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PEDIATRIC RESEARCH EQUITY ACT OF 2003

JUNE 27 (legislative day, JUNE 26), 2003.—Ordered to be printed

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

R E P O R T

together with

ADDITIONAL VIEWS

[To accompany S. 650]

The Committee on Health, Education, Labor, and Pensions, to which was referred the bill (S. 650) to authorize the Food and Drug Administration to require certain research into drugs used in pediatric patients, having considered the same, reports favorably thereon with an amendment and recommends that the bill (as amended) do pass.

CONTENTS

I. PURPOSE AND NEED FOR LEGISLATION

As part of the Food and Drug Administration Modernization Act ("FDAMA") of 1997 (Pub. L. No. 105–115), Congress established new incentives for drug manufacturers to conduct pediatric research. These pediatric exclusivity provisions were reauthorized and enhanced in 2002 by the Best Pharmaceuticals for Children

Act ("BPCA") (Pub. L. No. 107–109). The legislation works by providing an incentive of 6 months of additional market exclusivity for sponsors in exchange for the voluntary performance of clinical studies of drugs in the pediatric population in response to a written request from FDA. The BPCA also created programs administered by the NIH to issue grants and contracts for researchers to conduct additional pediatric studies with privately donated and publicly appropriated funds. These laws have made headway in rectifying the historical lack of clinical study data and labeling information on the appropriate use of medicines in children.

Notwithstanding the progress that these prior pediatric initiatives have produced, at least sixty-two percent of drugs on the market remain unstudied and labeled for use in children.[1] However, that number reflects research in accordance with the old Pediatric Rule. The authority for the new Pediatric Research Authority is based on the percentage of drugs projected to need pediatric labeling in light of ongoing commitments and research. Further action is needed to ensure that medications are adequately studied and labeled for use in children. The committee has approved this legislation to complement the existing voluntary pediatric exclusivity and NIH study provisions by providing FDA with new, unprecedented authority to require that drug manufacturers conduct pediatric studies and submit pediatric assessments to FDA. On December 2, 1998, FDA published in the Federal Register (63 FR 66632–66672) a final regulation known as the "Pediatric Rule" asserting the authority to mandate pediatric testing in certain circumstances. On October 17, 2002, a Federal court held that FDA lacked the statutory authority to promulgate the Pediatric Rule, and declared the Rule invalid. The legislation reported by the committee now provides FDA with statutory authority to require pediatric studies in certain defined circumstances.

There is a need to provide FDA legislative authority to require pediatric testing because of the particular importance of pediatric drug labeling. At the same time, the committee recognizes that appropriate safeguards must accompany this special grant of mandatory testing authority. The committee intends that the new legislation, the pediatric exclusivity incentive provisions, and the NIH study provisions of the BPCA will work in a comprehensive and complementary fashion. This legislation not only establishes provisions regarding new drugs but also provides a default mechanism by which FDA can require pediatric studies where the voluntary incentives and available contracts and grants have not produced needed pediatric treatment information.

Children suffer from many of the same diseases as adults and are often treated with the same medicines. Yet certain medicines have not been adequately 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 extrapolating safety or effectiveness for children for medicines found to be safe and effective in adults may not be appropriate. The lack of pediatric studies and

[1] "Testing Medications in Children," by Robert Steinbrook, M.D. October 31, 2002. The New England Journal of Medicine.

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.

There are a variety of reasons why greater pediatric testing has not been conducted historically despite its importance as a matter of public health. Drug sponsors have often lacked incentives to develop drugs for pediatric use because of the comparatively small size of the pediatric market for most products. Designing and completing pediatric research trials can also present heightened scientific, ethical, and logistical challenges, from recruiting sufficient study participants to obtaining consent from parents or guardians to developing formulations of a drug that can be administered to younger patients. Pediatric research can also present greater risks of legal liability for sponsors due, for example, to the tolling of the statute of limitations as applied to children, as well as other reasons. In the face of these obstacles, 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 drug sponsors 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 manufacturers' voluntary development of 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 a Pediatric Rule by regulation claiming authority to require manufacturers to submit needed pediatric testing. Before FDA finalized the Pediatric Rule Congress enacted the Better Pharmaceuticals for Children Act as part of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105–115). This act created a new section 505A of the FFDCA to provide a market incentive of 6 months of additional exclusivity to drug sponsors for completing and submitting studies of medicines in children in response to a written request from FDA for the studies. The studies must fairly respond to FDA's written request and be conducted in accordance with a subsequent written agreement with the FDA, or in the absence of such a written agreement in accordance with commonly accepted scientific principles and protocols. The 6-month pediatric 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 new incentives were intended to address the systemic disincentives that had previously existed to conducting pediatric studies. The results of the pediatric exclusivity incentives to date are

highly encouraging. As FDA reported to Congress in 2001, the incentives have "done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date."

Based in part on FDA's report, 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.

At the same time that the pediatric exclusivity provisions were being put in place by legislation, FDA proceeded with rulemaking proceedings for the Pediatric Rule, which the agency finalized in 1998, and which became effective in 1999. The rule remained in effect until October 17, 2002, when a Federal court in the District of Columbia in the *Association of American Physicians and Surgeons, Inc.* v. *FDA* case held that the rule exceeded FDA's existing statutory authority, and declared the rule invalid. In December 2002, the American Academy of Pediatrics and the Elizabeth Glaser Pediatric AIDS Foundation, which had participated as amici curiae in the district court, were permitted to intervene and to appeal the case to the U.S. Court of Appeals for the District of Columbia Circuit.

Prior to the court's decision, 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 was required to contain certain data, unless there were grounds for a waiver or deferral. Absent a waiver or deferral, the application was required to 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 was safe and effective.

With respect to an already-marketed drug or biological product that was used in a substantial number of pediatric patients or that provided 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 allowed FDA in these compelling circumstances or "high priority" situations to require the product's manufacturer or manufacturers to submit an application containing data adequate to assess whether the drug was 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 was also able to require the manufacturer or manufacturers to develop a pediatric formulation for a drug product that represented a meaningful therapeutic benefit over existing treatments for pediatric populations for whom a pediatric formulation was necessary, unless the manufacturer dem-

onstrated that reasonable attempts to produce a pediatric formulation necessary for that age group had failed.

Full and partial waivers could also be obtained for both new and already marketed products. A drug or biological product for which a full or partial waiver was granted because there was evidence that the product would be ineffective or unsafe in pediatric populations was required to be labeled with that information.

The Pediatric Rule was intended to work as a safety net to (or as a backstop to) pediatric exclusivity. While the FDAMA was intended to provide a substantial incentive for sponsors to conduct some pediatric studies, the rule was intended to increase the number of drug and biological products that have adequate labeling. Because of the voluntary nature of the incentive provided by the FDAMA the possibility arose that many drugs may still have remained unstudied for pediatric uses.

