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AMENDING THE FEDERAL FOOD, DRUG, AND COSMETIC ACT TO REQUIRE LABELING CONTAINING INFORMATION APPLICABLE TO PEDIATRIC PATIENTS

OCTOBER 8, 2002.—Ordered to be printed

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

REPORT

together with

ADDITIONAL VIEWS

[To accompany S. 2394]

The Committee on Health, Education, Labor, and Pensions, to which was referred the bill (S. 2394) to amend the Federal Food, Drug, and Cosmetic Act to require labeling containing information applicable to pediatric patients, having considered the same, reports favorably thereon with an amendment and recommends that the bill (as amended) do pass.

CONTENTS

		Page
I.	Purpose and Summary of the Bill	1
II.	Background and Need for the Legislation	3
III.	Legislative History and Committee Action	8
IV.	Explanation of the Legislation and Committee Views	10
V.	Cost Estimate	12
VI.	Application of Law to the Legislative Branch	12
VII.	Regulatory Impact Statement	12
VIII.	Section-by-Section Analysis	12
IX.	Additional Views	15
X.	Changes in Existing Law	17

I. PURPOSE AND SUMMARY OF THE BILL

To address a longstanding concern that only a small portion of prescription medications on the market have been tested and ap-

proved for use in children, the Food and Drug Administration (FDA) proposed its Pediatric Rule in 1997. FDA finalized the Pediatric Rule in 1998, and it became effective in 1999. That rule requires the manufacturers of certain new and marketed drugs and biological products to conduct studies and provide adequate labeling for the use of the products in children. The rule is an essential complement to the provisions in the Best Pharmaceuticals for Children Act (BPCA, Pub. L. 107–109), which provides a 6–month exclusivity period for completion of requested pediatric studies as well as additional mechanisms to assure that drugs are studied and appropriately labeled for pediatric uses. The Pediatric Rule is under legal challenge in Federal district court and under regulatory review. The committee has approved this legislation to eliminate the uncertainties surrounding the rule.

1. THE LEGISLATION "CODIFIES" FDA'S PEDIATRIC RULE AND ENSURES THAT THE RULE REMAINS IN EFFECT

The legislation amends the Federal Food, Drug, and Cosmetic Act (FFDCA) by adding a new section 505B, which codifies the essential provisions of FDA's Pediatric Rule. For example, with respect to drugs and biological products that are not yet approved, the legislation provides that each new drug application under section 505 of the FFDCA or biologics license application under section 351 of the Public Health Service Act (PHSA) for a new active ingredient, new indication (except for an orphan drug indication), new dosage form, new dosing regimen, or new route of administration must contain data adequate to assess the safety and effectiveness of the drug or biological product for its claimed indications, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With respect to drugs and biological products that are already marketed, the legislation allows FDA, having made certain findings and under certain conditions, to require the product manufacturer to submit data on safety and effectiveness and dosing and administration, after having provided the holder with notice and an opportunity for written response and a meeting.

Under the legislation, FDA is required to grant a full or partial waiver of the pediatric data requirement for a drug or biological product for certain reasons, including if necessary studies are impossible or highly impractical; if there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups; or if the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, the drug or biological product is not likely to be used by a substantial number of pediatric patients, and the absence of adequate labeling would not pose significant risks to pediatric patients. Under the legislation, when the Secretary grants a full or partial waiver because there is evidence that the drug or biological product would be ineffective or unsafe in pediatric populations, the information must be included in the labeling for the drug or biological product.

The legislation provides for meetings with a drug sponsor during the investigational new drug process to discuss plans and timelines of pediatric studies or requests for waiver or deferral of pediatric studies. In addition, the legislation provides that the FDA's Pedi-

atric Rule, except to the extent it is inconsistent with section 505B, shall be considered to implement section 505B.

2. THE LEGISLATION CLARIFIES THE INTERACTION OF PEDIATRIC RULE WITH THE PEDIATRIC EXCLUSIVITY PROVISION WHEN APPLIED TO ALREADY-MARKETED DRUGS

For already-marketed drugs, the legislation requires that, before FDA may invoke the Pediatric Rule (if it is applicable), FDA must ask the manufacturer to conduct the study voluntarily under section 505A of the FFDCA, which provides for 6 months of market exclusivity for completing pediatric studies, or section 409I of the PHSA and that the company does not agree or that FDA does not receive a response. This requirement is consistent with current FDA practice. The legislation also clarifies that it does not change the provisions in the BPCA that establish a process at NIH to contract for studies to gather pediatric information. The legislation further clarifies that use of the NIH contracting process does not preclude FDA from using the Pediatric Rule to require that a manufacturer study an already-marketed drug.

