

Calendar No. 184

107TH CONGRESS }
1st Session }

SENATE

{ REPORT
{ 107-79

BEST PHARMACEUTICALS FOR CHILDREN ACT

OCTOBER 4, 2001.—Ordered to be printed

Mr. KENNEDY, from the Committee on Health, Education, Labor,
and Pensions, submitted the following

REPORT

[To accompany S. 838]

The Committee on Health, Education, Labor, and Pensions, to which was referred the bill (S. 838) to amend the Federal Food, Drug, and Cosmetic Act to improve the safety and efficacy of pharmaceuticals for children, having considered the same, reports favorably thereon with an amendment and recommends that the bill (as amended) do pass.

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I. PURPOSE AND SUMMARY OF THE BILL

To address a longstanding concern that only 20 percent of prescription medications on the market have been tested and approved for use in children, Congress enacted a market incentive law, commonly referred to as the “pediatric exclusivity” or “pediatric testing” incentive, as part of the Food and Drug Administration Modernization Act of 1997 (FDAMA Pub. L. 105–115). By providing 6 months of additional market exclusivity on a drug for a holder of an approved application under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FFDCA) that has completed pediatric studies of the drug when requested by the Food and Drug Ad-

ministration (FDA), Congress sought to find an approach that would be more successful than previous efforts to have the pharmaceutical industry study the safety and effectiveness in children of drugs that, without such studies, would be prescribed “off-label” to children.

The Best Pharmaceuticals for Children Act, S. 838, is designed to continue the successes of and improve upon the current pediatric exclusivity law in generating studies of medicines for children. Drug companies have studied several drugs in children and those drugs now carry appropriate pediatric labeling because of the FDAMA pediatric exclusivity provision. It remains the case, however, that drug manufacturers have tested only 25 percent of medicines in children, and so FDA has approved only that small percentage of today’s drugs for use in children. The FDA, the General Accounting office (GAO), and others have issued reports describing how highly effective the pediatric exclusivity law has been in generating pediatric studies and useful new labeling information. They have also, however, expressed concerns about areas that need to be improved. This legislation seeks to stimulate additional pediatric testing and to provide for the testing of off-patent medicines for children, for timely labeling changes, and for testing in neonates so that they also benefit from additional studies and labeling information.

1. THE LEGISLATION AUTHORIZES THE TESTING OF DRUGS LACKING PATENT OR OTHER EXCLUSIVITY PROTECTIONS

The current pediatric testing incentive was not designed to stimulate pediatric studies for medicines that lack patent terms or other market exclusivities because there is no patent or other exclusivity on the drug to which to attach a 6-month period of additional market exclusivity. An FDA analysis of 1994 data found that 6 of 10 drugs most commonly prescribed for children were off-patent. This legislation creates an off-patent research fund to provide for studies of such drugs by pediatric pharmacology research units (PPRUs) or other entities, after the manufacturers of the drug have declined a right of first refusal to conduct the studies of the drug.

2. THE LEGISLATION PROVIDES FOR TIMELY LABELING CHANGES FOR DRUGS THAT ARE GRANTED EXCLUSIVITY AND THAT ARE STUDIED THROUGH THE OFF-PATENT RESEARCH FUND

The Prescription Drug User Fee Act (PDUFA), as amended by FDAMA, exempts supplements for a new indication for use in pediatric populations from the user fee that must ordinarily accompany filings with FDA. This provision has meant that manufacturers have not paid user fees when they submit their reports of studies in response to a request from FDA for pediatric studies, as such reports are submitted in the form of supplements to their new drug applications. This legislation removes this exemption by requiring companies to pay PDUFA fees at the time they submit pediatric supplements with reports of their completed studies to the FDA. It thereby helps ensure that FDA will have sufficient resources to review pediatric labeling supplements as “priority supplements.”

The legislation also provides a procedure for timely labeling of branded drugs granted pediatric exclusivity and for drugs tested under the off-patent research fund. If a manufacturer refuses to

make labeling changes requested by FDA, the agency must refer the issue to its Pediatric Advisory subcommittee of the Anti-Infective Drugs Advisory Committee, which then makes a recommendation to the agency about a labeling change. After considering this recommendation, FDA may request an appropriate labeling change and, if the company refuses to make the requested change, the FDA may deem the company's drug to be misbranded.

3. THE LEGISLATION CLARIFIES THAT WRITTEN REQUESTS FOR PEDIATRIC STUDIES MAY INCLUDE NEONATES WHEN APPROPRIATE

The legislation clarifies that written requests for pediatric testing may include neonates (newborns to 1 month old) in all appropriate cases.

4. THE LEGISLATION PROVIDES FOR THE PUBLIC DISSEMINATION OF PEDIATRIC TEST INFORMATION BEFORE LABELING CHANGES ARE MADE

The legislation requires the FDA to make public a summary of the medical and clinical pharmacology reviews of the pediatric studies, except that confidential commercial information or trade secrets contained in the pediatric supplement would not be disclosed.

5. THE LEGISLATION PROVIDES FOR THE INSTITUTE OF MEDICINE TO REVIEW FEDERAL REGULATIONS, REPORTS AND RESEARCH INVOLVING CHILDREN

The legislation recognizes the need to review current legal and ethical safeguards for children involved in clinical research and provides for a study of this matter by the Institute of Medicine (IOM). The IOM, with the involvement of pediatric experts, must complete its review and report to Congress with recommendations in 2 years.

II. BACKGROUND AND NEED FOR THE LEGISLATION

Although children suffer from many of the same diseases as adults and are often treated with the same medicines, the pharmaceutical industry has studied and labeled for use in children only about 25 percent of today's medicines. Dosing children based merely on their lower weight is often imprecise, since their bodies can metabolize medicines differently than adults. Some drugs may have different adverse side effects or toxicities in children than in adults, so estimating dosages for children from dosages found to be safe and effective in adults may not be appropriate. The lack of pediatric studies and labeling information may lead to unintended medical errors and place children at risk of being under-dosed or over-dosed with medication. The lack of age-appropriate formulations (e.g., liquid form) can also make it difficult to give children and infants prescribed amounts of a needed medication.

Before 1997, regulatory efforts to address the lack of pediatric studies and insufficient labeling information had been largely unsuccessful. In 1979, the FDA first issued a rule requiring specific pediatric indications, if any, to be described under the "Indications and Usage" section of the label, with pediatric dose information included in the "Dosage and Administration" section. The rule also required that recommendations for pediatric use must be based on

data from adequate and well-controlled studies in the pediatric population. The 1979 rule did not successfully encourage the pharmaceutical industry to conduct pediatric studies and appropriately label their products for children. Accordingly, in 1994, the FDA published a final rule requiring drug manufacturers to survey existing data and to determine whether it would support pediatric labeling, and if it did, to file a supplemental new drug application. FDA's December 1994 Pediatric Plan sought to encourage the pharmaceutical industry to develop voluntarily pediatric data both during the drug development process and after marketing. Neither of these 1994 initiatives increased substantially the number of drugs with adequate pediatric labeling.

Senators Dodd and Kassebaum first introduced the Better Pharmaceuticals for Children Act in the 102nd Congress, and it was re-introduced in each subsequent Congress until it was enacted in 1997 as part of FDAMA. In the 1997 report on the legislation, the committee stated, "there is little incentive for drug sponsors to perform studies for medications which they intend to market primarily for adults and whose use in children is expected to generate little additional revenue. Pediatric studies pose ethical and moral issues relating to using new unapproved drugs in young patients. Second, there are substantial product liability and medical malpractice issues. Third, pediatric patients are more difficult to attract into studies. Fourth, for some drugs, pediatric use represents more difficult issues of drug administration and patient compliance than adult use."