The Pediatric Rule was 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 was broader than pediatric exclusivity because the rule covered biological products approved under section 351 of the Public Health Service Act 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 was broader than pediatric exclusivity because it covered subsequent indications and pediatric subpopulations that pediatric exclusivity, with its associated contracting process at the Foundation and NIH, may not. For example, if FDA did not include studies of newborns and infants in a written request for a drug under the pediatric exclusivity provision (because FDA believed it would not be ethical or feasible to study these populations until older populations had been studied), pediatric exclusivity was generally not available to ensure that the drug would be studied for these children if subsequent data made it apparent the product was efficacious in the older population and warranted studies in the younger populations. However, FDA could have used 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, could have invoked the rule to require that the new indication be studied.

In some respects, the Pediatric Rule was narrower than pediatric exclusivity and its associated contracting process at the Foundation and NIH. For example, the rule could only have been used for an indication for which the drug was approved or approval was being 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 applied only to drugs that would be used by a substantial number of pediatric patients or that would 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.

Even given these differences in scope, the Pediatric Rule and the pediatric exclusivity provision worked together to ensure that a drug or biological product would be tested in and labeled for children when appropriate. When their scopes overlapped, Congress provided in section 505A(h) of the FFDCA that any pediatric studies required by regulation also satisfied the requirements for market exclusivity. There were many drugs for which the rule and the incentive worked together successfully to encourage a drug company to respond affirmatively to FDA's request for pediatric studies.

But the rule and pediatric exclusivity did not always both apply to a drug. 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, manufacturers submitted, or would have been required to submit, studies in one or more pediatric age groups (the remaining received complete waivers, typically as a result of safety concerns regarding the testing of the drug in children or because the drug's approved indication was not for a childhood disease). As of June 5, 2003, 129 submitted applications contained complete or partial pediatric use information. Because pediatric exclusivity incentives were not involved in these applications and these were not drugs primarily developed for children, FDA attributes 67 of these submissions to the Pediatric Rule alone. By comparison, FDA reports that as of June 2, 2003, 72 drugs have been granted exclusivity and 9 have been denied exclusivity, with 49 of these drugs currently labeled for use in the pediatric population. It is therefore clear that the Pediatric Rule and exclusivity have worked together to improve 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.

At the same time, the court's decision in the Association of American Physicians and Surgeons case invalidating the rule highlights the tension between a mandatory study requirement and the basic operation of the FFDCA, which leaves it to drug sponsors to determine the claims they wish to make for a product. In that case, the court held that FDA lacked authority under the existing FFDCA to require that drug sponsors conduct studies or develop formulations for claims or patient populations that the sponsor is not seeking to include in labeling for its product. In the court's words, FDA "has repeatedly stated that it may only regulate claimed uses of drugs, not all foreseeable or actual uses." The court further stated that it is a "long-established foundation of federal food and drug law" that manufacturers determine the intended uses of a product through the representations they make for the product.

This legislation responds to the court's holding by providing FDA new statutory authority to require pediatric assessments. The authority granted by the legislation tracks many elements of the former Pediatric Rule to ensure that the progress produced by the incentive and the Pediatric Rule will continue. There is a compelling basis for providing FDA such authority because of the importance of ongoing pediatric research. At the same time, the legislation establishes clear limitations on the new authority to require pediatric assessments to ensure that the unique needs of the pedi-

atric population continue to be met by the co-existence of the incentive and the mandate.

II. SUMMARY

1. The legislation gives FDA new statutory authority to require certain pediatric tests

The legislation amends the Federal Food, Drug, and Cosmetic Act (FFDCA) by adding a new section 505B, which provides FDA with unprecedented statutory authority to require that sponsors submit assessments regarding the use of drugs in pediatric patients in certain specified circumstances. 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, unless the Secretary requires otherwise by rulemaking), 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 in compelling circumstances, having made certain findings and under certain conditions, to require that all holders of approved applications for a product submit data on safety and effectiveness and dosing and administration, after having provided the holders 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 the FDA finds that necessary studies are impossible or highly impractical (because, for example, the number of such pediatric patients is so small or geographically dispersed); if there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in the 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. Also, if the Secretary grants a partial waiver because it is not possible to produce a pediatric formulation, the waiver will only cover the pediatric age groups requiring that formulation.

For new drugs, the Secretary, on his own initiative or by request from the applicant, may defer the submission of some or all of the assessments required under the amendment until a specified date after the approval of the drug or after the license for the biological product is granted if two requirements are met. The first is met if the Secretary finds that the drug is ready for approval for use in

adults before the pediatric studies are complete, or the pediatric studies should be delayed until additional safety or effectiveness data have been collected, or there is another appropriate reason for deferral. The second is met if the applicant has submitted to the Secretary certification for the grounds for deferring, a description of the planned or ongoing studies, and evidence that the studies are being conducted or will be conducted with due diligence at the earliest possible time.

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.

2. The legislation clarifies the interaction of the new pediatric study requirements with the pediatric exclusivity provisions when applied to already-marketed drugs

The legislation provides that FDA may only impose pediatric study requirements for already marketed drugs when the pediatric exclusivity incentives provisions of section 505A of the FFDCA and the NIH grant and contract programs of sections 409I and 499 of the PHSA have failed to yield necessary pediatric information. FDA must first allow an opportunity for these other BPCA mechanisms to work before invoking the new pediatric study requirements for marketed drugs. The new pediatric assessment requirement serves as a safety net to ensure that certain critical studies are performed and labeling adopted for marketed drugs if the other mechanisms from the BPCA do not work. The pediatric assessment requirement is the default, and not the first option. For already-marketed drugs, the legislation requires that, before FDA may invoke the Pediatric Research Authority (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. In addition, no later than 60 days after making such determination, FDA must certify that there are insufficient funds to complete the study under sections 409I and 499 and publish in the Federal Register that no contract or grant has been awarded.

This requirement is not inconsistent with current FDA practice.

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 may be considered misbranded and subject to relevant enforcement action. The Committee recognizes that the agency has generally found seizure of a drug or biological product to be an unsatisfactory remedy from a public health perspective because it denies adequately studied populations access to safe and effective medicines. As a result, the Committee intends for seizure of a drug or biological product to be used rarely, if at all, as a remedy for failure to conduct required pediatric studies. This legislation makes clear that the failure to submit required assessments shall not be the basis for criminal proceedings, withdrawal of approval as a new drug, or revocation of an approved biologics license. Apart from

those specifically exempted, however, all of the Secretary's misbranding enforcement authorities are available. The Secretary, as always, has discretion to choose the appropriate enforcement action, as well as discretion to choose whether to bring an enforcement action.