3. THE LEGISLATION PROVIDES FOR APPROPRIATE ENFORCEMENT OF THE REQUIREMENT TO SUBMIT TIMELY PEDIATRIC ASSESSMENTS

The legislation provides that a drug or biological product for which a pediatric assessment is not filed by the date specified by FDA is deemed misbranded and is subject to an injunction or seizure action, but is not subject to criminal proceedings, withdrawal of approval as a new drug, or revocation of its approved biologics license.

4. THE LEGISLATION PROVIDES THAT IT DOES NOT ALTER FDA'S CURRENT AUTHORITY TO REQUIRE PEDIATRIC OR OTHER SUBPOPULATION STUDIES AND LABELING

The legislation states that section 505B does not affect whatever existing authority FDA has to require studies, in addition to those required under section 505B, of the safety and effectiveness of drugs and biological products in pediatric populations. It also states that FDA's authority, if any, to require studies for specific populations other than the pediatric population shall be exercised under the FFDCA as in effect on the day before the date of enactment of the legislation.

II. BACKGROUND AND NEED FOR THE LEGISLATION

Children suffer from many of the same diseases as adults and are often treated with the same medicines, yet only about 25 percent of today's medicines have been studied and labeled for use in children. 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 sufficiently increased the number of drugs with adequate pediatric labeling.

In 1997, FDA proposed its Pediatric Rule, which it finalized in 1998, and which became effective in 1999. The rule requires the manufacturers of certain new and marketed drugs and biological products to provide adequate labeling for certain uses of the products in children.

Under FDA's Pediatric Rule, each new drug application under section 505 of the FFDCA or biologics license application under section 351 of the PHSA for a new active ingredient, new indication (except indications for which orphan designation has been granted), new dosage form, new dosing regimen, or new route of administration must contain certain data. In particular, the application must contain data adequate to assess the safety and effectiveness of the drug or biological product for its claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective.

The rule provides for deferred submission of these data when the drug or biological product is ready for approval in adults before pediatric studies are complete or if pediatric studies should be delayed until additional safety and effectiveness data are collected. A request for deferral must include certification of the grounds for delaying the studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time.

Under the rule, FDA may grant a full waiver of the pediatric data requirement for a new drug or biological product for 3 reasons: (1) the product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and it is not likely to be used by a substantial number of pediatric patients; (2) necessary studies are impossible or highly impractical, because, for example, the number of such patients is so small or geographically dispersed; or (3) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric

age groups. Partial waivers are available with respect to a particular pediatric age group if any of these 3 reasons applies to that age group, or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed. A drug or biological product for which a full or partial waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations must be labeled with that information.

Under the rule, pre-investigation new drug meetings may include a discussion of plans for studying the drug or biological product in pediatric populations. In addition, end-of-phase 2 meetings during the investigational new drug application process must address plans to assess pediatric safety and effectiveness, and "pre-NDA" and "pre-BLA" meetings include as a major purpose the identification of the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness.

With respect to an already-marketed drug or biological product that is used in a substantial number of pediatric patients or that provides a meaningful therapeutic benefit over existing treatments for pediatric patients and for which the absence of adequate pediatric labeling could pose significant risks to pediatric patients, the rule allows FDA in these compelling circumstances to require the product's manufacturer to submit an application containing data adequate to assess whether the drug is safe and effective in pediatric populations for the drug's approved indications, as well as adequate evidence to support dosage and administration in some or all pediatric populations, depending on the known or appropriate use of the drug in those pediatric subpopulations. FDA may require the manufacturer to develop a pediatric formulation for a drug product that represents a meaningful therapeutic benefit over existing treatments for pediatric populations for whom a pediatric formulation is necessary, unless the manufacturer demonstrates that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

Under the rule, after notifying the manufacturer and offering the manufacturer an opportunity for a written response and a meeting, which may include an advisory committee meeting, FDA may issue such an order provided FDA finds that the absence of adequate labeling could pose significant risks to pediatric patients and that one of two additional conditions holds: (1) the drug or biological product is used in a substantial number of pediatric patients for the labeled indications, or (2) there is reason to believe that the drug or biological product would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for 1 or more of the claimed indications.

Once the conditions necessary to invoke the rule have been met, FDA may grant a full waiver of the pediatric data requirement for an already-marketed drug or biological product for 2 reasons: (1) necessary studies are impossible or highly impractical, because, for example, the number of such patients is so small or geographically dispersed, or (2) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups. Partial waivers are available with respect to a particular pediatric age group if either of these 2 reasons applies to that age group, or if the applicant can demonstrate that reasonable

attempts to produce a pediatric formulation necessary for that age group have failed, or if each of the following three reasons applies: (1) the product does not represent a meaningful therapeutic benefit over existing treatments for patients in that age group, (2) it is not likely to be used by a substantial number of patients in that age group, and (3) the absence of adequate labeling could not pose significant risks to pediatric patients. A drug or biological product for which a full or partial waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations must be labeled with that information.