Accordingly, the pediatric exclusivity provision enacted by congress in 1997 provides a market incentive of 6 months of additional exclusive sales to drug companies for studies of medicines in children. Also in 1997, FDA proposed its Pediatric rule, which it finalized in 1998, and which became effective only 1999. That rule requires the manufacturers of certain new and marketed drugs and biological products to provide adequate labeling for the use of the products in children. The rule is both broader and narrower than the pediatric exclusivity provision enacted by congress in 1997. When their scopes overlap, Congress provided that pediatric studies required under the rule could also satisfy the requirements for market exclusivity.

The incentive provided by 6 months of market exclusivity has successfully encouraged drug companies to respond affirmatively to most of FDA's requests for pediatric studies. Yet the incentive varies widely from drug to drug. For example, nearly three quarters, or 27, of the first 37 drugs granted exclusivity would have sales in 6 months of less than \$150 million, based on 2000 sales data. The remaining 10 of those 37 drugs, by contrast, had sales in 6 months over \$200 million, and 1 of those had sales in 6 months exceeding \$2 billion, a second had sales exceeding \$1.2 billion, and 2 had sales exceeding \$800 million.

Because of pediatric exclusivity, FDA had granted 37 drugs pediatric exclusivity as of September 7, 2001. The results of the pediatric studies have provided new and useful information for use of these medicines in children, 19 of which have been relabeled to include pediatric information. As of August 6, 2001, FDA had issued 196 written requests for more than 422 studies of drugs for anti-

inflammatory, cardiovascular, anti-viral, oncology, neurology, and endocrine, among other, diseases and conditions.

In its January 2001 Status Report to Congress on the pediatric exclusivity provision, the FDA wrote:

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 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., gastro intestinal reflux disease, diabetes mellitus, pain, asthma, hypertension) have or soon will have pediatric use information in their labeling.

The GAO Director for Health Care, Janet Heinrich, testified at the committee's May 8, 2001, hearing that, "[s]ince enactment of the pediatric exclusivity provision, both the numbers of drugs studied in children and the therapeutic classes they represent have substantially increased. Hundreds of studies are being done on drugs that are important to pediatric patients." The pediatric exclusivity law has provided for pediatric research on different medicines in the same therapeutic class because it is important that children have a choice of medicines, as do adults, because some children may only tolerate 1 drug in a therapeutic class.

At a time when the infrastructure is now in place to accommodate the increasing pediatric studies, many pediatric experts are concerned about the January 1, 2002, sunset date in the current law. During the May 8, 2001, committee hearing, the GAO stated that, "Experts agree that, since FDAMA, there also has been significant growth in the infrastructure necessary to conduct pediatric studies. For example, NICHD [National Institute of Child Health and Development] has expanded the number of PPRUs from 7 to 13. * * * Prior to FDAMA, the PPRU Network had conducted 17 studies for drug sponsors. By 2000, the PPRUs were conducting 73 pediatric drug studies for drug sponsors. The pharmaceutical industry also has increased its capacity to conduct pediatric studies since enactment of FDAMA." This strong infrastructure for conducting pediatric studies will help to ensure the continuing success of this law, which has seen the study of a wide range of drugs in many therapeutic areas.

III. LEGISLATIVE HISTORY AND COMMITTEE ACTION

On May 7, 2001, Senators Dodd and DeWine introduced S. 838, the "Best Pharmaceuticals for Children Act." On May 8, 2001, the committee held a hearing entitled "Better Pharmaceuticals for Children: Assessment and Opportunities." In the hearing, the committee examined how the 1997 pediatric exclusivity law has worked and how it could be improved, so as to determine whether and how the provision should be reauthorized.

On August 1, 2001, the committee held an executive session to consider S. 838. Senators Dodd and DeWine offered an amendment in the nature of a substitute that the committee considered as original text for purposes of further amendment. Senators Dodd,

Kennedy, and DeWine offered an amendment that the committee accepted without objection. Also without objection, the committee directed that technical and conforming changes be made. The committee approved S. 838, as amended, by voice vote.

A. Amendment Adopted Without Objection During Executive Session

The committee adopted 1 amendment without objection.

1. Senator Dodd offered an amendment for himself, Senators Kennedy and DeWine that clarifies the interaction of pediatric market exclusivity under this provision and the market exclusivity awarded to an applicant for approval of a drug under section 505(j) of the FDCA. Under the 1997 pediatric exclusivity law, Congress created a 6-month market incentive for a holder of an approved application under section 505(b)(1) of the FDCA to conduct pediatric studies of a drug FDA's request, thereby rewarding companies that invest resources to test medicines for children. Under the 1984 Waxman-Hatch Act, Congress created a 6-month period of market exclusivity ("ANDA exclusivity") for the first applicant for approval of a drug under section 505(j) of the FDCA to challenge a patent on that drug, during which FDA may not approve subsequent abbreviated applications for the drug; this incentive rewards the first filer of an abbreviated application that pursues the risk and expense of challenging a patent.

When Congress passed the pediatric exclusivity provision in 1997, it had not meant to change the incentives for challenging patents under the Waxman-Hatch Act by reducing periods of ANDA exclusivity. The committee has since learned, however, that in some instances, pediatric exclusivity on a drug may run over all or a portion of the 180 days of ANDA exclusivity for the first applicant to challenge a patent on that drug.

The amendment clarifies how a period of ANDA exclusivity on a drug is to be extended when a pediatric exclusivity period on the drug overlaps with it. When there is overlap and the period of ANDA exclusivity expires after the period of pediatric exclusivity, the period of ANDA exclusivity is extended by the length of the overlap. When there is overlap and the period of ANDA exclusivity expires during the period of pediatric exclusivity, the period of ANDA exclusivity is extended by six months. The amendment gives the filer of an abbreviated drug application who challenges a patent no more and no less time to market his drug exclusively before subsequent abbreviated applications for the drug may be approved than it would have received but for the intervening period of pediatric exclusivity.

For example, the committee understands there may be instances in which 2 patents on a drug are challenged in an abbreviated new drug application, and that, in subsequent litigation, a court holds the first patent to expire to be valid and infringed, and the second patent to expire to be invalid. If the section 505(b)(1) drug is granted a period of pediatric exclusivity with respect to the first patent, and if the court decision, which triggers the beginning of the ANDA exclusivity, falls 60 days before that period of pediatric exclusivity begins (that is, 60 days before the first patent will expire), the ANDA exclusivity will overlap with the pediatric exclusivity for 120 days. In the absence of pediatric exclusivity, the holder of the ab-

breviated drug application would enjoy at most 120 days to market its drug before a subsequent abbreviated application for the drug could be approved. But for the amendment, because of pediatric exclusivity, the holder of the abbreviated drug application would enjoy no ANDA exclusivity, because the first 120 days of the pediatric exclusivity period would run over the last 120 days of its ANDA exclusivity. The amendment adds 6 months to the ANDA exclusivity period, so that the manufacturer of the section 505(j) drug would enjoy 120 days of ANDA exclusivity after the period of pediatric exclusivity expires.