4. The legislation does not provide FDA with authority to require studies or labeling for other populations or uses

The legislation states that section 505B does not provide FDA with any authority to require pediatric assessments, assessments regarding other populations, or assessments regarding other uses of drugs or biological products except as described in section 505B. As the Federal court stated in the case challenging the legality of FDA's former Pediatric Rule (Association of American Physicians and Surgeons, Inc. v. FDA), it is the long-established foundation of our food and drug laws that drug sponsors determine the "intended uses" of a product, and that FDA does not regulate foreseeable or actual uses of a product that the sponsor does not claim. The legislation makes clear, however, that the new authority it provides FDA does not go beyond the specified limits of section 505B.

III. History of Legislation and Votes in Committee

On March 18, 2003, Senator DeWine, for himself and Senators Clinton, Gregg, Dodd and Kennedy introduced S.650, to amend the Federal Food, Drug, and Cosmetic Act to authorize the FDA to require certain research into drugs used in pediatric patients if the voluntary mechanisms fail.

On March 19, 2003, the committee held an executive session to consider S.650. Senator Gregg offered an amendment that the committee passed by a vote of 11–10. The committee approved S.650, as amended, by a unanimous vote of 21–0.

A. Amendment adopted

The Committee adopted 1 amendment by a vote of 11–10. This amendment ensures the integration of the pediatric study mechanisms under the BPCA and this new authority for the FDA. The amendment further integrates the two programs by conforming the dates on which the programs require reauthorization (see for example section 505A(n) of the BPCA). By ensuring the co-existence of both the incentive mechanisms and the mandate, this amendment ensures FDA has every tool available to best protect children.

IV. Explanation of Bill and Committee Views

New authority for FDA to require pediatric assessments

The legislation amends the FFDCA by adding a new section 505B.

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 statutory authority to require that already-marketed drugs and biological products be tested in children for

approved indications in compelling circumstances 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 patients 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. Deferrals are appropriate where either (1) the product is ready for use in adults before pediatric studies are or will be complete, or (2) there are ethical or clinical grounds to delay some or all of the pediatric studies until additional safety or effectiveness data are available.

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 (in that age group) 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 that pediatric age group), (3) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients (in that age group), the drug or biological product is not likely to be used by a substantial number of pediatric patients (in that age group), and the absence of adequate labeling would not pose significant risks to pediatric patients, or (4) attempts to develop a formulation needed for certain age groups have failed. 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. If a partial waiver is granted based on the ground that it is not possible to develop a pediatric formulation, the waiver must cover only the pediatric groups requiring that formulation.

Special provisions for already marketed drugs

The legislation states that FDA may not require pediatric assessments for already marketed drugs unless FDA first issues a written request under the pediatric exclusivity provisions of section 505A and subsequently issues a request for contract or grant proposals under the sections 409I or 499 of the Public Health Service Act, as modified by the BPCA, before FDA may invoke the Pediatric Research Authority (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 pe-

diatric information. Section 1 further clarifies that use of the NIH contracting process does not preclude FDA from using the Pediatric Research Authority ("PRA") to require that a manufacturer study an already-marketed drug. Section 1 provides that the rule PRA may only be invoked to study approved indications, even if the written request is broader.

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.

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.

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 restrictions on the Secretary's authority to invoke the PRA, including a restriction on use of the authority before the Secretary has asked the company to conduct the studies voluntarily and the company has either declined or failed to respond.

This provision makes clear that before invoking section 505B, FDA must first ask a company to conduct the study of an already-marketed drug voluntarily and these requests must fail to yield the specified studies within the specified amount of time when the company does not agree or FDA has not received a response. FDA will then be able to invoke the new pediatric research authority. For already marketed drugs, the committee views section 505B as a provision that may apply only when the other available voluntary mechanisms have been used but have not resulted in the necessary studies.

Enforcement

The legislation provides that FDA has misbranding authority with respect to 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 relevant enforcement action. The committee stresses that seizure is generally an unsatisfactory remedy from a public health perspective because it denies adequately studied populations access to safe and effective medicines. As a result, the committee intends for seizure to be used rarely, if at all, as a remedy for failure to conduct required pediatric studies. This legislation makes clear that the failure to submit required assessments shall not be the basis for criminal proceedings, withdrawal of approval as a new drug, or revocation of an approved biologics license. The committee intends for FDA to enforce the mandate by using its injunction authority without affecting the availability of otherwise safe and effective products for other patients.

No effect on current authority

The legislation states that section 505B does not provide FDA with any authority to require pediatric assessments, or assessments of other populations or uses, except as provided in section 505B. The committee notes the court's holding in Association of American Physicians and Surgeons, Inc. v. FDA that FDA lacks the current authority to require pediatric assessments. This legislation does not expand FDA's current authority except as specifically enumerated in section 505B.

Integration with other pediatric provisions

The legislation is integrated with the pediatric exclusivity provisions of section 505A of the FFDCA. The committee views the two sections as working together in a complementary fashion. The committee understands that section 505A is set to be reviewed for reauthorization in 2007, and intends that the new section 505B be reviewed for reauthorization at the same time.

V. Regulatory Impact Statement

The committee has determined that there will be minimal increases in the regulatory burden imposed by this bill.

VI. Application of Law to the Legislative Branch

S. 650 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. 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.

VIII. SECTION-BY-SECTION ANALYSIS

Sec. 1. Short title

Section 1 entitles the Act the "Pediatric Research Equity Act of 2003."

Sec. 2. Pediatric labeling of drugs and biological products

Section 2 amends the FFDCA by adding a new section 505B, which grants FDA new authority to mandate pediatric data under certain circumstances in order to reinforce the existing provisions for generating pediatric information under the BPCA.

Section 505B(a): New Drugs and Biological Products

Section 505B(a)(1): With respect to new applications for drugs and biological products, subsection (a)(1) 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—see section 505B(g)), new dosage form, new dosing regimen, or new route of administration must include assessments containing pediatric data.

Section 505B(a)(2): The assessments required by subsection (a)(1) 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, however, that pediatric effectiveness can 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 or biological product are sufficiently similar in adults and pediatric patients. FDA may also determine that studies are not needed in each pediatric subpopulation if data from one subpopulation can be extrapolated to another subpopulation.

Section 505B(a)(3): FDA may, on its own initiative or that of an applicant, defer submission of pediatric data in certain circumstances, provided the applicant submits certain information to FDA. FDA may issue a deferral if it finds that the product is ready for approval for use in adults before pediatric studies are complete, pediatric studies should be delayed until additional safety or effectiveness data have been collected, or for other appropriate reasons. In order to secure a deferral, the applicant must submit to FDA certification of the grounds for deferring assessments, a description of planned or ongoing studies, and evidence that the studies are being or will be conducted diligently and as soon as possible.