Under the rule, a drug or biological product for which the manufacturer fails to submit the required supplemental application may be considered misbranded or an unapproved new drug or unlicenced biologic. The rule also defines "meaningful therapeutic benefit" to mean either (1) the drug would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population; or (2) the drug is in a class of drugs or for an indication for which there is a need for additional therapeutic options. The rule includes four examples of improvement under the first definition: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease, (2) elimination or substantial reduction of a treatment-limiting drug reaction, (3) documented enhancement of compliance, or (4) evidence of safety and effectiveness in a new subpopulation.

In sum, for new drugs and biological products with indications that should be tested in and labeled for children, the Pediatric Rule assures that they will be tested in and labeled for children when they are approved or, in the case of deferrals, shortly after approval. For already-marketed drugs and biological products, the rule gives FDA a means to require that they are tested in and labeled for children when doing so is important for children's health.

The Pediatric Rule works in tandem with pediatric exclusivity, which Congress enacted as the Better Pharmaceuticals for Children Act, part of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105–115). This act provided a market incentive of 6 months of additional exclusivity to drug companies for studies of medicines in children. The 6 month exclusivity period is added to any patent or exclusivity (such as orphan exclusivity or a 5- or 3-year Hatch-Waxman exclusivity) on the drug. The exclusivity has the nature of the patent or exclusivity that it extends. Congress reauthorized the pediatric exclusivity provision in 2001 in the BPCA. In the BPCA, Congress also provided an off-patent research fund at the National Institutes of Health (NIH) for the study of off-patent drugs and a process using first the Foundation of the National Institutes of Health (Foundation) and then the research fund for the study of drugs for which the manufacturers have declined written requests to study the drug under the pediatric exclusivity provision.

The Pediatric Rule is both broader and narrower than the pediatric exclusivity provision first enacted by Congress in 1997 and reauthorized by the BPCA in 2001. Most significantly, the rule is broader than pediatric exclusivity because the rule covers biological products while neither the pediatric exclusivity provision nor the

provisions for contracting for pediatric studies at the Foundation and at NIH applies to biological products.

In addition, the Pediatric Rule is broader than pediatric exclusivity because it covers subsequent indications and pediatric subpopulations that pediatric exclusivity, with its associated contracting process at the Foundation and NIH, may not. For example, if FDA does not include studies of newborns and infants in a written request for a drug under the pediatric exclusivity provision, pediatric exclusivity is generally not available to ensure that the drug will be studied for these children, but FDA may use the rule to require studies in those pediatric subpopulations. Moreover, if the pediatric exclusivity provision has been applied to a drug and subsequently the drug's manufacturer seeks approval for a new indication, pediatric exclusivity is generally not available to ensure that the new indication will be studied in children. FDA, however, may invoke the rule to require that the new indication is studied.

The Pediatric Rule is narrower than pediatric exclusivity and its associated contracting process at the Foundation and NIH in some respects also. For example, the rule may only be used for an indication for which the drug is approved or approval is sought in adults, whereas FDA may also use pediatric exclusivity to request pediatric studies of an indication not approved for adult use. In addition, the rule applies only to drugs that will be used by a substantial number of pediatric patients or that will provide a meaningful therapeutic benefit for pediatric patients, whereas pediatric exclusivity applies to drugs for which information relating to the use of the drug in the pediatric population may produce health benefits in that population.

Finally, for a drug or biological product for which approval is now being or will be sought, the rule ensures that children will be considered in the process of clinical development of the drug. This is true not merely because the rule requires that pediatric assessments must be performed for every new product, but also because the rule provides that significant meetings in the clinical development process—pre-investigation new drug meetings, end-of-phase 2 meetings during the investigational new drug application process, and "pre-NDA" and "pre-BLA" meetings—address the need for pediatric studies of a drug.

Even given these differences in scope, the Pediatric Rule and the pediatric exclusivity provision clearly work effectively together to ensure that a drug or biological product will be tested in and labeled for children when that is appropriate. When their scopes overlap, Congress provided in section 505A(h) of the FFDCA that pediatric studies required under the rule can also satisfy the requirements for market exclusivity. There are many drugs for which the rule and the incentive have worked together successfully to encourage a drug company to respond affirmatively to FDA's request for pediatric studies.

But the rule and pediatric exclusivity do not always both apply to a drug. It is those instances in which only the Pediatric Rule has assured the study and labeling of a drug for children that demonstrate most compellingly the need for the rule. FDA reports that, between April 1, 1999, when the rule first became effective, and March 31, 2002, 404 new drug applications and supplements fell within the scope of the rule. For approximately 266 of these drugs,

manufacturers have submitted, or will be required to submit, studies in one or more pediatric age groups (the remaining drugs received complete waivers, typically for safety reasons in children or because the drug's approved indication is not for a childhood disease). As of March 31, 2002, 94 submitted applications contained complete or partial pediatric use information. FDA attributes 48 of these submissions to the Pediatric Rule alone. By comparison, FDA reports that 57 drugs have been granted exclusivity and 8 have been denied exclusivity, with 35 of these drugs currently labeled for use in the pediatric population. It is therefore clear that the Pediatric Rule has made a substantial contribution to the slow but steady improvement in the pediatric labeling of drugs and biological products that has occurred since 1997, when Congress first provided for pediatric exclusivity and FDA first proposed the Pediatric Rule. The legislation assures that this progress will continue.

