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Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 00D-1537, Draft Guidance for Industry on Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications, *65 Federal Register 64225, October 26, 2000*

Dear Sir or Madam:

FDA has proposed a Guidance to allow generic applicants to reference discontinued labeling for listed drugs in Abbreviated New Drug Applications ("ANDAs"). Bristol-Myers Squibb is a worldwide health care company that develops innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders. As such, our company conducts the research that is the basis for the labeling of our drugs and subsequent generic copies. Thus, we are very interested in commenting on the Draft Guidance.

We believe that the Agency's Draft Guidance should not be adopted.

First, the Draft Guidance is inconsistent with the Federal Food, Drug & Cosmetic Act ("FFDCA") and FDA's own implementing regulations. These regulations require (with two inapplicable exceptions) ANDA sponsors to demonstrate that their labeling is the "same as the labeling of the reference listed drug." To effectuate the change proposed in the Draft Guidance, Congress would have to amend the FFDCA.

The Draft Guidance also violates basic procedural safeguards afforded to the public under the Administrative Procedure Act ("APA"). Because the Draft Guidance reflects a *significant* change in FDA policy and contradicts existing regulations, FDA's proposed approach of allowing ANDA applicants to reference discontinued labeling cannot lawfully be adopted through a guidance document. To comply with the APA, FDA would need to undertake notice and comment rulemaking to propose an amendment to FDA's existing regulations.

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Further, FDA's proposed standard for determining which discontinued labeling may be referenced is arbitrary and capricious. This standard would permit suboptimal labeling for generic drugs, which could compromise patient care.

Finally, the Guidance would discourage improvements in marketed drugs and disturb the balance between stimulating innovation and facilitating generic approvals struck by Congress in the Hatch-Waxman Amendments.

Each of these points is discussed more fully below.

A. FDA's Draft Guidance Violates the Language of the FFDCA

The Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Amendments") amended the FFDCA to require a drug approved through an Abbreviated New Drug Application ("ANDA") to contain labeling that is the "same as the labeling approved for the listed drug." FFDCA § 505(j)(2)(A)(v). The statute allows for only two exceptions to this "same labeling" requirement: (1) differences reflecting changes in the product approved under a suitability petition, and (2) differences reflecting the identity of the appropriate manufacturer or distributor of products that are manufactured or distributed by more than one entity. Id. FDA's Draft Guidance suggests an approach to generic drug labeling that contradicts the statutory language enacted by Congress. Because discontinued labeling would not be the same and does not fall within any of the exceptions to the same labeling requirement, the Agency seeks to adopt an approach that contravenes the governing statute.

One objective of the Hatch-Waxman Amendments generic drug provisions is to ensure safety by approving generic drugs that contain labeling that is the same as the reference listed drug. This approach, among other things, is intended to minimize prescriber confusion that can lead to medical errors. FDA has also expressed concern regarding confusing labels in its recent proposed rule: "An increase in the amount, detail, and complexity of labeling information . . . has made it harder for health care practitioners to find specific information and to discern the most critical information in product labeling." 65 Fed. Reg. 81,082, 81,083 (Proposed Rule, Dec. 22, 2000). Clearly, it is inconsistent with FDA's expressed intent of reducing the complexity of prescription drug labeling to allow the generic version of a reference listed drug to contain a different label. Further, FDA has not demonstrated that the benefit of using discontinued labeling outweighs the risk of adding to the complexity and confusion of prescription drug labeling.

When new labeling replaces previous labeling there is a presumption that the new labeling offers some degree of benefit or improvement over the discontinued labeling by virtue of FDA's approval of the labeling revision. Therefore, while FDA may determine in some instances that the discontinued labeling was not removed for reasons of safety or efficacy, the Agency's

proposed approach does not take into account the added benefit that the new labeling presumably provides.

FDA has recognized that the "same labeling" provision is a necessary safety measure because it allows patients to switch between different manufacturers' versions of the same drug. "Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart." 57 Fed. Reg. 17950, 17961 (April 28, 1992) (citation omitted). FDA continues to express a preference for same labeling in the Draft Guidance yet inexplicably abandons that policy. For example, FDA states that ANDA applicants that reference discontinued labeling should conform to the labeling of the marketed innovator product when the exclusivity or patent protecting the labeling expires. This requirement indicates that FDA considers the use of identical labeling important. In the absence of a compelling reason to do otherwise, which has not been provided in this guidance, ANDAs should contain the same labeling.

B. FDA's Draft Guidance Violates the Agency's Regulations

FDA enacted regulations pursuant to notice and comment rulemaking implementing the ANDA labeling provisions of the Hatch-Waxman Amendments. FDA's regulations require ANDA applicants to demonstrate that their labeling is the "same as the labeling of the reference listed drug." 21 C.F.R. § 314.94(a)(8)(iii). The FDA regulations provide for the same two exceptions as the FFDCA (see section A above). 21 C.F.R. § 314.94(a)(8)(iv).