Section 505B(a)(4): FDA shall grant, as appropriate, a full waiver of the pediatric data requirement for a new drug or biological product if: (1) necessary studies are impossible or highly impracticable; (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, and the drug or biological product is not likely to be used by a substantial number of pediatric patients. FDA shall grant, as appropriate a partial waiver of the pediatric data requirement for a new drug or biological product with respect to a particular pediatric subpopulation if any of these 3 reasons applies to that sub-

population, or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that pediatric subpopulation have failed. If a full or partial waiver is granted because of evidence that the product would be ineffective or unsafe in the pediatric population or a pediatric subpopulation, that information shall be included in the product's labeling.

Section 505B(b): Marketed Drugs and Biological Products

Section 505B(b)(1): With respect to drugs and biological products that are already marketed, FDA may, only after making certain findings and under limited circumstances, require the holder of an approved new drug application or biologics license application to submit data on safety and effectiveness, dosing, and administration as described in subsection (a)(2). Before issuing such an order, FDA must find 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. FDA may require this submission only after providing the holder with notice and an opportunity for written response and a meeting, which may include an advisory committee meeting.

Section 505B(b)(2): FDA shall grant, as appropriate a full waiver of the pediatric data requirement for an already marketed drug or biological product if: (1) necessary studies are impossible or highly impracticable; or (2) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups. FDA must grant a partial waiver of the pediatric data requirement for specific pediatric subpopulations if the applicant certifies and FDA finds that: (1) necessary studies are impossible or highly impracticable for a specific subpopulation; (2) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that subpopulation; (3) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for that subpopulation, the product is not likely to be used by a substantial number of patients in that subpopulation, and the lack of adequate labeling does not pose significant risks to pediatric patients; or (4) the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that pediatric subpopulation have failed. If a waiver is granted because FDA finds it is not possible to develop a pediatric formulation of the product, the waiver will only over the pediatric groups requiring that formulation. If a full or partial waiver is granted because the product would be ineffective or unsafe in the pediatric population or a pediatric subpopulation, that information shall be included in the product's labeling.

Section 505B(b)(3): Subsection (b)(3) clarifies that FDA may only impose the pediatric study requirements for already marketed drugs when the provisions of section 505A in the FFDCA, offering pediatric exclusivity incentives, and the NIH grant and contract programs of sections 409I and 499 of the PHSA, have both proven to be unsuccessful in producing the necessary pediatric information. If requests are made on the two provisions, and the secretary determines that there are insufficient funds under sections 409I

and 499 of the PHSA, the assessment may be required. The assessment may also be required if the Secretary certifies that no grant has been awarded and not less than 270 days have passed since the certification there are sufficient funds to conduct the study. This precondition ensures that the existing provisions of the BPCA will be utilized and establishes required pediatric studies as a default. Before invoking the agency's new authority to mandate pediatric studies under this Act, FDA must first have made a written request for the manufacturer to conduct the study voluntarily under section 505A of the FFDCA or section 409I of the PHSA, to which the manufacturer either did not agree or that FDA did not receive a timely response. Subsection (b)(3) also clarifies that the mandatory pediatric study provisions of this Act do not alter the provisions in the BPCA that establish a process at NIH to contract for studies to gather pediatric information. Before requiring submission of pediatric data of an already marketed drug product, subsection (b)(3) requires FDA to certify either that insufficient funds are available to contract for studies, or that sufficient funds are available but no contract or grant has been awarded within the specified time frame.

Section 505B(c): A product will be considered to offer a "meaningful therapeutic benefit" over existing therapies if FDA determines that it would represent a significant improvement in the treatment, diagnosis, or prevention of a disease compared with already marketed products labeled for that use in the relevant pediatric subpopulation, or that it is in a class of products or is used for an indication for which there is a need for additional options.

Section 505B(d): FDA has misbranding authority over a drug or biological product for which a pediatric assessment is not filed by the date specified by FDA but FDA does not have the ability to bring criminal proceedings or to withdrawal of approval as a new drug or revocation of an approved biologics license.

Section 505B(e): FDA shall meet with the sponsor of a drug or biological product at appropriate times during the investigational process to discuss plans and timelines for pediatric studies or requests for waivers or deferrals of pediatric studies.

Section 505B(f): Subsection (f) clarifies that this Act provides no authority for FDA to require pediatric studies of any drug or biological product, or studies regarding any other populations or uses of a drug or biological product, except under the conditions provided for in this Act.

Section 505B(g): The pediatric data requirements of this Act do not apply to any drug for an indication for which "orphan" drug designation has been granted under Section 526 of the FFDCA, unless FDA determines otherwise by regulation.

Section 505B(h): Subsection (h) ties the new authority provided under this Act to the pediatric exclusivity provisions codified at section 505A of the FFDCA. This Act provides, in essence, that the new authority to require pediatric studies shall only remain in effect so long as the pediatric exclusivity provisions also remain in effect. The pediatric exclusivity provisions currently have a sunset date of October 1, 2007.

Sec. 3. Technical corrections

Sec. 4. Effective date

Section 4 makes the Act effective on October 17, 2002.

IX. ADDITIONAL VIEWS

ADDITIONAL VIEWS OF SENATORS DEWINE, KENNEDY, DODD, CLINTON, MIKULSKI, MURRAY, AND REED

Relationship between this legislation, the Pediatric Rule, and pediatric exclusivity

The report asserts that the Pediatric Rule was intended to work as a "backstop" to pediatric exclusivity. This assertion is clearly incorrect, particularly in relation to new drugs and biological products. The final rule states that it is "designed to ensure that new drugs and biological products contain adequate pediatric labeling for the approved indications at the time of, or soon after, approval. The final rule establishes a presumption that all new drugs and biologics will be studied in pediatric patients." (Federal Register/ Vol. 63, No. 231, December 2, 1998, p. 66634) Neither the intent conveyed by FDA nor FDA's implementation of the rule supports the report's contention that the rule was intended to work as a "backstop" to pediatric exclusivity or to be employed only to fill the gaps in coverage left by the exclusivity.

The report also incorrectly asserts that the authors of this legislation introduced S. 650 "to authorize the FDA to require certain research into drugs used in pediatric patients if the voluntary mechanisms fail." While this assertion may hold for already-marketed products, it is simply incorrect in relation to new drugs and biological products. Nothing in the bill requires FDA to wait until the voluntary mechanisms have failed before invoking the pediatric studies requirement for new drugs or biologics.

