WILMER, CUTLER & PICKERING
2445 M STREET, N.W.
WASHINGTON, DC 20037-1420
TELEPHONE (202) 663-6000
FACSIMILE (202) 663-6363

WASHINGTON
NEW YORK
BALTIMORE
NORTHERN VIRGINIA
LONDON
BRUSSELS
BERLIN

December 26, 2001

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

CITIZEN PETITION

The undersigned submits this petition under section 505A of the Federal Food, Drug, and Cosmetics Act, 21 U.S.C. § 355a, including proposed amendments to the Act under the Best Pharmaceuticals for Children Act ("BPCA"), S. 1789, 107th Cong. (2001), to request the Commissioner of Food and Drugs to issue new regulations and/or amend existing regulations.

This petition asks the Food and Drug Administration ("FDA") to adopt expeditiously regulations implementing section 11 of the BPCA, which permits the FDA to approve certain generic drug applications that omit pediatric labeling information, while authorizing the FDA to continue to take action to protect children's health and safety. Section 11 reverses the FDA's longstanding (and well-justified) policy of disallowing generic drugs that fail to contain complete pediatric labeling, and hence presents very real and potentially serious risks to the public health. Moreover, section 11 is not self-executing, and how the FDA will balance the competing policies in section 11 is not immediately obvious. Both to protect the safety of children and to minimize the uncertainty for *all* groups of pharmaceutical manufacturers, Petitioner urges the FDA to act expeditiously to implement section 11, and Petitioner stands ready to assist the FDA in this task.

A. ACTION REQUESTED

The BPCA has been passed by both houses of Congress, is awaiting the President's signature, and appears likely to become law. Section 11 of the BPCA (to be codified at 21 U.S.C. § 355a(o)) permits the FDA to approve abbreviated new drug applications ("ANDAs") for generic drugs whose labeling omits pediatric use information protected by an innovator drug manufacturer's patent or pediatric market exclusivity rights.[1/] At the same time, section 11 authorizes the Secretary to require generic drug labels to include whatever pediatric contraindications, warnings, or precautions the Secretary deems necessary. Section 11 also expressly preserves the innovator drug manufacturer's exclusive rights to market the drug for pediatric uses and authorizes the Secretary to require generic drugs to carry label statements designed to protect those rights.

Petitioner Bristol-Myers Squibb Company ("BMS") respectfully asks the Commissioner to enact new regulations and amend existing ones, as necessary, to implement section 11 once the BPCA becomes effective. The differing goals and mandates of section 11 are in tension, and its precise implementation is not immediately apparent. The FDA needs to adopt general procedures for considering ANDAs under section 11 and for determining what types of labeling will protect both the safety of pediatric patients and the legitimate exclusivity rights of innovator drug manufacturers. In particular, any regulatory scheme for implementing section 11 should include the following:

1. Before approving any application for a generic drug whose labeling omits protected pediatric use information, the FDA should conduct a proceeding to determine whether the omission of pediatric labeling information presents a health

[1/] The phrase "pediatric market exclusivity," as used in this petition, refers to the innovator manufacturer's exclusive right to include pediatric use information in its drug labeling, which is conferred by the Hatch-Waxman Act, 21 U.S.C. § 355, and the Food and Drug Administration Modernization Act, 21 U.S.C. § 355a, and which section 11 leaves intact. *See infra* pp. 3-7.

or safety risk to pediatric patients and, if so, what additional labeling statements regarding pediatric use are necessary;

2. For each ANDA affected by section 11, the FDA should also determine what labeling information is necessary to protect the innovator drug manufacturer's pediatric market exclusivity, which section 11 expressly preserves;

3. With respect to both determinations, the FDA should specifically consider the prospect of off-label use of the generic drug and determine how such off-label use affects pediatric safety and protected pediatric market exclusivity; and

4. As part of the proceeding, the FDA should accept comments from the public addressing the necessity of additional labeling statements for each generic drug and the content of such labeling.