FDA's regulations further limit generic labeling to differences from the label of the reference listed drug obtained by "omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act." Id. Under this regulation, the ANDA label must contain current product labeling for the indications for which they are approved and for which they are intended to be used. However, the regulation does not allow for omission of an *aspect* of labeling concerning an indication for which the ANDA is seeking approval. In fact, FDA's Draft Guidance goes further by permitting not only the *omission* of current approved labeling, but the resurrection of discontinued labeling to *substitute* for current labeling required in a generic label. Such labeling simply would not be the "same" as that of the pioneer drug.

C. FDA's Draft Guidance Violates the APA

FDA's Draft Guidance amounts to an unlawful rulemaking in violation of the APA. Specifically, the Draft Guidance violates the principle that regulations promulgated through notice and comment rulemaking can only be modified through notice and comment rulemaking. See, e.g., Shalala v. Guernsey Memorial Hosp., 514 U.S. 87, 100 (1995) (rulemaking required if Agency adopts new position inconsistent with any of the Agency's existing regulations); First National Bank of Chicago v. Standard Bank & Trust, 172 F.3d 472, 479 (7th Cir. 1999) ("once a regulation is adopted by notice-and-comment rulemaking . . . its text may only be changed in the same manner") (citing Homemakers North Shore Inc. v. Bowen, 832 F.2d 408, 413 (7th Cir.

1987)); Columbia Falls Aluminum Co. v. EPA, 139 F.3d 914, 919 (D.C. Cir. 1998) ("Once a rule is final, an agency can amend it only through a new rulemaking"). Because the Agency's existing regulations are a product of notice and comment rulemaking, they may only be amended or modified through that same procedure.

Indeed, the legislative history of the Hatch-Waxman Amendments reinforces the notion that FDA may not issue regulations regarding generic drug approvals outside of the notice and comment rulemaking procedure. Section 105(a) requires the FDA to promulgate such regulations as are necessary to implement new subsection (j). These regulations must be promulgated in accordance with the informal rulemaking requirements of Title 5 of the United States Code. . . U.S.C.C.A.N. P.L. 98-417, 36 (emphasis added). FDA makes no attempt to reconcile the Draft Guidance with this fundamental requirement of administrative law.

Furthermore, the Draft Guidance proposes a substantive change so fundamental to the statute and to FDA's regulations that it in any case would require notice and comment rulemaking. Because the change FDA proposes presents a novel interpretation of the Hatch-Waxman Amendments and contradicts current FDA regulations, the Agency cannot assert that the Draft Guidance is a mere interpretation of existing law and regulations. The Draft Guidance is legislative in nature. In fact, FDA's own characterization of the Draft Guidance demonstrates the Agency's intent to promulgate a policy that will have legislative effect. FDA acknowledges that "this issue is not addressed directly in the regulations governing the approvals of ANDAs." (Draft Guidance at 1.) Rather than amending the current regulations to address this issue, FDA seeks to address it directly through an unlawful guidance document procedure. If FDA believes that this policy is appropriate, FDA should propose to amend its regulations and not attempt to undermine the legitimate process with an unlawful guidance document.

D. FDA's Proposed Approach to Determining Which Discontinued Labeling May Be Referenced is Arbitrary and Capricious and Could Compromise Patient Care

FDA's Draft Guidance approach involves a determination by FDA of whether the discontinued labeling was removed for reasons of safety or efficacy. FDA states in the Draft Guidance that in making this determination the Agency will use the same criteria used to determine if a drug *product* was removed from the market for reasons of safety or effectiveness. This criteria is inappropriate for determining the reason for discontinuing the use of an aspect of *labeling.*

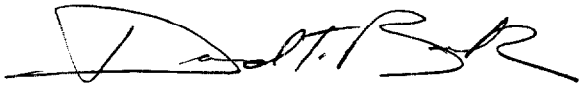
The standard should not be whether the removal of current aspect of labeling would justify removal of the product from market. The standard should be whether the resurrection of the discontinued labeling renders the product *less* safe or *less* effective than the product with the most current complete labeling. FDA should not permit a generic to be marketed with labeling that would compromise patient health to any extent. Drug products are generally removed from the market if they are clearly unsafe. But suboptimal labeling could result in substandard patient care, even if the lableing is not "unsafe". This is clear underpinning of the statutory requirement that generic labeling must be identical to the innovator labeling.

E. The Guidance Would Discourage Improvements to Marketed Drugs

The Hatch-Waxman Amendments represent a carefully drawn balance between the value of stimulating innovation and the value of facilitating the approval of generic drug products. The Draft Guidance would disrupt the balance struck by Congress. The value of innovation is reflected clearly in carefully drafted provisions that provide innovators with additional periods of exclusivity for certain drug improvements. The Draft Guidance would discourage innovators from undertaking clinical study programs yielding drug improvements, which merit additional Hatch-Waxman exclusivity but result in drug labeling changes that FDA discards to allow generics to reference - at least temporarily - discontinued labeling. This threat to innovation is too significant to make through an informal guidance procedure.

Bristol-Myers Squibb appreciates the opportunity to provide comment and requests that FDA give consideration to our recommendation. Upon request, we would be pleased to provide additional information.

Sincerely,



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