III. Legislative History and Committee Action

On April 29, 2002, Senator Clinton, for herself and Senators DeWine, Dodd, Murray, and Kennedy, introduced S. 2394, to amend the Federal Food, Drug, and Cosmetic Act to require drug labeling that contains information applicable to pediatric patients.

On August 1, 2002, the committee held an executive session to consider S. 2394. Senator Clinton offered an amendment for herself and Senators DeWine, Dodd, Gregg, and Frist that the committee accepted by unanimous voice vote. Also without objection, the committee directed that technical and conforming changes be made. The committee approved S. 2394, as amended, by unanimous voice vote.

A. AMENDMENT ADOPTED BY UNANIMOUS VOICE VOTE DURING EXECUTIVE SESSION

The committee adopted 1 amendment by unanimous voice vote.

1. Senator Clinton offered an amendment for herself and Senators DeWine, Dodd, Gregg, and Frist that clarifies the interaction of the Pediatric Rule and the pediatric exclusivity provision provided under section 505A of the FFDCA with respect to drugs already approved under section 505 of the FFDCA.

For already-marketed drugs, the legislation requires that, before FDA may invoke the Pediatric Rule (if it is applicable), FDA must ask the manufacturer to conduct the study voluntarily under section 505A of the FFDCA, which provides for 6 months of market exclusivity for completing pediatric studies, or section 409I of the PHSA and that the company does not agree or that FDA does not receive a response. This requirement is consistent with current FDA practice. The amendment also clarifies that the legislative provisions in S. 2394 do not change the provisions in the BPCA that establish a process for NIH to contract for studies to gather pediatric information. The amendment further clarifies that use of the NIH contracting process does not preclude the Secretary from using the authorities under the legislation to require that a manufacturer study an already-marketed drug.

The committee intends that, with respect to a drug already approved under section 505 of the FFDCA, the Secretary seek needed pediatric information by first asking the sponsor under section

505A(d) of the FFDCA and section 409I(c)(1) of the PHSA. Only if the company either does not agree or does not respond to these requests may the Secretary require the manufacturer to collect the needed pediatric information under an assessment for the drug under the legislation. Because the written request under section 505A and the assessment under the legislation should seek the same pediatric information, the amendment describes the pediatric studies under the written request as being "related" to the assessment under the legislation. The rule, however, may only be invoked for assessments in pediatric subpopulations of approved indications for the drug.

The committee intends for FDA to continue to issue broad written requests under section 505A of the FFDCA, section 409I of the PHSA, and the authorities of this legislation to capture the full scope of pediatric information desired, including for all uses of the drug in the pediatric population for which pediatric information may produce health benefits in that population. In the unusual circumstances when FDA makes an initial written request for pediatric studies of a drug under section 505A and FDA issues a subsequent request that the drug's manufacturer accepts, FDA may, when appropriate, invoke the rule to require the completion of studies included in the first written request and not included in the second written request without again invoking section 505A, provided that the criteria specified in the rule are met.

If the Secretary issues a written request for pediatric studies of a drug under section 505A(d) of the FFDCA and the recipient of the written request does not agree to conduct the studies, under section 505A(d)(4)(B) the Secretary must refer the drug for study to the Foundation for the National Institutes of Health established under section 499 of the PHSA. If the Secretary issues a written request for pediatric studies under section 409I(c) of the PHSA and the recipient of the written request does not agree to conduct the studies, section 409I(c)(2) requires the Secretary to issue a request for contract proposals to conduct the pediatric studies. As adequate funding is necessary for the contracting process to work effectively, the committee does not intend for the Secretary to issue requests for contract proposals without regard to the availability of funding needed for those proposals. At the same time, the committee also emphasizes that the Secretary should issue written requests under section 505A(d) or section 409I without regard for whether there are sufficient funds at the Foundation or NIH to fund the studies should the recipient of the written request not agree to conduct the studies. Therefore, insufficient funding to contract for studies under section 409I will not preclude the Secretary from requiring pediatric studies under the legislation.

This amendment adds only one prohibition on the Secretary's authority to invoke the Pediatric Rule, and that is the prohibition on use of the rule before the Secretary has asked the company to conduct the studies voluntarily and the company has either declined or failed to respond. Congress has provided several tools, including the contracting process, under the BPCA to see to it that needed pediatric studies are completed, but Congress never contemplated exhaustion of all the tools under BPCA before the Secretary can invoke the Pediatric Rule. This amendment makes clear that, so long as FDA has first asked a company to conduct the study of an al-

ready-marketed drug voluntarily and the company does not agree or FDA has not received a response, FDA will then be able to invoke the rule.