B. STATEMENT OF GROUNDS

BACKGROUND

1. Legal Background

Understanding how section 11 changes the process for generic drug approval requires a brief review of existing statutes and FDA regulations. The Hatch-Waxman Act, enacted in 1984, reflects a political compromise between the desire to provide low-cost generic drugs to the public and the need to allow innovator drug manufacturers to recover their substantial investments in drug research and clinical activities prior to the entrance of generic competitors to the market. *See* 21 U.S.C. § 355. The Act creates an abbreviated new drug application, or ANDA, procedure for generic drugs and, in return, grants innovator drug manufacturers five years of market exclusivity covering new chemical entities approved in a new drug application ("NDA") and three years of exclusivity for label changes approved in supplemental NDAs ("SNDAs"). *See id.* § 355(j)(5)(D)(i)-(v). With limited exceptions,[2/] the Act requires the generic drug label to be "the same" as that of the innovator, or "listed," drug label. *See id.* § 355(j)(2)(A)(v). The

[2/] The Hatch-Waxman Act permits two exceptions to the requirement that a generic product have the same labeling as the listed drug: (1) "changes required because of differences approved

FDA, however, has adopted regulations creating an exception to the same label requirement: generic drug labels may differ from the innovator drug label by the "omission of an indication or other aspect of labeling protected by or accorded exclusivity under [Hatch-Waxman]." 21 C.F.R. § 314.94(a)(8)(iv); *see also* 21 C.F.R. §§ 314.92(a)(1) (explaining that the term "same as" does not require identical conditions of use on a label when approval for that condition of use cannot be granted due to patent or market exclusivity) and 314.127(a)(7) (explaining that FDA will not refuse approval of a generic drug label that differs from the innovator drug label when the difference results from patent or market exclusivity held by the innovator drug). Nevertheless, the regulation allows omission of the protected information *only* if the omission "do[es] not render the proposed drug product *less safe or effective* than the listed drug for all remaining, nonprotected conditions of use." 21 C.F.R. § 314.127(a)(7) (emphasis added).

In an effort to "promote[] safer and more effective use of prescription drugs in the pediatric population,"[3/] the FDA adopted regulations in 1994 requiring all drug labels to include pediatric use information. *See* 21 C.F.R. § 201.57(f)(9). The regulations list six approved statements regarding pediatric use, one of which must be included in every drug label.[4/] When

---

under a [suitability] petition"; and (2) "because the [generic product] and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). Neither of these statutory exceptions to the same labeling requirement is applicable here.

[3/] Specific Requirements on Content and Format of Labeling for Human Prescription Drugs, 59 Fed. Reg. 64,240 (Dec. 13, 1994) (codified at 21 C.F.R. pt. 201).

[4/] 21 C.F.R. §§ 201.57(f)(9)(ii)-(vii) specify the following six types of permissible labels:

(ii) information on a specific pediatric indication that differs from the indication approved for adults, supported by clinical studies in pediatric patients;

(iii) information on an indication also approved for adults, supported by clinical studies in pediatric populations;

enacting these regulations, the FDA stated that any drug label lacking this pediatric information "would be considered misbranded and an unapproved new drug under the act."[5/]

Congress likewise recognized the need to protect pediatric patients by including pediatric use information based on pediatric research in drug labeling. The Food and Drug Administration Modernization Act ("FDAMA"), *see* 21 U.S.C. §§ 301-392, enacted in 1997, encourages greater pediatric labeling by allowing drug manufacturers to earn an additional six months of market exclusivity for conducting pediatric studies on approved drugs. *See* 21 U.S.C. § 355a(c).