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ADDITIONAL VIEWS OF SENATORS KENNEDY, DODD, CLINTON, MIKULSKI, MURRAY, AND REED

Enforcement

The report states that FDA has misbranding authority with respect to a drug or biological product for which a pediatric assessment is not filed by the date specified by FDA. While this statement helps to clarify that the bill is intended to give FDA the authority to deem a product misbranded solely on the basis that an assessment was not submitted in accordance with the requirements of the legislation, it is not a substitute for, and must be accompanied by, a modification to the legislation.

The legislation states that if a sponsor fails to submit an assessment, the product may be considered misbranded. The use of the word "may" in relation to the ability of FDA to determine a product to be misbranded or adulterated is an anomaly in the FFDCA. The use of "may be considered misbranded" rather than "shall be deemed misbranded", as occurs elsewhere in the FFDCA, may create uncertainty about the Committee's intent to give FDA full and unambiguous authority to enforce the requirements of S. 650.

The Committee clearly intends for a court to interpret this language as giving FDA new misbranding authority, the use of the word "may" creates a risk that a court will apply an interpretation that would be contrary to the Committee's intent. Given that the impetus for this legislation was to unequivocally provide FDA with the exact statutory authority to require pediatric studies that the federal district court ruled in October 2002 it lacked, it is critical that the statutory language be modified and that "may" be replaced with "shall" to comport with the term used elsewhere in the FFDCA.

In addition, the report incorrectly asserts that FDA has misbranding authority when a pediatric assessment is not filed by the date specified by FDA. In accordance with the plain language of the legislation, any misbranding authority extends to bringing an enforcement action for failure to comply with any of the requirements of the legislation related to the submission of assessments or requests for approval of a pediatric formulation, not just timeliness.

Effective date

We are also concerned that the current effective date in S. 650 may allow significant numbers of pediatric studies to be lost in the gap between the requirements of the Pediatric Rule and the requirements of this legislation, despite the stated intent of the Committee that the Rule and the legislation be "seamless." Because the current language applies the testing requirement to drug applications submitted on or after October 17, 2002, we are concerned that several categories of applications will not be subject to the require-

ments of S. 650. For example, the legislation may be incorrectly read as not applying to applications submitted to FDA before October 17, 2002, and pending before FDA on October 17, 2002. Also, it is not clear that sponsors with applications approved before October 17, 2002, that made commitments under the Rule to conduct pediatric studies at a later date would have to honor those commitments. According to FDA, in just the category of deferred studies alone, 192 studies may be lost. Also according to FDA, in total, more than 300 pediatric studies will be lost if the effective date of the legislation is not corrected to ensure a seamless transition of the pediatric testing requirement from the Pediatric Rule to this legislation.

We have raised the need to modify this provision, and the enforcement provision discussed previously, to ensure that S. 650 fully and seamlessly restores the protections of the 1998 Pediatric Rule. Although we would have preferred that these two issues had been resolved in the language of the bill reported out of the Committee, we are amenable to addressing them in a manager's amendment prior to full Senate consideration of this legislation. We expect that we can address and resolve these issues quickly so that this important legislation may be considered by the full Senate without further delay.

Sunset

The bill was amended by a majority of the committee to sunset the bill's requirements on October 1, 2007, the same date the pediatric exclusivity authority is sunset. The report asserts that this "integration" of the two programs ensures their co-existence, which "ensures FDA has every tool available to best protect children."

Some proponents of the amendment may believe that it ensures that the pediatric exclusivity provision will be reauthorized in 2007. They may also believe, as we do, that the pediatric exclusivity provision has been extremely beneficial to children's health and that it deserves serious consideration for reauthorization in 2007.

But it is simply not the case that requiring the reauthorization of the pediatric assessment authority in 2007 promotes children's health. Instead, it seriously undermines the goal of the legislation, which is to address the uncertainty surrounding pediatric drug testing and to eliminate the threat that children's protections may lapse. In addition, the requirement for reauthorization leaves open the possibility that the pediatric assessment requirement will be weakened, or will be eliminated altogether. This possibility shows the amendment as an anathema to the purpose of the legislation and the purpose of protecting children.

Adults can count on FDA to assure trials for drug safety and efficacy without returning to Congress every 5 years for that assurance. Because of the amendment, children will be denied that same protection. Once again they will have to seek legislation to assure what adults now take for granted, that the drugs we use have been shown to be safe and effective for us to use.

Intended use

FDA's Pediatric Rule to require the study in children of drugs and biological products for their approved uses was held to be invalid by a federal district judge. The report makes several references to and quotations from this ill-considered and obviously errant decision about how intended uses of FDA-regulated products are made and about the scope of FDA's authority under the FFDCA. We write to clarify these issues because we believe that both the court and the report fundamentally misconstrue the authority of FDA, and that FDA already has the authority to require studies on subpopulations that will use a drug. Although the district court concluded that FDA did not have sufficient authority to require studies on off-label uses, it ignored, without discussion, FDA's determination that use in children is not an "off-label" use, just as use in women is not an "off-label" use. It is a use in an expected, major subpopulation, which may raise some different questions than use in other populations. In choosing to ignore the agency's central argument in support of its authority, the decision fails to answer the question of the agency's pre-existing authority to require pediatric studies, or studies on other subpopulations.

The report also asserts, relying exclusively on the district court opinion, that it is "the long-established foundation of our food and drug laws" that drug sponsors determine the "intended uses" of a product, and that FDA does not regulate foreseeable or actual uses of a product that the sponsor does not claim." Although this assertion is often found in the arguments of the pharmaceutical industry in attempts to weaken FDA's long-standing authority, it is contradicted by decades of FDA practice and numerous judicial opinions from higher courts.

When determining a product's intended use, it is well-established that FDA may consider evidence other than express claims that a product is intended to have a certain effect. Indeed, the text of the FFDCA, longstanding FDA regulations, the legislative history of the Medical Device Amendments of 1976, appeals court decisions, and FDA's regulatory practice fully support this view.

For example, sections 201(g)(1)(C) and (h)(3) of the FFDCA make "intended" effects, not "market claims," the decisive factor. Although market claims are one important way to establish a product's intended effect, other circumstances can establish a product's intended effect, and nothing in the text of the operative definitions bars FDA from relying on such evidence.

Longstanding FDA regulations provide that "intended use" refers to "the objective intent of the persons legally responsible for labeling," and may be determined not only by "labeling claims" and "advertising matter," but also by other "oral or written statements" made by persons legally responsible for the labeling; "the circumstances surrounding the distribution of the article"; "the circumstances that the article is, with the knowledge of [the manufacturer], * * * offered and used for a purpose for which it is neither labeled nor advertised"; and (4) evidence that "a manufacturer knows, or has knowledge of facts that would give him notice" that a drug or device "is to be used" for purposes other than those for which the manufacturer offered the product. 21 CFR 201.128 and 801.4.

