

WASHINGTON LEGAL FOUNDATION

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January 28, 2002

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

**Re: Citizen Petition Filed by Bristol-Myers Squibb Co. Requesting FDA
To Enact New Regulations to Implement Section 11 of the BPCA
Docket No. 01P-0586**

COMMENTS IN SUPPORT OF CITIZEN PETITION

The Washington Legal Foundation (WLF) hereby submits these comments in support of the Citizen Petition filed on December 26, 2001 by Bristol-Myers Squibb Co. (BMS) requesting that the Food and Drug Administration (FDA) issue new regulations to implement § 11 of the Best Pharmaceuticals for Children Act (BPCA), Pub. L. No. 107-109. WLF has not yet formed a clear view regarding the provisions that should be included in such regulations. WLF nonetheless agrees with BMS that it is essential for FDA to adopt such regulations in order to establish a uniform set of standards for carrying out the mandate of Congress as expressed in § 11. Such standards are necessary to ensure that the balance struck by Congress -- between the goal of rewarding research and development and the goal of lowering the costs of drugs through competition -- is maintained. Such standards are also necessary to ensure that public health is not endangered.

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Section 11 of the BPCA amends the Federal Food, Drug, and Cosmetic Act ("FDCA") by adding a new § 505A(o) (codified at 21 U.S.C. § 355a(o)). On the one hand, § 11 permits FDA to issue abbreviated new drug applications ("ANDAs") to generic drug manufacturers without complete labeling for pediatric use, where the omitted indication is protected by the pioneer manufacturer's patent or pediatric market exclusivity rights. On the other hand, § 11 contemplates situations in which FDA should require inclusion of such labeling when inclusion is "necessary" for public health reasons. Moreover, § 11 makes clear that any ANDAs granted to generic drug manufacturers should under no circumstances undermine the patent or exclusivity rights of the pioneer drug manufacturer. Those various provisions of § 11 are in tension with one another. BMS is correct that regulations are warranted for the purpose of relieving that tension to the extent possible and to ensure that FDA adopts a uniform approach to issuance of ANDAs to which § 11 applies.

Interests of WLF. The Washington Legal Foundation is a public interest law and policy center with supporters in all 50 states. WLF devotes a substantial portion of its resources to defending and promoting free enterprise, individual rights, and a limited and accountable government. In particular, WLF has appeared in numerous federal and state courts in cases raising issues related to health care delivery. *See, e.g., Pharmaceutical Research and Manufacturers of America v. Concannon*, No. 00-2446 (1st Cir., *en banc* decision pending) (constitutionality of Maine prescription drug price controls). WLF recently successfully challenged the constitutionality of FDA restrictions on speech regarding off-label

uses of FDA-approved products. *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998), *appeal dismissed*, 202 F.3d 331 (D.C. Cir. 2000).

WLF believes that both "pioneer" and generic pharmaceutical manufacturers play an important role in our health care system. WLF believes that if advances in health care are to continue, it is vital that pioneer companies that develop new drugs and medical devices be afforded a substantial period of exclusivity, during which potential competitors are not permitted to market the same product. That exclusivity period provides an economic incentive for new product development by ensuring that pharmaceutical companies that gamble the substantial sums necessary for the development of new therapies will be able to reap substantial rewards in those few instances in which their research and development expenditures bear fruit. On the other hand, once an appropriate period of exclusivity has expired, consumers are well served by government policies that encourage other companies to market generic versions of the new drug, thereby ensuring the competition necessary to produce lower prices. Both of those goals must, of course, be subservient to the federal government's overriding interest in promoting public health and safety.

Regulatory Background. There is an inherent tension between the two goals cited above -- rewarding research and development while lowering the cost of drugs through competition. Congress has attempted to strike a balance between those competing interests through a series of statutes adopted over the past 18 years. In 1984, Congress adopted the Drug Price Competition and Patent Term Restoration Act, commonly referred to as the

Hatch-Waxman Act. *See* Pub. L. 98-417, 98 Stat. 1585 (1984), codified at 21 U.S.C. § 355 and 35 U.S.C. §§ 156 and 271(e). The Hatch-Waxman Act benefited generic manufacturers by creating the ANDA procedure, which greatly streamlined the process by which generic manufacturers can receive FDA approval to market generic copies of pioneer drugs. 21 U.S.C. § 355(j). The Act benefited pioneer manufacturers by granting patent-term extensions under certain circumstances. 35 U.S.C. § 156. The Act also provided pioneer manufacturers with three years of exclusivity for label changes approved in supplemental new drug applications ("SNDAs"). 21 U.S.C. § 355(j)(5)(D)(i)-(v).