Before the enactment of the BPCA, the interplay of the statutory market exclusivity provisions and the FDA's pediatric labeling rules operated to extend the market exclusivity rights of innovator manufacturers that performed pediatric studies with respect to *all* uses of the drug, including non-pediatric uses. Conducting new clinical research for pediatric uses would yield six months of market exclusivity for an innovator manufacturer pursuant to FDAMA, 21 U.S.C. § 355a, and, if the FDA approved an SNDA for label changes based on this new use, an additional three years of market exclusivity under the Hatch-Waxman Act, 21 U.S.C. §

(iv) information on pediatric use based on studies conducted in adults with additional information, which may include clinical trials, in pediatric patients;

(v) a statement that the requirements for a finding of substantial evidence to support a pediatric indication or pediatric use statement have not been met for a particular age group of the pediatric population;

(vi) a statement that the requirements for a finding of substantial evidence to support a pediatric indication or pediatric use statement have not been met for any pediatric population;

(vii) if the sponsor of a prescription drug believes that none of the above options are "appropriate or relevant to the labeling of a particular drug," the sponsor may request permission to omit the information and that FDA permit use of an alternative statement that FDA determines to be "accurate and appropriate."

[5/] Specific Requirements on Content and Format of Labeling for Human Prescription Drugs, 59 Fed. Reg. at 64,247.

355(j)(5)(D)(iv). The FDA's pediatric labeling rules, however, effectively extended this exclusivity to *all* uses. If a generic drug manufacturer sought to omit the pediatric label information protected by exclusivity, FDA rules would deem the product misbranded, since the rules require *all* products to contain pediatric use information. *See* 21 C.F.R. § 201.57(f)(9). Thus, a generic drug could not be approved for *any* use when its label omitted pediatric use information.

The BPCA ends the extension of pediatric market exclusivity to non-pediatric uses. Section 11 instructs that a generic drug application

> shall not be considered ineligible for approval . . . or misbranded . . . on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent or by exclusivity . . . .

S. 1789, § 11(a). The House Report for the BPCA explains that this provision "does make clear that if a manufacturer does claim supplemental exclusivity under section 505(j), the terms of that exclusivity will not prevent generic competition for the indications or aspects of labeling which are not protected." H.R. Rep. No. 107-277, at 38 (2001).

At the same time, Congress expressly recognized that the omission of pediatric labeling information could present serious pediatric health risks, given that these generic products are likely to be given to children despite their lack of pediatric labeling. For that reason, section 11 expressly authorizes the Secretary to require that the labeling of generic drugs "include . . . a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers necessary." S. 1789, § 11(a). Moreover, and just as importantly, Congress reaffirmed that innovator drug companies that perform pediatric research *do* have legitimate exclusivity rights in pediatric labeling information that must be protected. Congress expressly

stated that section 11 does not affect the availability or scope of exclusivity under FDAMA or Hatch-Waxman,[6/] and explicitly authorized the Secretary to "require that the labeling of a [generic] drug . . . that omits a pediatric indication . . . include (A) a statement that, because of marketing exclusivity for a manufacturer — (i) the drug is not labeled for pediatric use . . ." *Id.*

The provisions of section 11 clearly authorize the Secretary to take action to require generic drug labels to include additional statements disclaiming pediatric use or explaining the hazards of pediatric use, and they demonstrate Congress's expectation that the Secretary will in fact take such action. But it is not immediately apparent how the Secretary should make his determinations or what statements are required. Indeed, there are tensions within section 11 itself; for example, information that might be desirable for pediatric safety could be subject to continued exclusivity protection. As discussed below, new regulations are necessary to implement section 11 in a manner that protects the safety of pediatric patients, preserves the statutory market exclusivity of innovator drug manufacturers, and resolves the tensions inherent in section 11.

2. Factual Background

The FDA approved a NDA for BMS's innovator drug Glucophage® effective March 3, 1995. Glucophage, generically known as metformin hydrochloride ("metformin"), is the most widely prescribed oral medication indicated for use in the management of type 2 diabetes in the United States. Last year, American physicians wrote more than 25 million prescriptions for Glucophage.

[6/] *See* S. 1789, § 11(a) ("This subsection does not affect — (A) the availability or scope of exclusivity under [section 505A]; (B) the availability or scope of exclusivity under section 505 for pediatric formulations; [or] . . . (D) the operation of section 505.")