B. Five Amendments Offered and Subsequently Withdrawn

1. Senator Clinton offered and then withdrew an amendment to establish a council on pediatric cancer therapeutics to identify, evaluate, and prioritize new and promising oncology drugs for use in children, and to require manufacturers to include in an application for study of a new drug their intent for pediatric studies of the drug and their procedures for individual access to the drug.

2. Senator Bond offered and then withdrew an amendment to provide an additional 3 months of exclusivity when a company does studies of a drug in a pediatric population not studied under the first request for pediatric studies.

3. Senator Clinton offered and then withdrew an amendment to provide that, when a manufacturer does not accept a written request from FDA to study a drug, the drug could be studied under the process for studying off-patent drugs provided for in S. 838.

4. Senator Clinton offered and then withdrew an amendment to provide that drugs that have annual sales of \$800 million or more would receive 3 months rather than 6 months of pediatric exclusivity.

5. Senator Kennedy offered and then withdrew an amendment to require pediatric testing of new drugs for their approved uses in adults.

IV. EXPLANATION OF THE LEGISLATION AND COMMITTEE VIEWS

Priority lists of drugs to be studied

The FDA recommended that the requirement that the Secretary create and maintain a priority list of drugs to be studied for their pediatric use in children be eliminated. Development of the list was resource intensive, and diverted resources from other needed work on pediatric drugs. The list also did little to prioritize effectively which drugs should be studied in children. Finally, the priority list created the mistaken impression on the part of some drug manufacturers that only those drugs on the list could qualify for the pediatric incentive. Accordingly, the legislation has eliminated the list.

At the same time, the legislation establishes a process and standard by which the National Institutes of Health (NIH) and FDA are to prioritize the study of drugs that lack patents or other market exclusivity protections. The committee expects that this process and standard for the prioritization of drugs will produce a useful priority list for the study of such drugs. These drugs will be studied using limited Federal funds, and the committee believes that these funds can be used most efficiently to study drugs that will provide

significant benefit to significant numbers of children. The committee intends the standards in the legislation to guide the prioritization process, so that a rational plan for the study of off-patent drugs will emerge.

Fund and process for study of drugs lacking patents and other market exclusivities

The 1997 pediatric exclusivity law makes no provision for the study of drugs lacking patent and other market exclusivity protections, as such drugs lack any market exclusivity to which the 6-month period of pediatric exclusivity may attach. This legislation therefore addresses concerns raised by the FDA, GAO, and pediatric groups about the urgent need for pediatric studies of such drugs. Data from 1994 showed that 6 of 10 drugs most commonly prescribed for children lacked patent terms. By creating an off-patent research fund, this legislation creates a mechanism for the Secretary to contract with PPRUs and other entities that have expertise to conduct pediatric clinical trials (universities, hospitals, and other public or private institutions) for studies of an off-patent drug. Under this provision, the companies that market the drug would be offered the right of first refusal to conduct and fund the studies and, if the companies do not respond within 30 days, they would not be eligible to receive funds from the off-patent research fund to conduct the study. Only the entity awarded a contract by the Secretary to perform the study of the off-patent drug would have access to public funds in the off-patent research fund.

Under sections 505(c)(3)(D)(iii) and (iv) and 505(j)(5)(D)(iii) and (iv) of the FDCA, a company is eligible for three-year Waxman-Hatch exclusivity only if it submits a new drug application (NDA) to FDA containing reports of new clinical investigations that are essential to approval of the application and that are conducted or sponsored by the applicant. By regulation, FDA has required that a study is “conducted or sponsored by” a company if (1) the company is the sponsor named in the IND for the study submitted to FDA (i.e., the company conducts the study), or (2) the company provides 50 percent or more of the cost of conducting the study. 21 CFR 314.50(j)(4)(iii). Accordingly, if a company declines to conduct or sponsor studies of an off-patent drug and another entity (such as a PPRU) conducts the studies, it is the committee’s understanding that the company would not be able to benefit from an additional 3 years of Hatch-Waxman exclusivity. If the Secretary agrees with an off-patent study that shows that a formulation change is necessary, the legislation requires that the Secretary send a nonbinding letter recommending such formulation change to each holder of an approved application for the drug.

Timely labeling of drugs granted exclusivity and of off-patent drugs

The committee understands that some drug companies have been reluctant to relabel their products once pediatric studies are complete when the information from the study is adverse. The committee believes that all useful and appropriate information on the safety and effectiveness of a drug in children should appear in drug labeling, and that this information should appear in the drug label as soon as possible. Pediatricians and parents must have timely ac-

cess to all appropriate information when they are deciding whether and how to give a drug to a child.

Accordingly, the legislation provides a process by which FDA can seek labeling changes to drugs granted pediatric exclusivity and to off-patent drugs studied under the off-patent research fund. The committee intends the process to be a reasonably quick and open process, after which the government could initiate an enforcement action to require relabeling of the drug. The process requires referral to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee after a company has refused an FDA request to relabel a product. The FDA then makes a second request for a labeling change after considering the recommendation of the Pediatric Advisory Subcommittee and, if the company refuses to relabel its drug, the FDA can deem the drug to be misbranded.

The committee expects that, generally, the government would rely on the injunction provisions of the FFDCA to seek an order from the court for the company to label its product with appropriate pediatric labeling, not seizure or criminal provisions. The committee does not believe that the government should routinely seek an order enjoining the company from marketing what is a safe and effective drug for use in adults merely because it may lack appropriate pediatric labeling.

The committee believes that the government would make its case that a company's drug is misbranded before the court by showing that FDA made an initial request for relabeling that the company refused, that FDA referred the issue of the Pediatric Advisory Subcommittee, which reviewed the matter and made a recommendation about a labeling change to FDA, that FDA made a second request for a labeling change, which the company refused, and that FDA's second requested labeling change was appropriate because without the change the drug would lack adequate directions for use in children.

The committee expects this Pediatric Advisory process to be an open one, in that, in accordance with existing law and FDA policies and procedures, materials provided to the Pediatric Advisory Subcommittee will be made available to the public, including by posting the material on the FDA's website. All disclosures of information are subject to the Freedom of Information Act and the Trade Secrets Act. The committee understands that current FDA guidance on the disclosure of information provided to an advisory committee can be found in the following FDA Guidance Documents: "Disclosure of Materials Provided to Advisory Committee in Connection with Open Advisory Committees Convened by the Center for Drug Evaluation and Research Beginning on January 1, 2000" (Nov. 1999), and "Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of New Drugs and Convened by the Center for Drug Evaluation and Research, Beginning on January 1, 2000" (Dec. 1999).

As an additional means to provide for timely pediatric labeling changes on drugs, the legislation removes the exemption for pediatric indication supplements in PDUFA that excludes companies that perform pediatric drug studies at FDA's request from paying a user fee. By requiring that drug companies pay PDUFA fees when they submit their completed studies as supplements to the

FDA, the committee expects that FDA will have sufficient resources to review pediatric labeling supplements quickly as “priority supplements,” and that pediatric labeling changes can be made as quickly as possible.

Pediatric expertise at FDA

The committee is aware that the incentives created by the pediatric exclusivity provision have encouraged the drug industry to develop and expand its infrastructure and expertise in the study of drugs in pediatrics. The committee intends that both the payment of user fees for the review of pediatric labeling supplements and the establishment of an Office of Pediatric Therapeutics at FDA will facilitate similar gains in coordinated expertise and infrastructure at FDA.