A House report on the Medical Device Amendments of 1976, Pub. L. No. 94–295, supports the view that "intended" effects are not limited to manufacturer claims. That report specifically rejected the proposition that a claim is dispositive and explained that the Secretary "may consider actual use of a product in determining whether or not it is a device." H.R. Rep. No. 853, 94th Cong., 2d Ses. 14 (1976).

Many appeals courts have agreed that a manufacturer's intent with respect to effects or use may be determined on the basis of all relevant circumstances, including consumer use, not simply a manufacturer's market claims. *National Nutritional Foods Ass'n* v. *Mathews*, 557 F.2d 325, 334 (2d Cir. 1977) (intent may be determined from any relevant source, including consumer use); *United States* v. *An Article * * * Consisting of * * * 216 Cartoned Bottles*, 409 F.2d 734, 739, 742 (2d Cir. 1969) (the intended use of a product may be determined from its label, accompanying labeling, promotional material, advertising and any other relevant source, including consumer use); *United States* v. *Storage Spaces Designated Nos. "8" & "49"*, 777 F.2d 1363, 1366 (9th Cir. 1985), (manufacturer intent may be derived from any relevant source), cert. denied, 479 U.S. 1086 (1987); *Action on Smoking & Health* v. *Harris*, 655 F.2d 236, 239–240 (D.C. Cir. 1980) (consumer use can be relevant in determining manufacturer intent).

Finally, in its administration of the FFDCA, FDA has treated products as drugs or devices, despite the absence of explicit market claims. Among other products, FDA has treated as drugs or devices: (1) cosmetics containing hormones based on the absence of any legitimate cosmetic purpose for the hormones; (2) toothpaste containing fluoride because fluoride is widely accepted as an anticavity agent and affects the structure of the tooth; (3) thyroid-containing food supplements based on the recognized physiological effects of thyroid products; (4) interferon based on media coverage touting it as a possible miracle cure; (5) novelty condoms based on their likely use as prophylactics; (6) sun screen products based on consumer expectations that they will provide protection against the harmful effects of the sun on the body; and (7) tanning booths based on the known effects of ultraviolet rays on the structure or function of the body. In each of these cases, FDA found that the product was intended for use as a drug or a device based on the inherent nature of the product, its predominant use or effects, or both.

Some of these cases required FDA to determine whether a product was under its jurisdiction at all, while others required FDA to determine whether a product would be regulated merely as a cosmetic or food or instead as a drug or device. It is also the case that FDA may use its authority to regulate the off-label use of a drug or a device. Indeed, when a particular off-label use becomes widespread or endangers public health, FDA must investigate it thoroughly and take appropriate action to protect the public, including requiring a change in the product's labeling to warn against or approve the unapproved use, seeking substantial evidence to substantiate its use, restricting the distribution of the drug, or even withdrawing approval of the drug and removing it from the market.

Accordingly, some of the withdrawals of approved drugs in the last several years, including fenfluramine hydrochloride, dexfenfluramine hydrochloride, mibefradil dihydrochloride, and bromfenac sodium, have followed after off-label use of the drugs was associated with patient injuries and deaths. FDA has required the relabeling of other drugs, such as the anti-arrhythmic drugs, Encainide and Flecainide, because of wide-spread off-label use that was shown to have caused hundreds if not thousands of deaths. Indeed, numerous drugs carry FDA-required warnings about dangerous or unsubstantiated off-label uses. If FDA lacked authority over off-label uses, it would not be able to require warnings about such uses.

These cases illustrate most dramatically the importance of FDA determining a product's intended use by any available evidence, and not only by marketing claims, because nothing less than the public health and safety depends upon it.

It is therefore incorrect both as a matter of law and practice that the report asserts that FDA may only consider a manufacturer's claimed uses for its product when determining intended use. This legislation is limited to addressing FDA's authority to require pediatric testing of drugs. It does not alter or affect the authority of FDA under the FFDCA with respect to testing of drugs in other subpopulations, such as women and minorities, or for other uses, including off-label uses in appropriate circumstances. And it is outrageous that the report has been used as an opportunity to promote an unfounded and dangerous view of FDA's authority in these other areas.

Seizures

The report also asserts that FDA's seizure authority is an unsatisfactory remedy from a public health perspective because it denies adequately studied populations access to a safe and effective drug. It would be true that a mass seizure of all of a manufacturer's drug or biological product would disrupt patient access to a safe and effective product. It is not the case, however, that seizure of the lots of a drug in one warehouse, when there are other stores of the drug that are not seized, would disrupt consumer access to a drug or biological product.

In fact, such a seizure may be a particularly appropriate way for FDA to seek enforcement of a statutory or regulatory requirement, because it allows patients to have access to products that the government has not seized and because the manufacturer's interest in being able to distribute the seized product can facilitate quicker resolution of the dispute. In the instances under consideration here, that would mean quicker completion of pediatric studies that a manufacturer has failed to complete in a timely way.

The legislation clearly authorizes FDA to use the full range of its enforcement authorities with the single exception of criminal penalties. Under S. 650, the agency retains its full discretion as to whether to use its seizure authority.

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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):

PEDIATRIC RESEARCH EQUITY ACT OF 2003

* * * * * * *

FEDERAL FOOD, DRUG, AND COSMETIC ACT

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; *(F)* [and (F)] specimens of the labeling proposed to be used for such drug. 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 a 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 appropriate, on the inclusion of women and minorities in clinical trials required by clause (A)[.] *and (G) any assessments required under section 505B.*

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

(a) DEFINITIONS.—* * *

* * * * * * *

(b) MARKET EXCLUSIVELY FOR NEW DRUGS.—* * *

* * * * * * *

(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)⟧ *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)⟧ *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 EXCLUSIVELY FOR ALREADY-MARKETED DRUGS.—* * *

(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)(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)⟧ *505(j)(4)(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 RESEARCH 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.

(i) LABELING SUPPLEMENTS.—* * *

* * * * * * *

(i) LABELING SUPPLEMENTS.—

(1) PRIORITY STATUS FOR PEDIATRIC SUPPLEMENTS.—* * *

(A) * * *

(B) * * *

(2) DISPUTE RESOLUTION.—

(A) REQUEST FOR LABELING CHANGE AND FAILURE TO AGREE.—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, 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, the Commissioner shall refer the matter to the Pediatric [Advisory Subcommittee of the Anti-Infective Drugs] Advisory Committee.