At the time of the NDA approval, there were no clinical studies evaluating the use of Glucophage in children. Indeed, at the time, there was little perception that type 2 diabetes even occurred in the pediatric population. As a consequence, the drug was approved for use in adults only, and the label included an explanation that safety and effectiveness in pediatric patients had not been established. In 1998, in light of new information about the rising incidence of type 2 diabetes in children, BMS received approval from FDA to conduct Glucophage pediatric clinical trials. Using data from these studies, BMS submitted an SNDA seeking FDA approval to add pediatric use information to the Glucophage label. The FDA approved the SNDA on December 15, 2000. The Glucophage label now describes the BMS pediatric clinical studies, includes a pediatric adverse effects profile, specifies a different dosing regimen for children,[7/] and acknowledges the lack of information on the use of an extended release formulation of Glucophage in children.[8/] This critical prescribing information is not available elsewhere.

When the FDA approved the Glucophage pediatric labeling, the agency determined that BMS was entitled to 3 ½ years of statutory exclusivity covering the labeling changes approved in the SNDA. The 3 ½ year period derives from six months of pediatric market exclusivity under FDAMA, 21 U.S.C. § 355a, and three years of new use exclusivity for a SNDA under the Hatch-Waxman Act. The exclusivity period granted to Glucophage pediatric labeling, as reflected in the FDA's "Orange Book," expires on June 15, 2004. Enactment of the BPCA would limit BMS's exclusivity for non-pediatric uses conferred by the previous regulatory regime by allowing the FDA to approve generic ANDAs, notwithstanding the absence of pediatric use

---

[7/] The recommended maximum daily dose for children is 2000 mg per day, in contrast to the 2550 mg dose recommended for adults.

[8/] The label warns that the safety of Glucophage XR, an extended release form of the drug, has not been established in children, and instructs against its use in patients under 17 years of age.

information in the generic drug labels. At present, over a dozen generic drug applications are awaiting approval by the FDA in anticipation of the passage of the BPCA.

DISCUSSION

The FDA should implement section 11 by creating a new procedure to evaluate the safety risks of ANDAs submitted in accordance with that section and their effects on innovator drug manufacturers' continued pediatric market exclusivity rights, as Congress intended. The goal of the review is to determine what additional labeling information is required in light of these concerns. The new procedure must ensure that neither the safety of pediatric patients nor the pediatric market exclusivity rights of innovator drug manufacturers are compromised by the approval of generic drugs that omit pediatric use information from their labels.

Section 11 expressly authorizes the Secretary to regulate the content of generic drug labels to protect pediatric health and innovator drug manufacturers' exclusivity rights.[9/] Congress clearly expects the Secretary to pursue this task through an industry-wide notice and comment rulemaking. So that the Act may be applied "comprehensively and uniformly to all affected drugs" and so that "all interested parties have their voices heard," lawmakers directed that "the Secretary should provide for public notice and comment in implementing this important provision." 147 Cong. Rec. H 10,205 (daily ed. Dec. 18, 2001) (statement of Rep. Tauzin). *See also id.* at 10,209 (statement of Rep. Jackson-Lee) ("FDA cannot implement Section 11 without engaging in notice-and-comment rulemaking under the Administrative Procedure Act.") Although section 11 of the BPCA takes effect on the date of its enactment, it is hardly self-

[9/] *See* S. 1789, § 11 ("the Secretary may require that the labeling of a [generic] drug . . . include . . . a statement that, because of marketing exclusivity for a manufacturer . . . the drug is not labeled for pediatric use; . . . and . . . a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers necessary").

executing; the FDA cannot implement its provisions or approve generic ANDAs without first addressing the competing considerations posed by Congress' expressed intention both to allow the approval of additional generic drugs and to continue protecting pediatric safety and innovator manufacturers' pediatric market exclusivity.