Pediatric studies in neonates

The committee understands that, at times, FDA has awarded pediatric exclusivity without requesting studies in neonates (newborns less than a month old), often because study in neonates must follow studies in older children for scientific, medical, or ethical reasons. This practice recognizes that neonates are an especially vulnerable population and should be tested only with the highest regard for their safe and ethical treatment. For the same reasons, however, it is important that drugs be studied in neonates whenever appropriate; otherwise, any use in neonates will be unguided by the knowledge that could be appropriately gained in high quality clinical trials using neonates. The legislation therefore emphasizes that neonate testing should be included in a written request by FDA in appropriate cases.

The committee is not mandating that neonate studies be done. Nor does the committee intend this change to mean that neonate testing should be performed prematurely. However, it does intend that FDA will have broad discretion to structure its requests for pediatric trials so as to protect children and enhance the value of the information obtained through pediatric studies. For example, the committee intends that, if FDA concludes that it would be appropriate to conduct neonatal studies after it has had the opportunity to examine data from studies in older children, FDA may, in 1 written request for pediatric studies, request the submission of a report from studies in older children, to be followed by studies in younger children and neonates if the data from the earlier studies may allow appropriate studies in the younger children.

Dissemination of pediatric information

The committee believes that public dissemination of information about pediatric drug studies will facilitate improved understanding and use of drugs in children. The legislation accomplishes this goal by requiring that, subject to the Freedom of Information Act and the Trade Secrets Act, the FDA make public a summary of the medical and clinical pharmacology reviews of the pediatric studies, including by publication in the Federal Register. Confidential commercial information or trade secrets contained in the pediatric supplement could not be disclosed and would have to be redacted from any information released to the public.

Study of research involving children

The pediatric exclusivity provision has increased significantly the number of drug studies conducted in children. This increase, coupled with reports of unrelated incidents that have raised concern about human subject protection, has led some to request a thorough examination of safety and ethical controls on pediatric studies. The committee shares the concern that the ethical conduct of pediatric research and the safety of children be paramount. The legislation therefore requires that the IOM conduct a 2-year study of Federal regulations and reports to assess the adequacy of current legal and ethical safeguards. The committee expects the IOM to conduct an independent review and to consider a number of options to improve current legal and ethical safeguards, including those proposed in the May 2001 review by the Department of Health and Human Services mandated in the Children's Health Act of 2000 (P.L. 106-310).

V. COST ESTIMATE

Due to time constraints the Congressional Budget Office estimate was not included in the report. When received by the committee, it will appear in the Congressional Record at a later time.

VI. APPLICATION OF LAW TO THE LEGISLATIVE BRANCH

The Best Pharmaceuticals for Children Act reauthorizes and amends the section 505A of the Federal Food, Drug, and Cosmetic Act to further improve the safety and efficacy of pharmaceuticals for children. It also provides for the study of off-patent drugs by amending the Public Health Service Act. As such, it has no application to the legislative branch.

VII. REGULATORY IMPACT STATEMENT

By granting drug manufacturers a 6-month extension of market exclusivity for a drug upon satisfactory completion of requested pediatric studies of the product and delaying the availability of lower cost generic alternatives, the bill will make those prescription drugs, when provided under Medicaid, more expensive. This provision would not constitute a mandate under the Unfunded Mandates Reform Act because prescription drugs under Medicaid are provided at a State's option. In addition, there would be cost savings to the Medicaid program because, for example, safe and effective use of drugs in children is expected to reduce the need to hospitalize many children and to reduce errors in dosing and medicating children. The private sector is affected by the bill because it increases the nation's annual pharmaceutical bill by one half of one percent. There would also be cost savings to the private sector by, for example, the reduced need for hospitalization of children and reduced errors in medicating children. FDA calculated the aggregate increased cost of drugs from pediatric exclusivity to be \$695 million per year in undiscounted dollars and it estimated the direct medical cost savings from reduced hospitalizations of children for just 5 illnesses to be \$228 million annually.

VIII. SECTION-BY-SECTION ANALYSIS

*Sec. 1. Short title**Sec. 2. Pediatric studies of already-marketed drugs*

Section 2 deletes the requirement that the Secretary develop a priority list of on-patent drugs for which additional pediatric information may be beneficial. It provides that a drug may qualify for a written request for pediatric studies if the Secretary determines that information relating to the use of an approved drug in the pediatric population may produce health benefits in that population.

Sec. 3. Research fund for the study of drugs lacking exclusivity

Section 3 creates a research fund for the pediatric studies of off-patent drugs, authorized at \$200 million for FY 2002 (and such sums for each of the next 5 years), to be administered by the National Institutes of Health (NIH). The Secretary, acting through the Director of NIH in consultation with the Commissioner of Food and Drugs, would establish a prioritized list of off-patent drugs that need to be tested for children. Drugs would be prioritized considering the availability of information on safe and effective use of the drug in children, whether additional information is needed, whether new pediatric studies of the drug may produce health benefits for children, and whether a reformulation of the drug is necessary.

Section 3 specifies the process for contracts for the studies and labeling of drugs lacking patent and other market exclusivity protection. The Commissioner of Food and Drugs, in consultation with the Director of NIH, would issue a written request for pediatric studies of such a drug to all companies that produce the drug. If a company accepts, then that company would pay for the study and perform the study pursuant to the requirements stated in the FDA's written request. If no company responds within 30 days to the written request (or if companies decline to perform the study), the Secretary must publish a request for contract proposals to conduct the pediatric studies described in the written request. If the Secretary is able to enter into a satisfactory contract for the studies, and once the contractor completes the study, the contractor must submit a report, including all data generated by the study, to the Director and the Commissioner, and the report must then be made available to the public.

Within 180 days of submission of the report, the Commissioner must review the data and negotiate labeling changes with the drug's manufacturer indicating the labeling change sought by the Commissioner. The Commissioner must place a copy of the report and any requested labeling changes sought in a public docket file, and must publish a summary of the report and the requested labeling changes in the Federal Register. If a company refuses to make the labeling changes sought by the Commissioner within 180 days of submission of the report, the Commissioner must immediately refer the report, data, and labeling change request to the Pediatric Advisory Subcommittee of the Anti-Infective Drug Advisory Committee. The Pediatric Advisory Subcommittee then has 90 days to review the report, data, and labeling change request and recommend to the Commissioner appropriate labeling changes. The Commissioner would then have 30 days to consider the Subcommittee's rec-

ommendation, and then make a final request to the drug company regarding a labeling change. If the drug company fails to agree to the labeling changes within 30 days, the Commissioner may deem the drug to be misbranded under the FEDCA. If the pediatric studies indicate that formulation change is necessary (from a pill to a liquid form, for example), the Secretary must send a nonbinding letter of recommendation for such a formulation change to all drug companies that market the drug.

Sec. 4. Timely labeling changes for drugs granted exclusivity; drug fees

Section 4 requires drug companies to pay user fees at the time they submit their completed studies to the FDA. Payment of user fees would then trigger the PDUFA “priority supplement” goal of 6 months for FDA to review pediatric labeling supplements submitted by the company. Within 180 days of submission of the report, the Commissioner of Food and Drugs must request whatever labeling changes he deems appropriate. If the drug company does not agree within that 180-day period to make the changes sought by the FDA, then the Commissioner must immediately refer the matter to the agency’s Pediatric Advisory Subcommittee. Within 90 days, the Pediatric Advisory Subcommittee must review the pediatric study reports and make a recommendation to the Commissioner as to appropriate labeling changes. Within 30 days, the Commissioner must consider the recommendations of the Subcommittee and make a final request to the drug company for a labeling change. If the drug company does not agree with 30 days to this labeling change request from the Commissioner, the Commissioner may deem the drug misbranded.

