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Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
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Re: Bristol-Myers Squibb Company's Citizen Petition For New And/Or Amended Regulations For the BPCA; Docket No. 01P-0586.

RESPONSE TO CITIZEN PETITION

The undersigned counsel, on behalf of Watson Laboratories Inc. (Watson), submit this response to the citizen petition filed with the Food and Drug Administration (FDA) on December 26, 2001 on behalf of Bristol-Myers Squibb Company (BMS) requesting that the FDA "adopt expeditiously" regulations to implement certain provisions of the Best Pharmaceuticals for Children Act (BPCA), Pub. L. No. 107-109, ___ Stat. ___ (2002). Having failed in Congress to obtain legislative protection for its \$1.8 billion Glucophage® monopoly, BMS is resorting to bogus procedural arguments in a desperate attempt to

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prevent generic competition. Moreover, despite BMS's claim that the petition was filed "to assist" the FDA, the petition is deficient on its face by failing to include wording for the proposed regulations as required under 21 C.F.R. § 10.30(a)(1). The petition is wholly without merit and should be denied promptly. In any event, the FDA should not allow BMS to succeed in delaying the approval of any application for generic Glucophage®.

BACKGROUND

A. Regulatory Scheme

The Federal Food, Drug, and Cosmetic Act (FDCA) requires that a company that intends to market a new drug in the United States must file a new drug application (NDA) and obtain FDA approval before the drug may be marketed. See 21 U.S.C. § 355(a). Approval of an NDA requires proof of safety and efficacy based on adequate and well-controlled clinical studies. See id. at § 355(b)(1) and (d).

In 1984, the FDCA was amended by the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417 (the Hatch-Waxman Act), to expedite the approval of generic versions of prescription drugs to increase the availability of low-cost drugs. The Hatch-Waxman Act authorizes manufacturers of proposed generic versions of an innovator drug to obtain approval of an abbreviated new drug application (ANDA) based on proof of bioequivalence to the innovator drug, rather than requiring the ANDA applicant to conduct new clinical trials and proceed through a full-blown NDA process. See id. at § 355(j). The Hatch-Waxman Act also provides periods of marketing exclusivity to the NDA applicant

for the innovator drug. When an NDA holder obtains marketing exclusivity, the FDA cannot approve any ANDA submitted for a generic version of the innovator drug that relies on the same clinical investigations required for approval which are conducted or sponsored by the NDA applicant.

In 1997 the FDCA was amended by the Food and Drug Administration Modernization Act of 1997 (FDAMA). To encourage drug manufacturers to conduct clinical studies on pediatric uses for prescription drugs, one provision of FDAMA authorized the FDA to grant an additional six months marketing exclusivity to NDA holders conducting pediatric clinical studies on approved drugs. See 21 U.S.C. § 355a.

The pediatric exclusivity provision of the FDCA expired on January 1, 2002 pursuant to a sunset provision in the statute. See id. at § 355a(j). On December 18, 2001 Congress passed the BPCA. It is our understanding that President Bush signed the BPCA on January 4, 2002. The BPCA extends the sunset provision of section 355a until October 1, 2007.

Section 11 of the BPCA allows the FDA to approve ANDAs notwithstanding the fact that the innovator has received three years of Hatch-Waxman exclusivity for a pediatric use if the generic drug's labeling does not include pediatric indications or "any other aspect of labeling pertaining to pediatric use." The law also provides that the FDA may require that the labeling of any such generic drug that omits pediatric indications or uses contain statements that the drug is not labeled for pediatric use because of marketing exclusivity of

the pioneer manufacturer. See BPCA §11. The BPCA states that Section 11 takes effect on the date of enactment of the BPCA and applies to any ANDAs that are approved or pending on that date. Id. Watson has a pending ANDA for a generic of Glucophage®.

B. Citizen Petition

BMS manufactures and markets, among other products, Glucophage® (metformin hydrochloride), which is used in the management of Type 2 diabetes. The FDA approved BMS's NDA for Glucophage® on March 3, 1995. In 1998 BMS began pediatric clinical trials to study pediatric uses for Glucophage®. FDA subsequently approved a supplemental NDA (SNDA) for BMS to include pediatric use information in Glucophage® labeling. BMS was granted three years Hatch-Waxman exclusivity for the pediatric indication approved under the SNDA along with an additional six months pediatric exclusivity.