With these aims in mind, BMS requests that the FDA enact new procedural regulations to govern the ANDA approval process for those generic drugs within section 11's ambit. The regulations should require the FDA to (1) conduct a proceeding to determine whether approval of a generic drug label that omits pediatric use information poses a health risk to pediatric patients; (2) determine whether the omission of pediatric label information on a generic drug undermines the pediatric market exclusivity granted to innovator drug manufacturers; (3) consider the prospect of off-label use of a generic drug and how that off-label use potentially compromises the safety and efficacy of the drug or diminishes pediatric market exclusivity; and (4) solicit comments from the public addressing the necessity for, and content of, additional labeling for each different ANDA.

I. The Implementing Regulations Must Ensure That Approval of Generic Drugs Will Not Pose Health Risks to Pediatric Patients

The FDA has a legitimate and longstanding policy of ensuring that approved drugs do not pose health risks to pediatric patients due to inadequate labeling. The absence of pediatric use information from generic drugs eligible for approval under section 11 could pose grave safety threats to children. The FDA should therefore create a process enabling it to determine, for each ANDA, whether the absence of pediatric use information on a given generic drug will pose a risk to children, and if so, what additional labeling statements may reduce that risk.

Under the pre-BPCA regulatory scheme, the FDA required that *all* drug labels contain a "Pediatric Use" section describing the appropriate indications for use (if any) in pediatric

patients. *See* 21 C.F.R. § 201.57(f)(9)(ii)-(vii). These requirements addressed the well-recognized concern that, without proper pediatric use labeling, drugs approved only for adult use may pose a health risk to pediatric patients. The FDA observed that improper labeling may affect both the safety and efficacy of a drug:

> [Practitioners may prescribe drugs] inappropriately, choosing dosages, for instance, that are arbitrarily based on the child's age, body weight, or body surface area without specific information as to whether this is appropriate. As a result, pediatric patients may be exposed to an increased risk of adverse reactions, or decreased effectiveness of the drugs prescribed, or may be denied access to valuable therapeutic agents.[10/]

These concerns are reflected in both the FDA's and Congress' efforts to create more accurate and complete pediatric information in drug labels.[11/]

The enactment of section 11 in no way undermines the FDA's prior conclusions regarding pediatric safety and efficacy information, nor does it dilute the FDA's obligation to protect pediatric health. Rather than repudiating the FDA's finding that inadequate labeling may pose health risks to children, Congress merely instructed that the absence of a pediatric use indication should not pose an *automatic* bar to generic drug approval. It is quite clear, however,

---

[10/] Specific Requirements on Content and Format of Labeling for Human Prescription Drugs, 59 Fed. Reg. at 64,240.

[11/] *See* Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. 43,900, 43,901 (August 15, 1997) (codified at C.F.R. pts. 201, 312, 314, 601) ("Inadequate dosing information may expose pediatric patients to dangerously high doses or to ineffective treatment."); Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632, 66,637 (Dec. 2, 1998) (codified at 21 C.F.R. pts. 201, 312, 314, and 601) ("FDA agrees that the absence of adequate pediatric labeling puts pediatric patients at risk for adverse drug reactions and ineffective dosing."); 138 Cong. Rec. S16,999 (daily ed. Oct. 5, 1992) (statement of Sen. Kassebaum) (noting that physician estimates for pediatric dosage "are sometimes uncertain, owing to the fact that children — particularly those under 2 years of age — frequently metabolize drugs differently than do adults. Further, some drugs can be less safe in children than in adults, even when appropriate doses are used.").

that some generic drugs approved for adult use will nevertheless pose safety risks to children due to improper dosage or unknown adverse effects. Indeed, when passing the BPCA, lawmakers recognized the potential risks of section 11 for children:

> The only flaw in the bill is Section 11, which would actually permit the FDA to approve drugs that omit critical pediatric dosing information. Such omissions could cripple the very purpose — complete [and] accurate pediatric labeling — of the Best Pharmaceuticals for Children Act. Consequently, FDA cannot implement Section 11 without engaging in notice-and-comment rulemaking under the Administrative Procedure Act. This will ensure that if FDA does assert the discretion it is granted under Section 11, it will not do so in a way that would allow approval of any drug without complete, accurate and up-to-date pediatric labeling.