Congress later became concerned that not enough was known regarding the effects of approved drugs on children. Accordingly, a provision of the Food and Drug Administration Modernization Act ("FDAMA"), adopted by Congress in 1997, granted pioneer manufacturers financial incentives to undertake such research. FDAMA provided that manufacturers who performed such research would receive an additional six-month exclusivity period for the marketing of their drugs. 21 U.S.C. § 355a(c). FDAMA's pediatric exclusivity provision was a phenomenal success; the number of pediatric clinical trials increased from 11 in the seven years before adoption of FDAMA to over 400 in the past four years.

Congress revisited the issue in 2001 because the pediatric exclusivity provision was scheduled to expire on December 31, 2001. Members of Congress expressed general satisfaction with the balance that had been struck between the rights of pioneer manufacturers and generic manufacturers. Some Members were concerned, however, because Hatch-

Waxman's three-year pediatric marketing exclusivity provision had the effect, when combined with other FDA regulations, of creating an additional three-year bar on *all* generic competition for pioneer manufacturers that obtained SNDAs on the basis of pediatric clinical trials. Congress adopted the Best Pharmaceuticals for Children Act (BPCA) in December 2001 (and President Bush signed it into law on January 4, 2002) in order to: (1) extend FDAMA's pediatric exclusivity provision for six years; and (2) amend the law to permit FDA to approve ANDAs for generic manufacturers without regard to whether, due to Hatch-Waxman, those manufacturers are barred from including pediatric information on their product labels.

The latter issue is the subject of § 11 of the BPCA. In addition to permitting approval of ANDAs that were previously barred, § 11 provides: (1) FDA is permitted in appropriate circumstances to require generic manufacturers to include certain pediatric use information on product labels notwithstanding the pioneer manufacturer's pediatric marketing exclusivity rights (*see* 21 U.S.C. § 355a(o)(2)); and (2) none of the provisions of § 11 are intended to affect "the availability or scope" of exclusivity provisions otherwise provided to pioneer manufacturers (*see* 21 U.S.C. § 355a(o)(3)). Section 11 is silent regarding the circumstances under which FDA should exercise its authority to require pediatric labeling on generic drugs, and regarding how such authority is to be exercised in a manner that will not undermine "the availability or scope" of a pioneer manufacturer's pediatric marketing exclusivity rights.

The Importance of Pediatric Labeling. As BMS's Citizen Petition notes, FDA has long recognized that, without proper pediatric use labeling, drugs approved only for adult use may pose a health risk to pediatric patients. See Citizen Petition at 10-13. Improper labeling may affect both the safety and effectiveness 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 drug prescribed, or may be denied access to valuable therapeutic agents.

"Specific Requirements on Content and Format of Labeling for Human Prescription Drugs," 59 Fed. Reg. at 64,240 (Dec. 13, 1994).

FDA's legitimate concerns regarding proper pediatric use labeling led it, in 1994, to adopt regulations requiring every drug label to include pediatric use information. See 21 C.F.R. § 201.57(f)(9). For the many approved drugs for which no FDA-approved pediatric studies have been performed, manufacturers in most cases are required to include on the product label 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." 21 C.F.R. § 201.57(f)(9)(vi).

Members of Congress repeatedly have expressed their concerns regarding the absence of approved pediatric indications for drugs that are, in fact, being prescribed for use by children. Those concerns led to adoption of measures designed to encourage pioneer manufacturers to perform pediatric studies -- including Hatch-Waxman's three-year

exclusivity period for label changes approved in SNDAs and FDAMA's additional six-month marketing exclusivity for conducting pediatric studies on approved drugs.

Off-Label Use of Approved Drugs. The medical community's knowledge regarding the safety and efficacy of FDA-approved drugs and devices inevitably outpaces FDA-approved labeling. Physicians who regularly work with such drugs and devices learn of safe and efficacious uses for the drugs/devices that are not included within the labeling (generally referred to as "off-label" uses). In some fields such as oncology, the great majority of medically-accepted treatments involves off-label uses of FDA-approved drugs and medical devices. Accordingly, were doctors limited to using therapeutic products only as labeled, doctors would be providing sub-optimal care to their patients. In many cases, doctors simply could not treat their patients properly without resort to off-label uses. Indeed, just last year, the U.S. Supreme Court officially recognized off-label treatments as an important part of medical care in this country. See *Buckman Co. v. Plaintiffs' Legal Committee*, 121 S. Ct. 1012, 1018, 1019 n.5 (2001) ("'[O]ff-label' usage of medical devices (use of a device for some other purpose than that for which it has been approved by the FDA) is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine. . . . Off-label use is widespread in the medical community and often is essential to giving patients optimal medical care, both of which medical ethics, FDA, and most courts recognize.").