To delay the implementation of Section 11 and FDA approval of ANDAs for generic Glucophage®, BMS filed its citizen petition arguing, *inter alia*, that Section 11 is not self-executing and thus the FDA is required to promulgate regulations, following notice-and-comment rulemaking proceedings. BMS also maintains that the FDA is required to reevaluate and revise its existing labeling regulations to make them consistent with the provisions of Section 11 of the BPCA.

In addition, BMS contends that the FDA must adopt new regulatory procedures for considering ANDAs under Section 11 to avoid risk to the public health from the omission

of pediatric use information on generic drug labels. BMS apparently maintains that the FDA must conduct administrative proceedings - subject to public notice and comment - before approving any ANDAs for drugs that omit pediatric use information from labeling. In short, BMS is asking the FDA to adopt procedures that would bring the ANDA approval process to a standstill in derogation of the purpose of the Hatch-Waxman Act to expedite the approval of safe and effective generic drugs.

DISCUSSION

A. FDA Is Not Required To Promulgate Regulations To Implement Section 11 Or To Revise Its Existing Regulations.

Section 11 of the BPCA, entitled "Prompt Approval of Drugs Under Section 505(j) [21 U.S.C. § 355a(j)], When Pediatric Information is Added to Labeling," provides, in relevant part, that FDA "may require that the labeling of a drug approved under section 505(j) that omits a pediatric indication or other aspect of labeling . . . include" statements in regard to the extent or effect of pediatric exclusivity or statements of any appropriate contraindications or warnings for pediatric use. Nothing in the BCPA says that the FDA is required to adopt regulations or new regulatory procedures to approve ANDAs that omit pediatric labeling that is protected by exclusivity. Indeed, FDA already has in place one regulation that provides that an ANDA applicant's proposed labeling may vary from the innovator's labeling by omitting "an indication or other aspect of labeling protected by patent or accorded exclusivity." 21 C.F.R. § 314.94 (a)(8)(iv). Arguably, this provision

would have allowed approval of metformin ANDAs even prior to the enactment of the BPCA. Now that the BPCA has been passed, any uncertainty about the scope of § 314.94(a)(8)(iv) has been resolved in favor of the approval of generic drugs.

In addition, the law is clear that in the absence of a statutory mandate, an administrative agency is not required to promulgate regulations to implement a statute. See e.g. Pulido v. Heckler, 758 F. 2d 503, 506 (10th Cir. 1985); Travers v. Sullivan, 801 F. Supp. 394, 401 (E.D. Wash. 1992) citing SEC v. Chenery Corp., 332 U.S. 194 (1947); Weight Watchers of Greater Washington State, Inc. v. FTC, 1995-2 Trade Cases, 75, 297, 75,298 (1995). As stated by the Supreme Court in Chenery Corp.

Not every principle essential to the effective administration of a statute can or should be cast immediately into the mold of a general rule. Some principles must await their own development, while others must be adjusted to meet particular, unforeseeable situations. In performing its important functions in these respects, therefore, an administrative agency must be equipped to act either by general rule or by individual order. To insist on one form of action to the exclusion of another is to exalt form over necessity.

332 U.S. at 202. Instead, the FDA is entitled to deference in determining whether regulations are necessary. See Young v. Community Nutrition Institute, 476 U.S. 974, 981 (1986)(Despite statutory language that the FDA “shall” promulgate regulations establishing tolerance levels for the presence of a carcinogen in some foods, the FDA’s interpretation of the provision to require tolerance levels only to the extent the agency found them necessary for the protection of the public health was “sufficiently rational” to preclude the court from

substituting its judgment for that of the agency.) Where, in this case, the BPCA does not mention regulations, FDA is entitled to even greater deference in deciding whether to implement Section 11 without regulations.

BMS quotes statements by Representatives Tauzin and Jackson Lee during congressional debates on the BPCA as support for its assertion that the FDA is required to promulgate implementing regulations for Section 11. However, the language of the statute itself, which was approved by both representatives, neither requires nor expressly empowers the FDA to enact labeling requirements. Therefore, these statements cannot impose an obligation on FDA to issue regulations.¹ See U.S. v. Hansen, 566 F. Supp. 162, 168 (D.D.C. 1983 “[w]hile a court may seek from the public record to ascertain the collective intent of Congress when it interprets a statute, the subjective intent of any particular person involved in the legislative process is not determinative.”) citing NLRB v. Fruit and Vegetable Packers and Warehousemen, 377 U.S. 58, 66 (1964). It is telling that BMS does not provide any authority in support of its argument that statements by