Sec. 5. Office of Pediatric Therapeutics

Section 5 requires the Secretary to establish an Office of Pediatric Therapeutics within the FDA. This office would oversee and coordinate RDA activities that could have an effect on pediatrics. The office would include 1 or more people with expertise in pediatric ethics and 1 or more people with pediatric expertise to consult on FDA activities that might have an effect on pediatrics.

Sec. 6. Neonates

Section 6 clarifies that the pediatric age groups in which pediatric studies are to be performed in response to requests for such studies by FDA should include neonates when their inclusion is appropriate.

Sec. 7. Sunset

Section 7 sunsets the bill on October 1, 2007, and provides that a drug may receive pediatric exclusivity if, before that date, the Secretary makes a written request for pediatric studies of the drug and an approvable application for the drug has been submitted, and all requirements of section 505A of the FDCA are met.

Sec. 8. Dissemination of pediatric information

Section 8 requires that, within 6 months after a drug manufacturer has submitted a pediatric labeling change supplement to the FDA, the FDA must make public a summary of the medical and

clinical pharmacology reviews of the pediatric studies, including by publication in the Federal Register. All disclosures of information are subject to the Freedom of Information Act and the Trade Secrets Act.

Sec. 9. Clarification of interaction of market exclusivity under section 505 of the Federal Food, Drug, and Cosmetic Act and market exclusivity awarded to an applicant for approval of a drug under section 505(j) of that act

Section 9 clarifies the interaction of pediatric exclusivity provided under this legislation with ANDA exclusivity awarded under the Waxman-Hatch Law. It specifies that, when the pediatric exclusivity period for a drug overlaps with a period of ANDA exclusivity for the drug, the period of ANDA exclusivity is extended by an amount necessary to ensure that the holder of ANDA exclusivity enjoys the same possibility of exclusive commercial marketing that the holder would have enjoyed in the absence of pediatric exclusivity, no more and no less.

Sec. 10. Study concerning research involving children

Section 10 requires the Secretary to contract with the IOM to conduct a 2-year study of Federal regulations involving children in research; the written and oral processes for obtaining “assent, permission, and informed consent” of children in research from parents, guardians, and legal representatives; the definition of “minimal risk” with respect to children with illnesses or health children; the appropriateness of regulations applicable to children of differing ages and maturity; financial (or other) incentives that are or may be offered; the monitoring and enforcement of violations of existing regulations; the roles and responsibilities of institutional review boards (IRBs) in reviewing research involving children; and the composition of membership of such IRBs.

Sec. 11. Technical and conforming amendments

IX. CHANGES IN EXISTING LAW

In compliance with rule XXVI paragraph 12 of the Standing Rules of the Senate, the following provides a print of the statute or the part or section thereof to be amended or replaced (existing law proposed to be omitted is enclosed in black brackets, new matter is printed in italic, existing law in which no change is proposed is shown in roman):

PUBLIC HEALTH SERVICE ACT

* * * * *

TITLE IV—NATIONAL RESEARCH INSTITUTES

PART A—NATIONAL INSTITUTES OF HEALTH

ORGANIZATION OF THE NATIONAL INSTITUTES OF HEALTH

SEC. 401. [281] (a) * * *

* * * * *

SEC. [409C.] 409G. CLINICAL RESEARCH.

(a) IN GENERAL.—The director of National Institutes of Health shall undertake activities to support and expand the involvement of the National Institutes of Health in clinical research.

(b) REQUIREMENTS.—In carrying out subsection (a), the Director of National Institutes of Health Shall—

(1) consider the recommendations of the Division of Research Grants Clinical Research Study Group and other recommendations for enhancing clinical research; and

(2) establish intramural and extramural clinical research fellowship programs directed specifically at medical and dental students and a continuing education clinical research training program at the National Institutes of Health.

(c) SUPPORT FOR THE DIVERSE NEEDS OF CLINICAL RESEARCH.—The Director of National Institutes of health, in cooperation with the Directors of the Institutes, Centers, and Divisions of the National Institutes of Health, shall support and expand the resources available for the diverse needs of the clinical research community, including inpatient, outpatient, and critical care clinical research.

(d) PEER REVIEW.—The Director of National Institutes of Health shall establish peer review mechanisms to evaluate applications for the awards and fellowships provided for in subsection (b)(2) and section 409D. Such review mechanisms shall include individuals who are exceptionally qualified to appraise the merits of potential clinical research training and research grant proposals.

SEC. [409D.] 409H. ENHANCEMENT AWARDS.

(a) MENTORED PATIENT-ORIENTED RESEARCH CAREER DEVELOPMENT AWARDS.—

(1) GRANTS.—

(A) IN GENERAL.—The Director of the National Institutes of Health shall make grants (to be referred to as “Mentored Patient-Oriented Research Career Development Awards”) to support individual careers in clinical research at general clinical research centers or at other institutions that have the infrastructure and resources deemed appropriate for conducting patient-oriented clinical research.

(B) USE.—Grants under subparagraph (A) shall be used to support clinical investigators in the early phases of their independent careers by providing salary and such other support for a period of supervised study.

(2) APPLICATIONS.—An application for a grant under this subsection shall be submitted by an individual scientist at such time as the Director may require.

(3) AUTHORIZATION OF APPROPRIATIONS.—For the purpose of carrying out this subsection, there are authorized to be appropriated such sums as may be necessary for each fiscal year.

(b) MID-CAREER INVESTIGATOR AWARDS IN PATIENT-ORIENTED RESEARCH.—

(1) GRANTS.—

(A) IN GENERAL.—The Director of the National Institutes of Health shall make grants (to be referred to as “Mid-Career Investigator Awards in Patient-Oriented Research”) to support individual clinical research projects at general clinical research centers or at other institutions that have

the infrastructure and resources deemed appropriate for conducting patient-oriented clinical research.

(B) USE.—Grants under subparagraph (A) shall be used to provide support for mid-career level clinicians to allow such clinicians to devote time to clinical research and to act as mentors for beginning clinical investigators.

(2) APPLICATIONS.—An application for a grant under this subsection shall be submitted by an individual scientists at such time as the Director requires.

(3) AUTHORIZATION OF APPROPRIATIONS.—For the purpose of carrying out this subsection, there are authorized to be appropriated such sums as may be necessary for each fiscal year.

(c) GRADUATE TRAINING IN CLINICAL INVESTIGATION AWARD.—

(1) IN GENERAL.—The Director of the National Institutes of Health shall make grants (to be referred to as “Graduate Training in Clinical Investigation Awards”) to support individuals pursuing master’s or doctoral degrees in clinical investigation.

(2) APPLICATIONS.—An application for a grant under this subsection shall be submitted by an individual scientist at such time as the Director may require.

(3) LIMITATIONS.—Grants under this subsection shall be for terms of 2 years or more and shall provide stipend, tuition, and institutional support for individual advanced degree programs in clinical investigation.

(4) DEFINITION.—As used in this subsection, the term “advanced degree programs in clinical investigation” means programs that award a master’s or Ph.D degree in clinical investigation after 2 years of training in areas such as the following:

(A) Analytical methods, biostatistics, and study design.