IV. Explanation of the Legislation and Committee Views

CodificatIon of FDA's Pediatric Rule

The legislation amends the FFDCA by adding a new section 505B to codify FDA's Pediatric Rule.

The legislation assures that, when appropriate, new drugs and biological products will be studied for safety and effectiveness and dosing and administration in children before new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are approved, unless a deferral or waiver is obtained. It also gives FDA the express statutory authority to require that already-marketed drugs and biological products be tested in children for approved indications if the agency finds, after certain conditions are met, that the absence of adequate labeling could pose significant risks to pediatric patients and that either (1) the drug or biological product is used for a substantial number of pediatric patients for the labeled indications, or (2) there is reason to believe that the drug or biological product would represent a meaningful therapeutic benefit over existing therapies for pediatric patents for 1 or more of the claimed indications.

The legislation allows FDA to conclude that pediatric effectiveness may be extrapolated from studies in adults, usually supplemented with information about pediatric patients, if the course of a disease and the effects of a drug are sufficiently similar in adults and pediatric patients. The legislation also allows FDA, on its own initiative or that of an applicant, to defer submission of these data in those circumstances provided for in the Pediatric Rule.

Under the legislation, FDA may grant a full or partial waiver of the pediatric assessment for a drug or biological product under certain conditions, including if (1) necessary studies are impossible or highly impractical, because, for example, the number of patients is so small or geographically dispersed (2) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups, or (3) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, the drug or biological product is not likely to be used by a substantial number of pediatric patients, and the absence of adequate labeling would not pose significant risks to pediatric patients. Because of a technical error, these waiver provisions differ from those in the Pediatric Rule. In particular, the first two of these conditions are those provided by the Pediatric Rule for full waivers for already-marketed drugs and biological products (with the third condition mirroring the finding FDA must make to require study of the drug or biological product, and available as a third condition for a partial waiver), and the Pediatric Rule provides each of these three conditions for a waiver for a new drug or biological product, except that the third condition lacks the "absence of adequate labeling" prong. The committee intends to correct this technical error before the full Senate acts on the legislation. Like the Pediatric Rule, the legislation requires that, when the Secretary grants a full or partial waiver because

there is evidence that the drug or biological product would be ineffective or unsafe in pediatric populations, the information must be included in the labeling for the drug or biological product.

The legislation provides that the FDA's Pediatric Rule, except to the extent that it is inconsistent with section 505B, is considered to implement section 505B. As an example, the legislation provides for meetings with a drug sponsor during the investigational new drug process to discuss plans and timelines of pediatric studies or requests for waiver or deferral of pediatric studies. The committee regards the provisions in the Pediatric Rule regarding meetings to implement and be consistent with this provision on meetings in the legislation. In addition, the rule requires a pediatric use section in a new drug or biologic license application, as well as postmarketing reports directed at pediatric use issues. The committee regards these and other provisions of the Pediatric Rule to implement and be consistent with the legislation.

The legislation includes no definition of meaningful therapeutic benefit, a term that identifies when a drug should be studied in children. The term is defined in the Pediatric Rule, however, and the committee considers that definition to be consistent with the legislation. Although the legislation includes no explicit exemption for orphan drugs, the committee views the current exemption in the Pediatric Rule for indications with orphan designations to be consistent with the legislation.

Enforcement of FDA's Pediatric Rule

The legislation provides that a drug or biological product for which a pediatric assessment is not filed by the date specified by FDA may be considered misbranded and subject to an injunction or seizure action, but is not subject to criminal proceedings nor to withdrawal of approval as a new drug or revocation of its approved biologics license.

Under FDA's Pediatric Rule, a drug for which a pediatric assessment is not timely filed could also be considered an unapproved new drug, and a biological product for which a pediatric assessment is not timely filed could also be considered an unlicensed biologic. The committee considers this provision of the Pediatric Rule to be inconsistent with the legislation. In addition, unlike the legislation, the rule includes no provision limiting enforcement of the rule to injunction or seizure action. Nonetheless, the committee understands that FDA would only enforce the rule using its seizure or injunction authorities. This restriction in the legislation therefore has no effect on what actual FDA practice would be under the rule, but it does reflect the committee's concern that neither criminal charges nor withdrawal of a drug from the market be used when a drug company violates the requirement to submit timely pediatric assessments.

Current authority for studies in and labeling for pediatric and other subpopulations

The legislation states that section 505B does not affect whatever existing authority FDA has to require studies, in addition to those required under section 505B, of the safety and effectiveness of drugs and biological products in pediatric populations. It also states that FDA's authority, if any, to require studies for specific popu-

lations other than the pediatric population shall be exercised under the FFDCA as in effect on the day before the date of enactment of the legislation.