Accordingly, there will be many instances in which drugs that have been approved by

FDA for use only by adults (and thus are not labeled for pediatric use) will quite properly be prescribed for use by children. In those instances, it is very important that prescribing physicians have access to the medical profession's most accurate, up-to-date information regarding such off-label uses. Indeed, the First Amendment protects the right of manufacturers to disseminate (and of doctors and patients to receive) truthful information about off-label uses of their FDA-approved products, if that information is in the form of "enduring materials" (medical texts and peer-reviewed journal articles). *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998), *appeal dismissed*, 202 F.3d 331 (D.D.C. 2000).

But issues raised by § 11 of the BPCA do not involve "off-label use" of generic drugs, as that term is generally understood. Once FDA has approved a pioneer manufacturer's SNDA and has authorized labeling for an approved pediatric use, pediatric use of that drug in accordance with the approved labeling can no longer be deemed "off-label," in the traditional sense of a use endorsed by the medical profession but not yet approved by FDA. Thus, pediatric use of a generic drug being marketed without the pioneer manufacturer's pediatric labeling (due to Hatch-Waxman's labeling exclusivity provision) should not be viewed in the same light as traditional "off-label" uses. Rather, it is the "on-label" use of a product -- but a use for which the prescribing physician is being denied full access to FDA-approved prescribing information. For all the reasons cited above, FDA has good reason to be concerned about pediatric use of such generic drugs being marketed without complete FDA-approved pediatric labeling information.

The BPCA's Inherent Tensions. Although the sale of generic drugs that are likely to be prescribed for children yet do not include accurate pediatric labeling raises legitimate safety concerns, Congress indicated its willingness to accept a certain amount of risk by its adoption of the BPCA. Congress determined that those risks were outweighed, in at least some instances, by the cost advantages provided to consumers by the marketing of generic drugs. Thus, it provided that a generic drug shall not be ineligible for an ANDA and shall not be deemed misbranded because its labeling "omits a pediatric indication or any other aspect of labeling pertaining to pediatric use," when the information is omitted because the pioneer manufacturer has been granted exclusive pediatric labeling rights under the Hatch-Waxman Act. 21 U.S.C. § 355a(o)(1).

At the same time, Congress recognized the safety concerns raised by the absence of pediatric labeling on generic drugs. Accordingly, it granted FDA authority -- notwithstanding a pioneer manufacturer's Hatch-Waxman pediatric labeling exclusivity -- to require certain pediatric labeling on generic drugs where necessary to alleviate those safety concerns. 21 U.S.C. § 355a(o)(2). The BPCA even authorizes FDA to mandate, where "necessary," "a statement of any appropriate pediatric contraindications, warnings, or precautions." 21 U.S.C. § 355a(o)(2)(B). At the same time, the BPCA makes clear that any such pediatric labeling should not be deemed to affect "the availability or scope" of exclusivity provisions otherwise provided to pioneer manufacturers. 21 U.S.C. § 355a(o)(3).

The BPCA leaves to FDA's discretion the decision whether to require pediatric

labeling under § 355a(o)(2). Accordingly, FDA needs to adopt some sort of procedure for determining when it will exercise that discretion. WLF agrees with BMS that establishing such a procedure would be best handled through a notice-and-comment rulemaking.

Moreover, in light of FDA's longstanding commitment to providing doctor's and patients with the best-available pediatric information on product labeling, WLF respectfully suggests that FDA create a presumption that pediatric information *should* be included on generic drug labels, unless an interested party can demonstrate that the absence of such information is highly unlikely to affect safety and effectiveness.

Any final regulation must seek to balance the conflicting interests recognized by Congress as legitimate. On the one hand, Congress sought to provide consumers with lower prices by authorizing manufacturers to market generic versions of drugs to adults notwithstanding any Hatch-Waxman pediatric marketing exclusivity rights possessed by the pioneer manufacturer. On the other hand, Congress sought to encourage increased research into pediatric indications for approved drugs, by providing financial incentives to pioneer manufacturers to engage in such research. Moreover, Congress sought to ensure that the marketing of generic drugs under circumstances covered by § 11 of the BPCA did not adversely affect the health and safety of children. WLF does not claim to have come up with the perfect solution for balancing those competing interests, but what follows are some tentative suggestions.