147 Cong. Rec. H 10,209 (daily ed. Dec. 18, 2001) (statement of Rep. Jackson-Lee).

The prospect of generic entry into the metformin market illustrates the risks posed by incomplete generic drug labels. BMS's Glucophage label complies with 21 C.F.R. § 201.57(f)(9)(iv), which requires a manufacturer to explain pediatric uses derived from studies conducted in adults, supplemented by additional data from pediatric clinical trials. In contrast to the recommended maximum daily dosage of 2550 mg for adults, the maximum recommended daily dosage of Glucophage for children is only 2000 mg per day. This critical dosage information not only ensures that the dose prescribed to a pediatric patient is safe, but also that it is efficacious — that is, that the patient receives a dosage sufficient to treat the disease effectively. The Glucophage label also describes BMS pediatric clinical studies, includes a pediatric adverse effects profile, and acknowledges the lack of information on the use of an extended release formulation of Glucophage in children. Because BMS has properly earned the right to exclusively market the pediatric use of Glucophage metformin, no other manufacturer may include this information in its label.

If the generic metformin ANDAs are approved, Glucophage will likely lose the vast majority of its metformin sales to generic products within a few weeks of the entry of generic drugs to the market. It is clear that, whether or not generic products are properly labeled for pediatric use, they will be given to children, even when Glucophage is prescribed.[12/] Thus, within weeks of the first wave of generic approvals, the overwhelming proportion of metformin sold in the United States would have substandard pediatric labeling.

As the FDA has learned from experience,[13/] such widespread prescription of drugs with incomplete pediatric labeling poses a serious risk of injury or death to children on the one hand, and ineffective dosage or treatment on the other. Faced with such a potential for harm, the FDA must exercise the authority granted to it to require some kind of additional statement on each generic product's label disclaiming pediatric use. The FDA should therefore adopt regulations explaining how this authority will be exercised, establishing a process to review the labeling of section 11 generic drugs for safety and efficacy concerns, and determining what label statements are appropriate in light of those concerns.

[12/] *See* Donald O. Beers, *Generic and Innovator Drugs: A Guide to FDA Approval Requirements*, 4-47 (Aspen Law & Business 5th ed. 1999) ("Many states in fact require substitution of the generic, without any regard to the exclusivity that may apply to the indication for which the drug is prescribed.")

[13/] The FDA has cited its unfortunate experience with the "gray baby syndrome" caused by the antibiotic chloramphenicol as an example of why pediatric labeling requirements are necessary. *See* Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. at 43,901. Neonates were prescribed this drug, despite the fact that it had not been adequately studied in pediatric patients. *See id.* "After an initial report of 5 deaths and a subsequent report of 18 deaths in neonates, it was learned that the immature livers of these infants were unable to clear chloramphenicol from the body, allowing toxic doses of the drug to accumulate." *Id.*

II. The Implementing Regulations Must Ensure That Approval of Generic Drugs Will Not Diminish the Pediatric Market Exclusivity Right that Section 11 Expressly Reaffirms.

The protection of children through medically sound pediatric labeling is the paramount reason for adopting regulations implementing section 11. But on its face, section 11 also protects innovator companies' pediatric market exclusivity, and the FDA must give effect to this stated purpose of Congress as well. To preserve this exclusivity as Congress intended, the FDA needs to promulgate regulations requiring generic drug labels to include statements disclaiming and discouraging pediatric use. Without such a requirement, the pediatric market exclusivity conferred by FDAMA and Hatch-Waxman and reaffirmed by section 11 will be effectively nullified, contrary to the expressed intention of Congress.