The committee wants it to be clear that, with this legislation, it takes no view as to the existence or scope of current authority of FDA to require pediatric or other subpopulation studies. This limitation neither limits nor expands such authority, if it exists under current provisions in the FFDCA. The committee does regard the legislation as providing explicit statutory authority for FDA's current Pediatric Rule, however, except insofar as that rule is inconsistent with this legislation, as described above.

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

S. 2394 adds section 505B to the Federal Food, Drug, and Cosmetic Act to further improve the safety and efficacy of both drugs and biological products for children. As such, it has no application to the legislative branch.

VII. Regulatory Impact Statement

The legislation repeats the major provisions of existing regulation, with only two exceptions. Although the Pediatric Rule is currently under legal challenge, the rule is currently in force, and FDA has affirmed its intention to continue implementing the rule, which has been in place since 1999. Therefore, this legislation is unlikely to increase the costs associated with the development of drugs and biological products. Accordingly, S. 2394 is not expected to increase costs to government or to drug manufacturers.

VIII. Section-by-Section Analysis

Sec. 1. Pediatric labeling of drugs and biological products

Section 1 amends the FFDCA by adding a new section 505B to codify FDA's Pediatric Rule. With respect to drugs and biological products that are not yet approved, the legislation provides that each new drug application under section 505 of the FFDCA or biologics license application under section 351 of the PHSA for a new active ingredient, new indication (except for an orphan drug indication), new dosage form, new dosing regimen, or new route of administration must contain data adequate to assess the safety and effectiveness of the drug or biological product for its claimed indications, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. FDA may conclude that pediatric effectiveness may be extrapolated from studies in adults, usually supplemented with information about pediatric patients, if the course of a disease and the effects of a drug are sufficiently similar in adults and pediatric patients. FDA, on its own initiative or that of an applicant, may defer submission of these data in certain circumstances, provided the applicant submits certain information to FDA.

With respect to drugs and biological products that are already marketed, section 1 allows FDA, having made certain findings and under certain circumstances, to order the holder of an approved new drug application or biologics license application to submit data on safety and effectiveness and dosing and administration, after having provided the holder with notice and an opportunity for written response and a meeting, which may include an advisory committee meeting. To issue such an order, FDA must find that the absence of adequate labeling could pose significant risks to pediatric patients and that one of two additional conditions holds: (1) that the drug or biological product is used for a substantial number of pediatric patients for the labeled indications, or (2) that there is reason to believe that the drug or biological product would represent a meaningful therapeutic benefit over existing therapies for pediatric patents for 1 or more of the claimed indications.

In addition, for already-marketed drugs, section 1 requires that, before FDA may invoke the Pediatric Rule (if it is applicable), FDA must ask the manufacturer to conduct the study voluntarily under section 505A of the FFDCA or section 409I of the PHSA and that the company does not agree or that FDA does not receive a response. Section 1 also clarifies that it does not change the provisions in the BPCA that establish a process at NIH to contract for studies to gather pediatric information. Section 1 further clarifies that use of the NIH contracting process does not preclude FDA from using the Pediatric Rule to require that a manufacturer study an already-marketed drug. Section 1 provides that the rule may only be invoked to study approved indications, even if the written request is broader.

Section 1 provides that a drug or biological product for which a pediatric assessment is not filed by the date specified by FDA is deemed misbranded and is subject to an injunction or seizure action, but is not subject to criminal proceedings nor to withdrawal of approval as a new drug or revocation of its approved biologics license.

Section 1 requires FDA to grant a full waiver of the pediatric data requirement for a drug or biological product if (1) necessary studies are impossible or highly impractical; (2) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups; or (3) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, the drug or biological product is not likely to be used by a substantial number of pediatric patients, and the absence of adequate labeling would not pose significant risks to pediatric patients. Partial waivers are available for new drugs and biological products with respect to a particular pediatric subpopulation if any of these 3 reasons applies to that subpopulation, or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that pediatric subpopulation have failed. Under section 1, when the Secretary grants a full or partial waiver because there is evidence that the drug or biological product would be ineffective or unsafe in pediatric populations, the information must be included in the labeling for the drug or biological product.

Section 1 provides for meetings with a drug sponsor during the investigational new drug process to discuss plans and timelines of

pediatric studies or requests for waiver or deferral of pediatric studies. In addition, section 1 provides that the FDA's Pediatric Rule, except to the extent it is inconsistent with section 505B, shall be considered to implement section 505B.

Finally, section 1 states that section 505B does not affect whatever existing authority FDA has to require studies, in addition to those required under section 505B, of the safety and effectiveness of drugs and biological products in pediatric populations. It also states that FDA's authority, if any, to require studies for specific populations other than the pediatric population shall be exercised under the FFDCA as in effect on the day before the date of enactment of the legislation.