¹ The United States District Court of the District of New Hampshire in Cohen v. Georgia-Pacific Corp., 819 F. Supp. 133, 140 (D.N.H. 1993), summed up the appropriate weight to be given to statements of individual legislators: “[i]t is very common for Members of the Senate to try to affect the way in which a court will interpret a statute by putting things into the Congressional Record. . . . Whatever is said on the floor of the Senate about a bill is the view of the Senator who is saying it. . . . [A] court would be well advised to take with a large grain of salt floor debate and statements placed into the Congressional Record to create an interpretation for the legislation before us.” Id.

individual lawmakers in the Congressional Record should control the implementation of the BPCA.

In contrast, in another section of the BPCA Congress clearly exercised its authority to require FDA to act in a certain manner. Section 3 of the BPCA amends the Public Health Service Act and provides that “not later than 270 days after the date of enactment of this section, the Commissioner of [FDA] shall promulgate guidance to establish procedures for the submission of responses” pursuant to written requests for pediatric studies for specific drugs by the FDA. Public Health Service Act, Pub. L. No. 107-109, _____ Stat. _____, § 409I(c)(4)(emphasis supplied). Had Congress required the FDA to promulgate implementing regulations for Section 11, it would have clearly done so by stating, for example, that the FDA “shall promulgate regulations” rather than saying “may” require certain labeling statements. See Brown v. Gardner, 514 U.S. 115, 120 (1994) quoting Russello v. United States, 464 U.S. 16, 23 (1983) (“Where Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion.”); cf. Pulido 758 F. 2d at 506 (the word “shall” does not merely empower agency action, but commands action) citing McCoy v. Schweiker, 683 F.2d 1138, 1143 (8th Cir. 1982).

BMS in effect concedes that the BPCA does not require regulations by repeatedly stating that the BPCA “authorizes” the FDA to issue regulations to implement Section 11. Of course, FDA has broad authority under Section 701(a) of the FDCA to promulgate regulations for the efficient enforcement of the Act. See 21 U.S.C. § 371(a). The BPCA does not add or subtract from this authority.

Moreover, even if Congress had expressly required the FDA to promulgate implementing regulations, there is nothing in the BPCA nor any authority provided by BMS, that would prevent FDA from regulating from the statute until any regulations were finalized. In fact, Section 105(a) of the Hatch-Waxman Act ordered the FDA to promulgate implementing regulations within one year. See Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585-97 (1984). However, the implementing regulations for approval of ANDAs were not issued until April of 1992. See FDA Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950 (Apr. 28, 1992). Yet the FDA approved ANDAs as directed under of the Hatch-Waxman Act throughout the eight years before issuance of the implementing regulations. Similarly, the FDA can regulate drug approval and drug labeling as directed under the BPCA without promulgating implementing regulations.

The FDA’s authority to regulate directly from the FDCA and to make drug approval determinations on a case-by-case basis, without issuing regulations, has been recognized by

the United States Court of Appeals for the District of Columbia Circuit with respect to determining an ANDA applicant's entitlement to 180 days of market exclusivity under the Hatch-Waxman Act. In Teva Pharmaceuticals, USA, Inc. v. FDA, 182 F.3d 1003 (D.C. Cir. 1999), the court upheld the FDA's decision to make decisions on 180-day generic exclusivity on a case-by-case basis, unless and until such time as the agency promulgated rules for determination of such market exclusivity, stating that "the FDA may regulate directly from the statute . . . in determining the first applicant's entitlement to 180 days of market exclusivity." Id. at 1005; see also, Purepac Pharmaceutical Co. v. Friedman, 162 F.3d 1201, 1204-5 (D.C. Cir. 1998). The FDA similarly can approve on a case-by-case basis any pending ANDAs for generic Glucophage® that are not labeled for pediatric use unless and until such time as the agency determines that amendments to the labeling regulations and requirements are necessary.

Nothing in BMS's petition supports the position that the FDA is required to promulgate regulations, subject to public notice and comment, to establish drug labeling requirements before implementing the BPCA. Thus, BMS's petition should be denied.

B. FDA Does Not Need To Implement Any Additional Procedures To Determine Whether the Lack of Pediatric Use Information On A Generic Drug Label Will Create a Public Health Risk.