Statements Discouraging Pediatric Use of Generic Drugs. As noted above, WLF

believes that, in general, FDA should create a presumption against the marketing of generic drugs without *any* labeling regarding pediatric use. Rather, in most cases, the choice should come down to whether to require labeling along the lines envisioned in § 355a(o)(2)(A) or labeling along the lines envisioned in § 355a(o)(B). In those cases in which pediatric use does not implicate any serious contraindications, precautions, or warnings that are not already present for adult use, labeling along the lines envisioned in § 355a(o)(2)(A) should be sufficient.

WLF agrees with BMS regarding the wording of labeling to be required by § 355a(o)(2)(A). A statement that "because of manufacturing exclusivity, the drug is not labeled for pediatric use" would be inappropriate because it would be highly misleading. It might cause the prescribing physician to believe (falsely) that the active ingredient in the generic drug should never be administered to children. Rather, the labeling should actively discourage pediatric use of the generic drug without in any way suggesting that the active ingredient is harmful to children. WLF suggests the following statement: "THIS MANUFACTURER'S PRODUCT IS NOT TO BE ADMINISTERED TO CHILDREN."

Mandatory Licensing Scheme. WLF recognizes, of course, that many parents will end up obtaining the generic version of a drug for use by their children even though a pioneer manufacturer holds pediatric marketing exclusivity for the drug under the Hatch-Waxman Act. In any such instances in which there are serious contraindications, warnings, or precautions that need to be supplied to pediatric populations and are not already being

supplied in connection with the adult labeling, safety concerns dictate that FDA exercise its authority under § 355a(o)(2)(B) to mandate the inclusion of that information on the generic product labeling.

But any order mandating the inclusion of such information will require FDA to resolve the inherent tension between § 355a(o)(2) and § 355a(o)(3). If the pediatric labeling for generic drugs includes information on contraindications, warnings, and/or precautions, then the pioneer manufacturer's pediatric labeling exclusivity becomes largely meaningless. If all or most pertinent information for pediatric use is included on the generic product labeling, there is nothing left to the economic advantage that Congress intended to grant to pioneer manufacturers in order to encourage SNDA applications. But § 355a(o)(3) makes crystal clear that Congress did not intend the BPCA to deprive pioneer manufacturers of that economic advantage.

WLF respectfully suggests that a mandatory licensing scheme is the proper method by which FDA can resolve the tension between the two BPCA provisions. The FDA regulations should require generic manufacturers, as a condition of their receipt of an ANDA, to agree to pay a fee to the pioneer manufacturer for the use of the information developed by the pioneer manufacturer regarding contraindications, warnings, and/or precautions.

The licensing fee should be set at a level that would not unduly discourage the production of generic drugs but at the same time would ensure that -- for so long as the Hatch-Waxman pediatric marketing exclusivity is in force -- the pioneer manufacturer

captures all profits derived from the sale of the drug for pediatric uses. For drugs that are only rarely prescribed for pediatric use, the licensing fee would be minimal. For drugs that are predominantly prescribed for pediatric use, the licensing fee would be considerably higher; but that is only as it should be, given Congress's intent to reward pioneer manufacturers that perform pediatric studies that provide information of great value to large numbers of patients.

So long as a generic manufacturer agrees to pay a licensing fee, issuance of the ANDAs should not be delayed pending completion of their negotiations with the pioneer manufacturer over the precise amount of the fee. If the two manufacturers cannot come to an agreement, FDA regulations should provide a mechanism by which it will resolve the dispute.

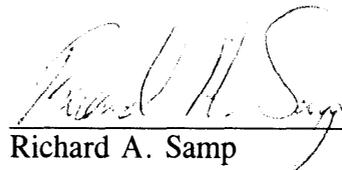
WLF can think of no method, other than the licensing scheme described above, by which FDA can square the need to ensure the safety and effectiveness of generic drugs (by mandating the inclusion of "necessary" information on product labeling) with the need to protect the legitimate interests of pioneer manufacturers in the value of the pediatric use information they developed in reliance on government promises of exclusivity. Any other resolution of this issue risks either unnecessary endangerment of children's health or the uncompensated taking of private property, in violation of the BPCA's clear mandate as well as the Fifth Amendment rights of pioneer manufacturers.

Conclusion. The Washington Legal Foundation respectfully requests that FDA grant BMS's Citizen Petition. FDA should initiate a rulemaking proceeding and issue a regulation that would specify the circumstances under which FDA will, pursuant to 21 U.S.C. § 355a(o)(2), require the inclusion of pediatric labeling on generic drugs. The regulation should address the issue of how pioneer manufacturers will be compensated when the inclusion of pediatric labeling on generic drugs has the effect of denying them pediatric marketing exclusivity rights afforded them under the Hatch-Waxman Act.

Respectfully submitted,



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