Sec. 2. Technical correction

IX. Additional Views of Senators Gregg and Frist

The incentives created by the BPCA and reauthorized in the Best Pharmaceuticals for Children Act (P.L. 107–109) to encourage new research into the proper use of medicines in children have been tremendously successful. In fact, in its January 2001 Status Report to Congress, the Food and Drug Administration (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 of August 31, 2002, FDA had issued 253 written requests for 580 pediatric studies. In just over four years, the pediatric exclusivity incentive has resulted in the submission of pediatric studies for 60 medicines used to treat a wide range of critical therapeutic areas, including juvenile rheumatoid arthritis (in which studies found that a higher dose was needed to treat pain in younger children than in adults), gastroesophageal reflux, hepatitis B, diabetes, heart disease, cancer, kidney disease, obsessive compulsive disorder, and many others. The pediatric testing incentive has also encouraged pharmaceutical companies to develop pediatric formulations (also resulting in better pediatric labeling information) for medicines used to treat HIV infection, malaria, seizures, asthma, and other serious diseases and conditions. Just as significantly, the pediatric exclusivity incentive that is the driving force behind these studies has resulted in increased investments in pediatric training and research infrastructure to support current and future pediatric research.

The Pediatric Rule cannot, and should not, work alone. Without the broader incentives provided by the Best Pharmaceuticals for Children Act, the rule alone would not be nearly as effective in encouraging research and providing important information regarding the use of pharmaceuticals in children. For example, under the rule, the FDA can only require pediatric studies for a claimed indication and cannot require the study of pediatric diseases that differ from the claimed or approved indication. For example, juvenile rheumatoid arthritis is a different disease than osteoarthritis and rheumatoid arthritis in adults. Therefore, if those adult indications are the only approved or claimed indications, the rule may not be invoked to encourage testing for children with the juvenile rheumatoid arthritis. Other diseases and infections that affect newborns and other pediatric populations but not adults include: bronchopulmonary dysplasia, croup, and bronchiolitis. While certain types of cancer affect adults but not children, medicines used to treat such adult cancers may prove to be promising treatments for different cancers that uniquely affect children (such as Wilms tumor and neuroblastoma).

Earlier this year, the pediatric exclusivity incentive was reauthorized with provisions to address off-patent drugs and certain on-

patent drugs for which written requests are declined. The bipartisan support that Congress and two administrations have shown for the pediatric testing incentive makes clear that FDA should continue its policy (as stated in the preamble to the rule) of only invoking the Pediatric Rule in "compelling circumstances" and should continue to grant deferrals, as appropriate, rather than allow the Pediatric Rule's testing mandate to delay the availability of new therapies in adults.

BILL FRIST.
JUDD GREGG.

X. 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):

* * * * * * *

FEDERAL FOOD, DRUG, AND COSMETIC ACT

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NEW DRUGS

SEC. 505. (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug.

(b)(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; [and (F)] *(F)* specimens of the labeling proposed to be used for such drug[.], *and (G) any assessments required under section 505B.* The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as ap-

propriate, on the inclusion of women and minorities in clinical trials required by clause (A).

* * * * * * *

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

(a) DEFINITIONS.— * * *

(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) * * *

* * * * * * *

(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).

* * * * * * *

(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), the holder agrees to the request, the studies are completed within such timeframe, and the reports thereof submitted in accordance with subsection (d)(2) or accepted an in accordance with subsection (d)(3)—

(1)(A)(i) * * *

* * * * * * *

(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)] *505(j)(5)(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)] *505(j)(5)(B)* shall be extended by a period of six months after the date the patent expires (including any patent extensions).

* * * * * * *

(h) RELATIONSHIP TO [REGULATIONS] *PEDIATRIC STUDY REQUIREMENTS.*—Notwithstanding any other provision of law, if any pediatric study is required [pursuant to regulations promulgated by the Secretary] *by a provision of law (including a regulation) other than this section* 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.

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SEC. 505B. PEDIATRIC LABELING OF DRUGS AND BIOLOGICAL PRODUCTS.

(a) NEW DRUGS AND BIOLOGICAL PRODUCTS.—

(1) IN GENERAL.—A person that submits an application (or supplement to an application)—

(A) under section 505 for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration; or

(B) under section 351 of the Public Health Service Act (42 U.S.C. 262) for a biological product license;

shall submit with the application the assessments described in paragraph (2).

(2) ASSESSMENTS.—

(A) IN GENERAL.—The assessments referred to in paragraph (1) shall contain data, gathered using appropriate formulations, that are adequate—

(i) to assess the safety and effectiveness of the drug, or the biological product licensed under section 351 of the Public Health Service Act (42 U.S.C. 262), for the claimed indications in all relevant pediatric subpopulations; and

(ii) to support dosing and administration for each pediatric subpopulation for which the drug, or the biological product licensed under section 351 of the Public Health Service Act (42 U.S.C. 262), is safe and effective.

(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT.—If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.