(B) ACTION BY THE PEDIATRIC [ADVISORY SUBCOMMITTEE OF THE ANTI-EFFECTIVE DRUGS] ADVISORY COMMITTEE.—Not later than 90 days after receiving a referral under subparagraph (A)(ii), 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) CONSIDERATION OF RECOMMENDATIONS.—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.

(D) MISBRANDING.—If the sponsor of the application, within 30 days after receiving a request under subparagraph (C), dose 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.

(E) NO EFFECT ON AUTHORITY.—Nothing in this subsection limits the authority of the United States to bring an enforcement action under this Act when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric [Advisory Subcommittee of the Anti-Infective Drugs] Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action.

* * * * * * *

Best Pharmaceuticals for Children Act

HISTORICAL AND STATUTORY NOTES

Pediatric [Pharmacology] *Therapeutics* Advisory Committee. Pub. L. 117–109, § 14, Jan. 4, 2002, 115 Stat. 1419, provided that:

"(a) IN GENERAL.—The Secretary of Health and Human Services shall, under section 222 of the Public Health Service Act [42 U.S.C. 217a),] *(42 U.S.C. 217a) or other appropriate authority,* convene and consult an advisory committee on pediatric [pharmacology] *therapeutics* (referred to in this section as the "advisory committee").

"(b) PURPOSE.—

"(1) IN GENERAL.—The advisory committee shall advise and make recommendations to the Secretary, through the Commissioner of Food and Drugs [and in consultation with the Director of the National Institutes of Health] on matters relating to pediatric [pharmacology] *therapeutics*.

"(2) MATTERS INCLUDED.—The matters referred to in paragraph (1) include—

"(A) pediatric research conducted under sections 351, 409I, and 499 of the Public Health Service Act [42 U.S.C. A. §§ 262, 284m, and 290b] and sections 501, 502, 505, and [505A] *505B* of the Federal Food, Drug, and Cosmetic Act [21 U.S.C.A. §§ 351, 352, 355, and 355a];

"(B) identification of research priorities related to pediatric [pharmacology] *therapeutics* and the need for additional treatments of specific pediatric diseases or conditions; and

"(C) the ethics, design, and analysis of clinical trials related to pediatric [pharmacology] *therapeutics*.

* * * * * * *

SEC. 15. PEDIATRIC SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE.

(a) CLARIFICATION OF AUTHORITIES.—

(1) IN GENERAL.—* * *

(A) * * *

(B) * * *
(C) * * *

(2) MEMBERSHIP.—

(A) IN GENERAL.—The Secretary shall appoint not more than 11 voting members to the Pediatric Subcommittee from the membership of the Pediatric [Pharmacology] Advisory Committee and the Oncologic Drugs Advisory Committee.

* * * * * * *

SEC. 16. REPORT ON PEDIATRIC EXCLUSIVITY PROGRAM.

* * * * * * *

(1) The effectiveness of section 505A of the Federal Food, Drug, and Cosmetic Act and section 409I of the Public Health Service Act (as added by this Act) in ensuring that medicines used by children are tested and properly labeled, including—

(A) * * *
(B) * * *

(C) the number of drugs for which testing is being done, exclusivity granted, and labeling changes required, including the date pediatric exclusivity is granted and the date labeling changes are made and which labeling changes required the use of the dispute resolution process established pursuant to the amendments made by this Act, together with a description of the outcomes of such process, including a description of the disputes and the recommendations of the Pediatric [Advisory Subcommittee of the Anti-Infective Drugs] Advisory Committee.

* * * * * * *

SEC. 17. ADVERSE-EVENT REPORTING.

(a) TOLL-FREE NUMBER IN LABELING.—* * *

(1) * * *
(2) * * *
(3) * * *

(b) DRUGS WITH PEDIATRIC MARKET EXCLUSIVITY.—

(1) IN GENERAL.—During the one year beginning on the date on which a drug receives a period of market exclusivity under 505A of the Federal Food, Drug, and Cosmetic Act, any report of an adverse event regarding the drug that the Secretary of health and Human Services receives shall be referred to the Office of Pediatric Therapeutics established under section 6 of this Act. In considering the report, the Director of such Office shall provide for the review of the report by the Pediatric [Advisory Subcommittee of the Anti-Infective Drugs] Advisory Committee, including obtaining any recommendations of such subcommittee regarding whether the Secretary should take action under the Federal Food, Drug, and Cosmetic Act in response to the report.

* * * * * * *

SEC. 505B. RESEARCH INTO PEDIATRIC USES FOR 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 new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration;

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 for each age group for which the assessment is required, that are adequate—

(i) to assess the safety and effectiveness of the drug or the biological product 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 is safe and effective.

(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT.—

(i) IN GENERAL.—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.

(ii) EXTRAPOLATION BETWEEN AGE GROUPS.—A study may not be needed in such pediatric age group if data from 1 age group can be extrapolated to another age group.

(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;

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

(iii) there is another appropriate reason for deferral; and

(B) the applicant submits to the Secretary—

(i) certification of the grounds for deferring the assessments;

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

(iii) evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

(4) WAIVERS.—

(A) FULL WAIVER.—On the initiative of the Secretary or at the request of an applicant, the Secretary shall grant a full waiver, as appropriate, of the requirement to submit assessments for a drug or biological product under this subsection if the applicant certifies and the Secretary finds that—

(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed);

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

(iii) 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 in a substantial number of pediatric patients.

(B) PARTIAL WAIVER.—On the initiative of the Secretary or at the request of an applicant, the Secretary shall grant a partial waiver, as appropriate, of the requirement to submit assessments for a drug or biological product under this subsection with respect to a specific pediatric age group if the applicant certifies and the Secretary finds that—

(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed);

(ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group;

(iii) the drug or biological product—

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

(II) is not likely to be used by a substantial number of pediatric patients in that age group; or

(iv) the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(C) PEDIATRIC FORMULATION NOT POSSIBLE.—If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver shall cover only the pediatric groups requiring that formulation.

(D) 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 inn pediatric populations, the information shall be included in the labeling for the drug or biological product.

(b) MARKETED DRUGS AND BIOLOGICAL PRODUCTS.—

(1) IN GENERAL.—After providing notice in the form of a letter and an opportunity for written response and a meeting, which may include an advisory committee meeting, the Secretary may (by order in the form of a letter) require the holder of an approved application for 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 assessment described in subsection (a)(2) 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 risks to pediatric patients.