(B) Principles of clinical pharmacology and pharmacokinetics.

(C) Clinical epidemiology.

(D) Computer data management and medical informatics.

(E) Ethical and regulatory issues.

(F) Biomedical writing.

(5) AUTHORIZATION OF APPROPRIATIONS.—For the purpose of carrying out this subsection, there are authorized to be appropriated such sums as may be necessary for each fiscal year.

(d) CLINICAL RESEARCH CURRICULUM AWARDS.—

(1) IN GENERAL.—The Director of the National Institutes of Health shall make grants (to be referred to as “Clinical Research Curriculum Awards”) to institutions for the development and support of programs of core curricula for training clinical investigators, including medical students. Such core curricula may include training in areas such as the following:

(A) Analytical methods, biostatistics, and study design.

(B) Principles of clinical pharmacology and pharmacokinetics.

(C) Clinical epidemiology.

(D) Computer data management and medical informatics.

(E) Ethical and regulatory issues.

(F) Biomedical writing.

(2) APPLICATIONS.—An application for a grant under this subsection shall be submitted by an individual institution or a consortium of institutions at such time as the Director may require. An institution may submit only one such application.

(3) LIMITATIONS.—Grants under this subsection shall be for terms of up to 5 years and may be renewable.

(4) AUTHORIZATION OF APPROPRIATIONS.—For the purpose of carrying out this subsection, there are authorized to be appropriated such sums as may be necessary for each fiscal year.

SEC. 409I. PROGRAM FOR PEDIATRIC STUDIES OF DRUGS LACKING EXCLUSIVITY.

(a) LIST OF DRUGS LACKING EXCLUSIVITY FOR WHICH PEDIATRIC STUDIES ARE NEEDED.—

(1) IN GENERAL.—Not later than 1 year after the date of enactment of this section, the Secretary, acting through the Director of the National Institutes of Health and in consultation with the Commissioner of Food and Drugs and experts in pediatric research, shall develop, prioritize, and publish an annual list of approved drugs for which—

(A)(i) there is an approved application under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j));

(ii) there is a submitted application that could be approved under the criteria of section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)); or

(iii) there is no patent protection or market exclusivity protection under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.); and

(B) additional studies are needed to assess the safety and effectiveness of the use of the drug in the pediatric population.

(2) CONSIDERATION OF AVAILABLE INFORMATION.—In developing the list under paragraph (1), the Secretary shall consider, for each drug on the list—

(A) the availability of information concerning the safe and effective use of the drug in the pediatric population;

(B) whether additional information is needed;

(C) whether new pediatric studies concerning the drug may produce health benefits in the pediatric population; and

(D) whether reformulation of the drug is necessary;

(b) CONTRACTS FOR PEDIATRIC STUDIES.—The Secretary shall award contracts to entities that have the expertise to conduct pediatric clinical trials (including qualified universities, hospitals, laboratories, contract research organizations, federally funded programs such as pediatric pharmacology research units, other public or private institutions, or individuals) to enable the entities to conduct pediatric studies concerning one or more drugs identified in the list described in subsection (a).

(c) PROCESS FOR CONTRACTS AND LABELING CHANGES.—

(1) WRITTEN REQUEST TO HOLDERS OF APPROVED APPLICATIONS FOR DRUGS LACKING EXCLUSIVITY.—

(A) IN GENERAL.—The Commissioner of Food and Drugs, in consultation with the Director of National Institutes of Health, may issue a written request (which shall include a

timeframe for negotiations for an agreement) for pediatric studies concerning a drug identified in the list described in subsection (a) to all holders of an approved application for the drug under section 505 of the Federal Food, Drug, and Cosmetic Act. Such a request shall be made in accordance with section 505A of the Federal Food, Drug, and Cosmetic Act.

(B) *PUBLICATION OF REQUEST.*—If the Commissioner of Food and Drugs does not receive a response to a written request issued under subparagraph (A) within 30 days of the date on which a request was issued, the Secretary, acting through the Director of National Institutes of Health and in consultation with the Commissioner of Food and Drugs, shall publish a request for contract proposals to conduct the pediatric studies described in the written request.

(C) *DISQUALIFICATION.*—A holder that receives a first right of refusal shall not be entitled to respond to a request for contract proposals under subparagraph (B).

(D) *GUIDANCE.*—Not later than 270 days after the date of enactment of this section, the Commissioner of Food and Drugs shall promulgate guidance to establish the process for the submission of responses to written requests under subparagraph (A).

(2) *CONTRACTS.*—A contract under this section may be awarded only if a proposal for the contract is submitted to the Secretary in such form and manner, and containing such agreements, assurances, and information as the Secretary determines to be necessary to carry out this section.

(3) *REPORTING OF STUDIES.*—

(A) Upon completion of a pediatric study in accordance with a contract awarded under this section, a report concerning the study shall be submitted to the Director of National Institutes of Health and the Commissioner of Food and Drugs. The report shall include all data generated in connection with the study.

(B) *AVAILABILITY OF REPORTS.*—Each report submitted under subparagraph (a) shall be considered to be in the public domain, and shall be assigned a docket number by the Commissioner of Food and Drugs. An interested person may submit written comments concerning such pediatric studies to the Commissioner of Food and Drugs, and the written comments shall become part of the docket file with respect to each of the drugs.

(C) *ACTION BY COMMISSIONER.*—The Commissioner of Food and Drugs shall take appropriate action in response to the reports submitted under subparagraph (A) in accordance with paragraph (4).

(4) *REQUEST FOR LABELING CHANGES.*—During the 180-day period after the date on which a report is submitted under paragraph (3)(A), the Commissioner of Food and Drugs shall—

(A) review the report and such other data as are available concerning the safe and effective use in the pediatric population of the drug studied; and

(B) negotiate with the holders of approved applications for the drug studied for any labeling changes that the Com-

missioner of Food and Drugs determines to be appropriate and requests the holders to make; and

(C)(i) place in the public docket file a copy of the report and of any requested labeling changes; and

(ii) publish in the Federal Register a summary of the report and a copy of any requested labeling changes.

(5) DISPUTE RESOLUTION.—If, not later than the end of the 180-day period specified in paragraph (4), the holder of an approved application for the drug involved does not agree to any labeling change requested by the Commissioner of Food and Drugs under that paragraph—

(A) the Commissioner of Food and Drugs shall immediately refer the request to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee; and

(B) not later than 90 days after receiving the referral, the Subcommittee shall—

(i) review the available information on the safe and effective use of the drug in the pediatric population, including study reports submitted under this section; and

(ii) make a recommendation to the Commissioner of Food and Drugs as to appropriate labeling changes, if any.

(6) FDA DETERMINATION.—Not later than 30 days after receiving a recommendation from the Subcommittee under paragraph (5)B(ii) with respect to a drug, the Commissioner of Food and Drugs shall consider the recommendation and, if appropriate, make a request to the holders of approved applications for the drug to make any labeling change that the Commissioner of Food and Drugs determines to be appropriate.

(7) FAILURE TO AGREE.—If a holder of an approved application for a drug, within 30 days after receiving a request to make a labeling change under paragraph (6), does not agree to make a requested labeling change, the Commissioner may deem the drug to be misbranded under the Federal Food, Drug, and Cosmetic Act.