Although section 11 removes a barrier to approval for generic drugs, it also provides that approval of those drugs may not affect the market exclusivity granted to innovator drug manufacturers under FDAMA or Hatch-Waxman. Congress clearly stated that section 11 "does not affect . . . the availability or scope of exclusivity under [FDAMA]; the availability or scope of exclusivity under section 505 for pediatric formulations; . . . or (D) . . . the operation of section 505 [Hatch-Waxman Act]." S. 1789, § 11(a). *See also* H.R. Rep. No. 107-277, at 38 ("This Section does not prevent any manufacturer from earning six months of exclusivity and then claiming three years of supplemental exclusivity pursuant to section 505(j) [Hatch-Waxman]"). If the FDA is not careful in how it implements section 11, it will do precisely what Congress prohibited: it will nullify the pediatric market exclusivity rights that section 11 expressly reaffirms.

First, the FDA needs to resolve the conflicting mandates of section 11 itself. The section authorizes the Secretary to require generic manufacturers to include "a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers

necessary." S. 1789, § 11(a). This provision essentially permits the Secretary to warn against unsafe pediatric use.[14/] But the pediatric labeling information on which the warnings are based may be the very information for which the innovator has been granted market exclusivity under Hatch-Waxman and/or FDAMA — exclusivity that section 11 also preserves. With such a tension apparent on the face of the statute, application of section 11 is not immediately self-evident, and the FDA needs to resolve the ambiguity through notice and comment rulemaking.

Second, the FDA must consider the potential for off-label use of a given drug as part of its approval decision, and consider how that practice undermines the innovator drug manufacturer's legitimate pediatric market exclusivity rights. Although the FDA approves drugs only for certain specified uses, off-label prescription and use of approved drugs is extremely common and widely recognized.[15/] Indeed, the prevalence of off-label prescription and use of drugs labeled only for adult indications was the catalyst for enacting the pediatric market exclusivity statutory provisions in the first instance.[16/] Without regulations requiring generic drug labels to include some kind of statement indicating that such drugs have not been approved for pediatric use, physicians again will be prescribing these drugs to children without any guidance at all from the drug manufacturer. At a minimum, the educated guesses of doctors as to the appropriate pediatric dosage poses a risk to children, as discussed above. Moreover, if

---

[14/] *See* H.R. Rep. No. 107-277, at 38 ("This provision allows the Secretary to require that [generic] drugs . . . that omit protected pediatric labeling include . . . warnings against unsafe pediatric use.")

[15/] *See* Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. at 43,907 (finding that "there is extensive evidence that many drugs labeled only for adult use are in fact widely used in pediatric patients for the same indications.")

[16/] *See* 138 Cong. Rec. S16,999 (daily ed. Oct. 5, 1992) (statement of Sen. Kassebaum) (recognizing that "[u]nder current law, physicians have the discretion to use any lawfully marketed drug for any patient, according to their best judgment.")

generic drug manufacturers attempt to mitigate this risk by implicitly relying upon the labels and research associated with market-protected drugs, these manufacturers will essentially be able to free-ride on the research of innovator drug manufacturers. Unguided off-label use, therefore, threatens not only the safety of pediatric patients, but also the market incentives of innovator manufacturers to test and label their products for pediatric use, and hence the very purpose of granting exclusivity in the first place.[17/]

Third, it is no easy task to design label statements that protect the innovator manufacturer's legitimate pediatric exclusivity rights, address the realities of (and attempt to discourage) off-label use, and are still simple for consumers and physicians to understand. Accordingly, careful deliberations with appropriate input from the public are clearly desirable. Simply adopting the language in section 11 wholesale ("[B]ecause of marketing exclusivity . . . [this] drug is not labeled for pediatric use") is not workable. The public cannot be expected to appreciate the subtleties of the FDA's labeling regime and fully understand the significance of a drug not being labeled for a certain use. Moreover, the public may not understand the meaning of the term "drug" in this context.[18/] The term may be interpreted as applying to the active

