: Sensitivity Analyses – Discounted Lost Sales to Generic Drug Industry ("Best" Estimate in Bold)

Generic Market Share	Discount Rate	Generic Price	Sales Loss (billions)
70%	7%	0.53	**$5.7**
60%	7%	0.53	$5.0
80%	7%	0.53	$6.5
70%	7%	0.40	$4.4
70%	7%	0.60	$6.5
70%	3%	0.53	$8.0
70%	10%	0.53	$4.6

Lost New Revenues for Retail Pharmacies

Projections pertaining to the drug distribution sector are also affected by our assumptions. Table 3 presents the effect of these assumptions on the future sales revenues of these firms. We compared our base estimate of 70 percent against the alternative rates of 60 percent and 80 percent for generic drug market penetration; our base estimate of 0.53 percent against values of 0.40 and 0.60 for the relative price of generics to innovator products; and the 7 percent discount rate against values of 3 percent and 10 percent for annual discount rates. Total discounted sales loss over the affected 20-year period using our "best" assumptions was $2.6 billion. Changing these assumptions caused the estimated sales loss to the drug distribution sector to vary between $3.7 billion and $2.1 billion, or a range of $1.6 billion.

Table 3: Sensitivity Analyses – Discounted Costs to Retail/Wholesale Sector ("Best Estimate in Bold)

Generic Market Share	Discount Rate	Generic Price	Sales Loss (billions)
70%	7%	0.53	**$2.6**
60%	7%	0.53	$2.3
80%	7%	0.53	$3.0
70%	7%	0.40	$2.0
70%	7%	0.60	$3.0
70%	3%	0.53	$3.7
70%	10%	0.53	$2.1