(8) RECOMMENDATION FOR FORMULATION CHANGES.—If a pediatric study completed under public contract indicates that a formulation change is necessary and the Secretary agrees, the Secretary shall send a nonbinding letter of recommendation regarding that change to each holder of an approved application.

(d) AUTHORIZATION OF APPROPRIATIONS.—

(1) IN GENERAL.—There are authorized to be appropriated to carry out this section—

(A) \$200,000,000 for fiscal year 2002; and

(B) such sums as are necessary for each of the 5 succeeding fiscal years.

(2) AVAILABILITY.—Any amount appropriated under paragraph (1) shall remain available to carry out this section until expended.

* * * * *

FEDERAL FOOD, DRUG, AND COSMETIC ACT

* * * * *

CHAPTER II—DEFINITIONS

SEC. 201 [21 U.S.C. 321] For the purposes of this Act—
 (a)(1) * * *

* * * * *

(kk) *PRIORITY SUPPLEMENT.*—The term “priority supplement” means a drug application referred to in section 101(4) of the Food and Drug Administration Modernization Act of 1997 (111 Stat. 2298).

* * * * *

SEC. 505A. [21 U.S.C. 355a] PEDIATRIC STUDIES OF DRUGS.

[(g)] (a) DEFINITIONS.—As used in this section, the term “pediatric studies” or “studies” means at least one clinical investigation (that, at the Secretary’s discretion, may include pharmacokinetic studies) in pediatric age groups (*including neonates in appropriate cases*) in which a drug is anticipated to be used.

[(a)] (b) MARKET EXCLUSIVITY FOR NEW DRUGS.—If, prior to approval of an application that is submitted under section 505(b)(1), the Secretary determines that information relating to the use of a new drug in the pediatric population may produce health benefits in that population, the Secretary makes a written request for pediatric studies (which shall include a timeframe for completing such studies), and such studies are completed within any such timeframe and the reports thereof submitted in accordance with subsection (d)(2) or accepted in accordance with subsection (d)(3)—

(1)(A)(i) the period referred to in subsection (c)(3)(D)(ii) of section 505, and in subsection [(j)(4)(D)(ii)] (j)(5)(D)(ii) of such section, is deemed to be five years and six months rather than five years, and the references in subsections (c)(3)(D)(ii) and [(j)(4)(D)(ii)] (j)(5)(D)(ii) of such section to four years, to forty-eight months, and to seven and one-half years are deemed to be four and one-half years, fifty-four months, and eight years, respectively; or

(ii) the period referred to in clauses (iii) and (iv) of subsection (c)(3)(D) of such section, and in clauses (iii) and (iv) of subsection [(j)(4)(D)] (j)(5)(D) of such section, is deemed to be three years and six months rather than three years; and

(B) if the drug is designated under section 526 for a rare disease or condition, the period referred to in section 527(a) is deemed to be seven years and six months rather than seven years; and

(2)(A) if the drug is the subject of—

(i) a listed patent for which a certification has been submitted under subsection (b)(2)(A)(ii) or (j)(2)(A)(vii)(II) of section 505 and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or

(ii) a listed patent for which a certification has been submitted under subsections (b)(2)(A)(iii) or (j)(2)(A)(vii)(III) of section 505,

the period during which an application may not be approved under section 505(c)(3) or section [505(j)(4)(B)] shall be extended by a period of six months after the date the patent expires (including any patent extensions); or

(B) if the drug is the subject of a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 505, and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under section 505(c)(3) or section 505(j)(4)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions).

[(b) SECRETARY TO DEVELOP LIST OF DRUGS FOR WHICH ADDITIONAL PEDIATRIC INFORMATION MAY BE BENEFICIAL.—Not later than 180 days after the date of enactment of the Food and Drug Administration Modernization Act of 1997, the Secretary, after consultation with experts in pediatric research shall develop, prioritize, and publish an initial list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population. The Secretary shall annually update the list.]

(c) MARKET EXCLUSIVITY FOR ALREADY-MARKETED DRUGS.—If the Secretary *determines that information relating to the use of an approved drug in the pediatric population may produce health benefits in that population and* makes a written request to the holder of an approved application under section 505(b)(1) for pediatric studies (which shall include a timeframe for completing such studies) **[concerning a drug identified in the list described in subsection (b)],** the holder agrees to the request, the studies are completed within any such timeframe, and the reports thereof are submitted in accordance with subsection (d)(2) or accepted in accordance with subsection (d)(3)—

(1)(A)(i) the period referred to in the subsection (c)(3)(D)(ii) of section 505, and in subsection **[(j)(4)(D)(ii)] (j)(5)(D)(ii)** of such section, is deemed to be five years and six months rather than five years, and the references in subsections (c)(3)(D)(ii) and **[(j)(4)(D)(ii)] (j)(5)(D)(ii)** of such section for four years, to forty-eight months, and to seven and one-half years are deemed to be four and one-half years, fifty-four months, and eight years, respectively; or

(ii) the period referred to the clauses (iii) and (iv) of subsection (c)(3)(D) of such section, and in clauses (iii) and (iv) of subsection **[(j)(4)(D)] (j)(5)(D)** of such section, is deemed to be three years and six months rather than three years; and

(B) if the drug is designated under section 526 for a rare disease or condition, the period referred to in section 527(a) is deemed to be seven years and six months rather than seven years; and

(2)(A) if the drug is the subject of—

(i) a listed patent for which a certification has been submitted under subsection (b)(2)(A)(ii) or (j)(2)(A)(vii)(II) of section 505 and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or

(ii) a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iii) or (j)(2)(A)(vii)(III) of section 505, the period during which an application may not be approved under section 505(c)(3) or section 505(j)(4)(B) shall be extended

by a period of six months after the date the patent expires (including any patent extensions); or

(B) if the drug is the subject of a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 505, and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during an application may not be approved under section 505(c)(3) or section 505(j)(4)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions).

(d) CONDUCT OF PEDIATRIC STUDIES.—

(1) AGREEMENT FOR STUDIES.—The Secretary may, pursuant to a written request from the Secretary under subsection [(a) or (c)] *(b) or (c)*, after consultation with—

(A) the sponsor of an application for an investigational new drug under section 505(i);

(B) the sponsor of an application for a new drug under section 505(b)(1); or

(C) the holder of an approved application for a drug under section 505(b)(1),

agree with the sponsor or holder for the conduct of pediatric studies for such drug. Such agreement shall be in writing and shall include a timeframe for such studies.

(2) WRITTEN PROTOCOLS TO MEET THE STUDIES REQUIREMENT.—If the sponsor or holder and the Secretary agree upon written protocols for the studies, the studies requirement of subsection [(a) or (c)] *(b) or (c)* is satisfied upon the completion of the studies and submission of the reports thereof in accordance with the original written request and the written agreement referred to in paragraph (1). Not later than 60 days after the submission of the report of the studies, the Secretary shall determine if such studies were or were not conducted in accordance with the original written request and the written agreement and reported in accordance with the requirements of the Secretary for filing and so notify the sponsor or holder.

(3) OTHER METHODS TO MEET THE STUDIES REQUIREMENT.—If the sponsor or holder and the Secretary have not agreed in writing on the protocols for the studies, the studies requirement of subsection [(a) or (c)] *(b) or (c)* is satisfied when such studies have been completed and the reports accepted by the Secretary. Not later than 90 days after the submission of the reports of the studies, the Secretary shall accept or reject such reports and so notify the sponsor or holder. The Secretary's only responsibility in accepting or rejecting the reports shall be to determine, within the 90 days, whether the studies fairly respond to the written request, have been conducted in accordance with commonly accepted scientific principles and protocols, and have been reported in accordance with the requirements of the Secretary for filing.