---

[17/] The BCPA, if signed by the President, will take BMS's property rights to market Glucophage for non-pediatric uses. The failure to require generic manufacturers to include an effective disclaimer for pediatric use could also effect a taking of BMS's property right in the pediatric market exclusivity provisions of section 505A, 21 U.S.C. § 355a, which section 11 preserves. *See generally Ruckleshaus v. Monsanto Co.*, 467 U.S. 986, 1001-1004 (1984) (indicating that intellectual property — including the exclusive right to use such property — is protected by the Takings Clause). The mandates of Executive Order No. 12,630, *Governmental Actions and Interference with Constitutionally Protected Property Rights* (March 1988), as implemented by the *Attorney General's Guidelines for the Evaluation of Risk and Avoidance of Unanticipated Takings*, also suggest that caution should be observed before implementing section 11 because Executive Branch agencies must evaluate any agency action that could potentially raise a takings claim and try to avoid such action where possible.

[18/] *See generally* Beers, *supra*, at 1-8 - 1-23 (chronicling the lengthy debate over the proper definition of "new drug" as applied to generic drugs).

moiety of a drug or it may refer to the generic drug manufacturer's specific product. Under the former definition, "the drug" referenced in the cautionary labeling statement would be metformin hydrochloride. To say that metformin hydrochloride is not labeled for pediatric use, however, is not accurate — Glucophage is certainly labeled for (and is safe for) pediatric use. With such a potential for confusion, mere blanket statements suggesting that the drug is not safe for pediatric use will not suffice. This type of statement may actually undermine consumer confidence in the safety of the innovator drug and, consequently, may diminish the value of the pediatric market exclusivity right.

III. Implementation of Section 11 Requires the FDA To Review and Revise Existing Regulations.

The above-stated problems are merely the most obvious difficulties raised by the implementation of section 11. Congress has sketched only the broadest contours of the goals for the FDA to pursue — approving new generic drugs without pediatric labeling while continuing to safeguard pediatric health and preserve the legitimate pediatric market exclusivity rights that give manufacturers an incentive to conduct pediatric research in the first place — while giving no indication about how those goals must be balanced. Nor has Congress explained how section 11 affects FDA's existing regulations. The FDA clearly needs to revisit a number of its rules in light of section 11, including (but not limited to) the following:

- rules requiring pediatric use information to be included in all drug labels, *see* 21 C.F.R. § 201.57(f)(9)(ii)-(iv);
- rules implementing the statutory and regulatory requirements that the generic drug label be "the same" as the innovator drug label, *see* 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8); and
- rules mandating that any differences in the labels between "listed" drugs and generic drugs cannot "render the drug product less safe or effective," 21 C.F.R. § 314.127(a)(7).

Notice and comment rulemaking would assist the FDA in identifying relevant rules and the modifications that are necessary.

CONCLUSION

Section 11 of the BPCA does not merely provide for broader generic drug approval. By its express terms, it authorizes the Secretary to take action to protect pediatric safety and to preserve innovator manufacturers' pediatric market exclusivity rights. Improper application of section 11 could threaten those goals and pose serious harm to children. For that reason, the FDA should exercise the authority granted by section 11 to enact a regulatory process that can effectively deal with the practical obstacles proposed by its implementation. Ultimately, this process must ensure that generic drug products and their labels do not present a health risk for pediatric patients or diminish the market exclusivity Congress sought to protect.

C. ENVIRONMENTAL IMPACT STATEMENT

This petition is categorically excluded from the environmental impact statement requirement under 21 C.F.R. § 25.31.

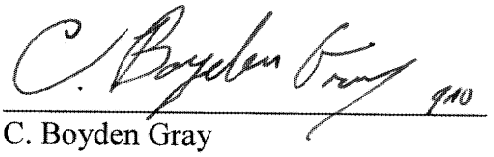
D. ECONOMIC IMPACT STATEMENT

The Commissioner has not requested economic impact information at this time.

E. CERTIFICATION

The undersigned certifies, that, to the best of his knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



C. Boyden Gray
WILMER, CUTLER & PICKERING
2445 M Street, N.W.
Washington, D.C. 20037
(202) 663-6000

Counsel for Petitioner