(2) WAIVERS.—

(A) FULL WAIVER.—At the request of an applicant, the Secretary shall grant a full waiver, as appropriate, of the requirement to submit assessments under this subsection if the applicant certifies and the Secretary finds that—

(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed); or

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

(B) PARTIAL WAIVER.—At the request of an applicant, the Secretary shall grant a partial waiver, as appropriate, of the requirement to submit assessments under this subsection with respect to a specific pediatric age group if the applicant certifies and the Secretary finds that—

(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed);

(ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group;

(iii)(I) the drug or biological product—

(aa) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and

(bb) is not likely to be used in a substantial number of pediatric patients in that age group; and

(II) the absence of adequate labeling could not pose significant risks to pediatric patients; or

(iv) the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(C) PEDIATRIC FORMULATION NOT POSSIBLE.—If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver shall cover only the pediatric groups requiring that formulation.

(D) 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.

(3) 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 a related pediatrict study under section 505A(c) of this Act or section 409I of the Public Health Service Act (42 U.S.C. 284m);

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

(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 (42 U.S.C. 284m)—

(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; and

(iii)(I) the Secretary certifies under subparagraph (B) that there are insufficient funds under sections 409I and 499 of the Public Health Service Act (42 U.S.C. 284m, 290b) to conduct the study; or

(II) the Secretary publishes in the FEDERAL REGISTER a certification that certifies that—

(aa) no contract or grant has been awarded under section 409I or 499 of the Public Health Service Act (42 U.S.C. 284m, 290b); and

(bb) not less than 270 days have passed since the date of a certification under subparagraph (B) that there are sufficient funds to conduct the study.

(B) NO AGREEMENT TO REQUEST.—Not later than 60 days after determining that no holder will agree to the written request (including a determination that the Secretary has not received a response specified under section 505A(d) of this Act or section 409I of the Public Health Service Act (42 U.S.C. 284m), the Secretary shall certify whether the Secretary has sufficient funds to conduct the study under section 409I or 499 of the Public Health Service Act (42 U.S.C.

284m 290b), taking into account the prioritization under section 409I.

(c) MEANINGFUL THERAPEUTIC BENEFIT.—For the purposes of paragraph (4)(A)(iii)(I) and (4)(B)(iii)(I) of subsection (a) and paragraphs (1)(B)(i) and (2)(B)(iii)(I)(aa) of subsection (b), a drug or biological product shall be considered to represent a meaningful therapeutic benefit over existing therapies if the Secretary estimates that—

(1) if approved, the drug or biological product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared with marketed products adequately labeled for that use in the relevant pediatric population; or

(2) the drug or biological product is in a class of products or for an indication for which there is a need for additional options.

(d) SUBMISSION OF ASSESSMENTS.—If a person fails to submit an assessment described in subsection (a)(2), or a request for approval of a pediatric formulation described in subsection (a) or (b), in accordance with applicable provisions of subsections (a) and (b)—

(1) the drug or biological product that is the subject of the assessment or request may be considered misbranded and subject to relevant enforcement action (except that the drug or biological product shall not be subject to action under section 303); but

(2) the failure to submit the assessment or request shall not be the basis for a proceeding—

(A) to withdraw approval for a drug under section 505(e); or

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

(e) MEETINGS.—Before and during the investigational process for a new drug or biological product, the Secretary shall meet at appropriate times with the sponsor of the new drug or biological product to discuss—

(1) information that the sponsor submits on plans and timelines for pediatric studies; or

(2) any planned request by the sponsor for waiver or deferral of pediatric studies.

(f) SCOPE OF AUTHORITY.—Nothing in this section provides to the Secretary any authority to require a pediatric assessment of any drug or biological product, or any assessment regarding other populations or uses of a drug or biological product, other than the pediatric assessments described in this section.

(g) ORPHAN DRUGS.—Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526.

(h) INTEGRATION WITH OTHER PEDIATRIC STUDIES.—The authority under this section shall remain in effect so long as an application subject to this section may be accepted for filing by the Secretary on or before the date specified in section 505A(n).

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PUBLIC HEALTH SERVICE ACT

PART F—LICENSING—BIOLOGICAL PRODUCTS AND CLINICAL LABORATORIES

Subpart 1—Biological Products

REGULATION OF BIOLOGICAL PRODUCTS

SEC. 351. (a)(1) * * *

(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—

(i) on the basis of a demonstration that—

(I) the biological product that is the subject of the application is safe, pure, and potent; and

(II) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent; and

(ii) if the applicant (or other appropriate person) consents to the inspection of the facility that is the subject of the application, in accordance with subsection (c).

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SEC. 409I. [284m] PROGRAM FOR PEDIATRIC STUDIES OF DRUGS.

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

(1) IN GENERAL.—* * *

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(c) PROCESS FOR CONTRACTS AND LABELING CHANGES.—

(1) WRITTEN REQUEST TO HOLDERS OF APPROVED APPLICATION FOR DRUGS LACKING EXCLUSIVITY.—The Commissioner of Food and Drugs, in consultation with the Director of the 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)(1)(A) (except clause (iv)) to all holders of an approved application for the drug under section 505 of the Federal Food, Drug and Cosmetic Act. Such a written request shall be made in a manner equivalent to the manner in which a written request is made under subsection (a) or (b) of section 505A of the Federal Food, Drug and Cosmetic Act, including with respect to information provided on the pediatric studies to be conducted pursuant to the request.

(2) REQUESTS FOR CONTRACT PROPOSALS.—* * *

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(7) REQUESTS FOR LABELING CHANGE.—During the 180-day period after the date on which a report is submitted under paragraph (6)(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;

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

(8) DISPUTE RESOLUTION.—

(A) REFERRAL TO PEDIATRIC [ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS] ADVISORY COMMITTEE.—If, not later than the end of the 180-day period specified in paragraph (7), the holder of an approved application for the drug involved does not agree to any labeling change requested by the Commission of Food and Drugs under that paragraph, the Commissioner of Food and Drugs shall refer the request to the Pediatric [Advisory Subcommittee of the Anti-Infective Drugs] Advisory Committee

(B) ACTION BY THE PEDIATRIC [ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS] ADVISORY COMMITTEE.—Not later than 90 days after receiving a referral under subparagraph (A), the Pediatric [Advisory Subcommittee of the Anti-Infective Drugs] Advisory Committee 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.

(9) FDA DETERMINATION.—Not later than 30 days after receiving a recommendation from the Pediatric [Advisory Subcommittee of the Anti-Infective Drugs] Advisory Committee under paragraph (8)(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.

(10) 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 (9), 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 Art (21 U.S.C. 301 et seq.).

(11) NO EFFECT ON AUTHORITY.—Nothing in this subsection limits the authority of the United States to bring an enforcement action under the Federal Food, Drug, and Cosmetic Act when a drug lacks appropriate pediatric labeling. Neither

course of action (the Pediatric [Advisory Subcommittee of the Anti-Infective Drugs] Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action.

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