BMS also maintains that the FDA must prevent great risk to the public health by implementing procedures for evaluating ANDAs that, due to innovator pediatric exclusivity

rights, omit pediatric indication and use information from generic drug labeling. In fact, BMS argues that the FDA should solicit public comment on each generic drug and the content of each drug's labeling, before approving any ANDA that omits protected pediatric labeling. This is a transparent attempt, disguised as a concern for the public interest, to unreasonably delay approval of ANDAs for generic competitors to Glucophage® and continue BMS's monopoly on the market for a drug that is important to the management of Type 2 diabetes.

BMS fails to cite any legal authority or provision in either the FDCA or the BPCA that would require the FDA to implement any new approval procedures above and beyond existing ANDA approval and labeling requirements. See 21 U.S.C. § 355; 21 C.F.R. §§ 201.56-59, 314.105. Moreover, the FDA makes decisions about ANDAs and the content of labeling for generic drugs every day. That is what the Office of Generic Drugs (OGD) does. Often these decisions involve labeling that is different from the innovator's labeling because of patent or exclusivity issues. BMS's contention that OGD must convene some type of public proceeding for each ANDA that omits protected pediatric use information is not only legally insupportable, it would create an unprecedented intrusion into the drug approval process.

C. BMS's Concern For Potential Off-Label Use Of Generic Drugs Does Not Support An FDA Requirement For New Labeling Regulations.

BMS contends that the omission of pediatric use information may result in the prescribing of generic drugs for off-label uses and that such off-label use will undermine an innovator's exclusivity rights. However, as BMS well knows², the FDA does not regulate the off-label use of drugs by physicians and patients. Off-label use of drugs by physicians and consumers is a long standing practice that has been recognized by the courts. See Washington Legal Foundation v. Henney, 202 F.3d 331, 333 (D.C. Cir. 2000). Congress had the opportunity to consider the effect of off-label use on the exclusivity rights of drug innovators when passing the BPCA. However, Section 11 was passed with no language restricting off-label uses of drugs and despite BMS's concerns of any perceived adverse effect on BMS's marketing exclusivity rights. In fact, the BPCA expressly states that Section 11 does not affect

(A) the availability or scope of exclusivity under [Section 505a(o)]; (B) the availability or scope of exclusivity under section 505 for pediatric formulations; (C) the question of eligibility for approval of any application under section 505(j) that omits any other conditions of approval entitled to exclusivity under clause (iii) or (iv) of section 505(j)(5)(D); or (D) except as provided in paragraphs (1) and (2) the operation of section 505.

² Many of BMS's cancer drugs are used off-label.

Any marketing exclusivity rights held by BMS will not be infringed by the implementation of Section 11 of the BPCA.

D. BMS's Petition Does Not Comply with 21 C.F.R. § 10.30

An FDA regulation sets forth the requirements for submission of a citizen petition. See 21 C.F.R. § 10.30. The regulation requires that “[i]f the petition requests the Commissioner to issue, amend, or revoke a regulation, the exact wording . . . of the proposed regulation” must be set forth in the petition. Id. at § 10.30(b)(1). BMS's Petition argues that the FDA is required to promulgate substantial implementing regulations, amend existing regulations and implement a new procedure for ANDA approval. Despite BMS's expressed concern for the public health and its purported desire to assist the FDA, BMS has failed to meet the threshold requirements for a citizen petition. One might expect that BMS, with its extensive knowledge of metformin, would have been able, for example, to propose specific amendments to FDA's regulations, or even suggested labeling for metformin generics, to address BMS's professed concerns. BMS did not do so because its real concern is delaying generic competition.

CONCLUSION

Section 11 expressly authorizes the FDA to approve ANDAs that do not include pediatric use information that is subject to statutory exclusivity. The law does not mandate the FDA to promulgate any regulations to implement Section 11 of the BPCA, nor does BMS's petition provide any evidence or authority which supports the issuance of

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implementing regulations. Further, nothing in BMS's petition supports the company's argument that the FDA must establish new approval procedures for each generic drug that omits pediatric use information from labeling - procedures which would include public comment on each drug and the content of that drug's labeling.

Finally, BMS's petition is not only deficient in substance, but also fails to meet the FDA's requirements for filing a citizen petition requesting the promulgation of regulations by not providing proposed language for such regulations. Therefore, BMS's petition should be denied.

Respectfully submitted,



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