(e) DELAY OF EFFECTIVE DATE FOR CERTAIN APPLICATION.—If the Secretary determines that the acceptance or approval of an application under section 505(b)(2) or 505(j) for a new drug may occur after submission of reports of pediatric studies under this section, which were submitted prior to the expiration of the patent (includ-

ing any patent extension) or the applicable period under clauses (ii) through (iv) of section 505(c)(3)(D) or clauses (ii) through (iv) of section, **505(j)(4)(D)** *505(j)(5)(D)*, but before the Secretary has determined whether the requirements of subsection (d) have been satisfied, the Secretary shall delay the acceptance or approval under section 505(b)(2) or 505(j) until the determination under subsection (d) is made, but any such delay shall not exceed 90 days. In the event that requirements of this section are satisfied, the applicable six-month period under subsection **[(a) or (c)]** *(b) or (c)* shall be deemed to have been running during the period of delay.

(f) NOTICE OF DETERMINATIONS ON STUDIES REQUIREMENT.—The Secretary shall publish a notice of any determination that the requirements of subsection (d) have been met and that submissions and approvals under subsection (b)(2) or (j) of section 505 for a drug will be subject to the provisions of this section.

[(h)] *(g)* **LIMITATIONS.**—A drug to which the six-month period under subsection **[(a) or (b)]** *(b) or (c)* has already been applied—

(1) may receive an additional six-month period under subsection (c)(1)(A)(ii) for a supplemental application if all other requirements under this section are satisfied, except that such a drug may not receive any additional such period under subsection (c)(2); and

(2) may not receive any additional such period under subsection (c)(1)(B).

[(i)] *(h)* **RELATIONSHIP TO REGULATIONS.**—Notwithstanding any other provision of law, if any pediatric study is required pursuant to regulations promulgated by the Secretary and such study meets the completeness, timeliness, and other requirements of this section, such study shall be deemed to satisfy the requirement for market exclusivity pursuant to this section.

[(j)] **SUNSET.**—A drug may not receive any six-month period under subsection **[(a) or (c)]** *(b) or (c)* unless the application for the drug under section 505(b)(1) is submitted on or before January 1, 2002. After January 1, 2002, a drug shall receive a six-month period under subsection (c) if—

[(1)] the drug was in commercial distribution as of the date of enactment of the Food and Drug Administration Modernization Act of 1997;

[(2)] the drug was included by the Secretary on the list under subsection (b) as of January 1, 2002;

[(3)] the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population and that the drug may provide health benefits in that population; and

[(4)] All requirements of this section are met. **]**

[(l)] *(i)* **LABELING SUPPLEMENTS.**—

(1) PRIORITY STATUS FOR PEDIATRIC SUPPLEMENTS.—*Any supplement to an application under section 505 proposing a labeling change pursuant to a report on a pediatric study under this section—*

(A) shall be considered to be a priority supplement; and

(B) shall be subject to the performance goals established by the Commissioner for priority drugs.

(2) DISPUTE RESOLUTION.—*If the Commissioner determines that an application with respect to which a pediatric study is*

conducted under this section is approvable and that the only open issue for final action on the application is the reaching of an agreement between the sponsor of the application and the Commissioner on appropriate changes to the labeling for the drug that is the subject of the application—

(A) not later than 180 days after the date of submission of the application—

(i) the Commissioner shall request that the sponsor of the application make any labeling change that the Commissioner determines to be appropriate; and

(ii) if the sponsor of the application does not agree to make a labeling change requested by the Commissioner by that date, the Commissioner shall immediately refer the matter to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee;

(B) not later than 90 days after receiving the referral, the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee shall—

(i) review the pediatric study reports; and

(ii) make a recommendation to the Commissioner concerning appropriate labeling changes, if any;

(C) the Commissioner shall consider the recommendations of the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee and, if appropriate, not later than 30 days after receiving the recommendation, make a request to the sponsor of the application to make any labeling change that the Commissioner determines to be appropriate; and

(D) if the sponsor of the application, within 30 days after receiving a request under subparagraph (C), does not agree to make a labeling change requested by the Commissioner, the Commissioner may deem the drug that is the subject of the application to be misbranded.

[(m)] (j) DISSEMINATION OF PEDIATRIC INFORMATION.—

(1) **IN GENERAL.**—Not later than 180 days after the date of submission of a report on a pediatric study under this section, the Commissioner shall make available to the public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted for the supplement, including by publication in the Federal Register.

(2) **EFFECT OF SUBSECTION.**—Nothing in this subsection alters or amends in any way section 552 of title 5 or section 1905 of title 18, United States Code.

[(n)] (k) CLARIFICATION OF INTERACTION OF MARKET EXCLUSIVITY AWARDED TO AN APPLICANT FOR APPROVAL OF A DRUG UNDER SECTION 505(J).—

(1) **IN GENERAL.**—If a 180-day period under section 505(j)(5)(B)(iv) overlaps with a 6-month extension under this section, so that the applicant for approval of a drug under section 505(j) entitled to the 180-day period under that section loses a portion of the 180-day period to which the applicant is entitled for the drug, the 180-day period shall be extended—

(A) if the 180-day period would, but for this subsection, expire after the 6-month extension, by the number of days of the overlap; or

(B) if the 180-day period would, but for this subsection, expire during the 6-month extension, by 6 months.

(2) EFFECT OF SUBSECTION.—Under no circumstances shall application of this section result in enabling an applicant for approval of a new drug under section 505(j) to commercially market the drug to the exclusion of a subsequent applicant for approval of a new drug under section 505(j) for more than 180 days.

[(k)] (l) REPORT.—The Secretary shall conduct a study and report to Congress not later than January 1, 2001, based on the experience under the program established under this section. The study and report shall 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 inventive 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.

[(j)] (m) SUNSET.—A drug may not receive any 6-month period under subsection (b) or (c) unless—

- (1) on or before October 1, 2007, the Secretary makes a written request for pediatric studies of the drug;
- (2) on or before October 1, 2007, an approvable application for the drug is submitted under section 505(b)(1); and
- (3) all requirements of this section are met.

* * * * *

SEC. 736. [21 U.S.C. 379h] AUTHORITY TO ASSESS AND USE DRUG FEES.

(a) **TYPES OF FEES.**—Beginning in fiscal year 1998, the Secretary shall assess and collect fees in accordance with this section as follows:

- (1) **HUMAN DRUG APPLICATION AND SUPPLEMENT FEE.**—
(A) * * *

* * * * *

[(F) EXCEPTION FOR SUPPLEMENTS FOR PEDIATRIC INDICATIONS.—A supplement to a human drug application proposing to include a new indication for use in pediatric populations shall not be assessed a fee under subparagraph (A).]

[(G)] (F) REFUND OF FEE IF APPLICATION WITHDRAWN.—If an application or supplement is withdrawn after the application or supplement was filed, the Secretary may refund the fee or a portion of the fee if no substantial work was performed on the application or supplement after the application or supplement was filed. The Secretary shall have the sole discretion to refund a fee or a portion of the fee under this subparagraph. A determination by the Sec-

retary concerning a refund under this paragraph shall not
be reviewable.

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