(3) DEFERRAL.—On the initiative of the Secretary or at the request of the applicant, the Secretary may defer submission of some or all assessments required under paragraph (1) until a specified date after approval of the drug or issuance of the license for a biological product if—

(A) the Secretary finds that—

(i) the drug or biological product is ready for approval for use in adults before pediatric studies are complete; or

(ii) pediatric studies should be delayed until additional safety or effectiveness data have been collected; and

(B) the applicant submits to the Secretary—

(i) a certified description of the planned or ongoing studies; and

(ii) evidence that the studies are being conducted or will be conducted with due diligence.

(b) MARKETED DRUGS AND BIOLOGICAL PRODUCTS.—

(1) IN GENERAL.—After providing notice and an opportunity for written response and a meeting, which may include an advisory committee meeting, the Secretary may by order require the holder of an approved application relating to a drug under section 505 or the holder of a license for a biological product under section 351 of the Public Health Service Act (42 U.S.C. 262) to submit by a specified date the assessments described in subsection (a) if the Secretary finds that—

(A)(i) the drug or biological product is used for a substantial number of pediatric patients for the labeled indications, and

(ii) the absence of adequate labeling could pose significant risks to pediatric patients; or

((B)(i) there is reason to believe that the drug or biological product would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for 1 or more of the claimed indications; and

(ii) the absence of adequate labeling could pose significant risk to pediatric patients.

(2) RELATIONSHIP TO OTHER PEDIATRIC PROVISIONS.—

(A) NO ASSESSMENT WITHOUT WRITTEN REQUEST.—No assessment may be required under paragraph (1) for a drug

subject to an approved application under section 505 unless—

(i) the Secretary has issued a written request for related pediatric studies under section 505A(d) or section 409I of the Public Health Service Act; and

(ii)(I) if the request was made under section 505A(d)—

(aa) the recipient of the written request does not agree to the request; or

(bb) the Secretary does not receive a response as specified under section 505A(d)(4)(A); or

(II) if the request was made under section 409I of the Public Health Service Act—

(aa) the recipient of the written request does not agree to the request; or

(bb) the Secretary does not receive a response as specified under section 409I(c)(2) of that Act.

(B) NO EFFECT ON OTHER AUTHORITY.—Nothing in this subsection shall be construed to alter any requirement under section 505A(d)(4) or section 409I of the Public Health Service Act. Subject to paragraph (2)(A), nothing in this subsection, section 505A(d)(4), or section 409I or 499 of the Public Health Service Act shall be construed to preclude the Secretary from exercising the authority of the Secretary under this subsection.

(c) DELAY IN SUBMISSION OF ASSESSMENTS.—If a person delays the submission of assessments relating to a drug or biological product beyond a date specified in subsection (a) or (b)—

(1) the drug of biological product—

(A) shall be deemed to be misbranded;

(B) shall be subject to action under sections 302 and 304; and

(C) shall not be subject to action under section 303; and

(2) the delay shall not be the basis for a proceeding to withdraw approval for a drug under section 505(e) or revoke the license for a biological product under section 351 of the Public Health Service Act (42 U.S.C. 262).

(d) WAIVERS.—

(1) FULL WAIVER.—At the request of an applicant, the Secretary shall grant a full waiver, as appropriate, of the requirement to submit assessments under subsection (a) or (b) if—

(A) necessary studies are impossible or highly impracticable;

(B) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups; or

(C)(i) the drug or biological product—

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

(II) is not likely to be used for a substantial number of pediatric patients; and

(ii) the absence of adequate labeling would not pose significant risks to pediatric patients.

(2) PARTIAL WAIVER.—At the request of an applicant, the Secretary shall grant a partial waiver, as appropriate, of the requirement to submit assessments under subsection (a) with respect to a specific pediatric subpopulation if—

(A) any of the grounds stated in paragraph (1) applies to that subpopulation; or

(B) the applicant demonstrates that reasonable attempts to produce a pediatric formulation necessary for that subpopulation have failed.

(3) LABELING REQUIREMENT.—If the Secretary grants a full or partial waiver because there is evidence that a drug or biological product would be ineffective or unsafe in pediatric populations, the information shall be included in the labeling for the drug or biological product.

(e) MEETINGS.—The Secretary shall meet at appropriate times in the investigational new drug process with the sponsor to discuss background information that the sponsor shall submit on plans and timelines for pediatric studies, or any planned request for waiver or deferral of pediatric studies.

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PUBLIC HEALTH SERVICES ACT

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SEC. 351. (a)(1) No person shall introduce or deliver for introduction into interstate commerce any biological product unless—* * *

(2)(A) The Secretary shall establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses.

(B) PEDIATRIC STUDIES.—A person that submits an application for a license under this paragraph shall submit to the Secretary as part of the application any assessments required under section 505B of the Federal Food, Drug, and Cosmetic Act.

[(B)] (C) The Secretary shall approve a biologics license application— * **

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