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January 24, 2001

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

Re: Docket No. 00D-1537: Draft Guidance for Industry on Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications

Dear Sir or Madam:

Purepac Pharmaceutical Company ("Purepac"), a division of Faulding Pharmaceuticals, develops and manufactures prescription pharmaceutical products for a broad range of therapeutic markets. Purepac respectfully submits the following comments on the Food and Drug Administration's ("FDA's" or "the Agency's") draft guidance document, "Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications," 65 Fed. Reg. 64225 (Oct. 26, 2000) (Docket No. 00D-1537) (hereinafter, "Guidance Document"). Comments are due by January 24, 2001.

The Guidance Document proposes that in certain circumstances an Abbreviated New Drug Application ("ANDA") should be permitted to reference discontinued labeling for a listed drug where safety and efficacy are not implicated. Purepac supports FDA's proposed approach to referencing discontinued labeling for listed drugs in ANDAs, and is encouraged by publication of the Guidance Document.

The Guidance Document should be adopted for several reasons.

1. The Guidance Document is consistent with the Federal Food, Drug, and Cosmetic Act ("FDC Act") and FDA's ANDA regulations. See 21 C.F.R. § 314.94(a)(8)(iv) (labeling - comparison of approved and proposed labeling).

2. The Guidance Document allows FDA to exercise its expertise in determining safety and effectiveness on a case-by-case basis.

3. The Guidance Document is good public policy that maintains the purpose and spirit of the "Hatch-Waxman Act"[1] by promoting the prompt development and marketing of low-cost generic drugs.

[1] Pub. L. No. 98-417, 98 Stat. 1585 (codified at 15 U.S.C. §§ 68b-68c, 70b (1994)); 21 U.S.C. §§ 301 note, 355, 360cc; 28 U.S.C. § 2201 (1994); 35 U.S.C. §§ 156, 271, 282 (1994).

In submitting these comments, Purepac hopes to assist FDA in achieving swift resolution of this issue, and requests that FDA issue a final version of the Guidance Document in as expeditious a manner as possible.

I. The Guidance Document is Consistent with the FDC Act, Appropriately Clarifies FDA's Implementing Regulations, and is a Proper Exercise of FDA Authority.

A. The FDC Act Supports Implementation of the Guidance Document.

The Hatch-Waxman Act established the generic drug approval process. This process requires that an ANDA must contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for [the reference listed drug]."[2] The Guidance Document, which allows a generic applicant to reference discontinued labeling in an ANDA, is clearly consistent with this provision of the FDC Act. A generic applicant who references the discontinued labeling of a listed drug in an ANDA has met the burden of proof required by the plain meaning of the FDC Act. That is, merely because an innovator has obtained approval for a new label of a listed drug, and has discontinued the original labeling for reasons not concerning safety or effectiveness, does not detract from the fact that FDA already approved the "conditions of use prescribed, recommended, or suggested" in generic applicant's proposed labeling. Similarly, § 505(j)(2)(A)(v) of the FDC Act requires an ANDA to include "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug."[3] Once again, an ANDA that references the discontinued labeling of a listed drug meets the plain meaning of the statute. Despite the fact that the innovator has discontinued the labeling of the listed drug, the discontinued labeling referenced in an ANDA is "the same as the labeling approved for the listed drug."[4]

Thus, the Guidance Document, which allows a generic applicant to reference discontinued labeling in an ANDA, is consistent with the plain meaning of the FDC Act.

B. FDA's Regulations Support Implementation of the Guidance Document.

The generic drug approval process established by the Hatch-Waxman Act requires an ANDA sponsor to establish that the generic product that is the subject of the ANDA is the same as the reference listed drug with respect to active ingredient, dosage form, strength, route of administration, conditions of use, and labeling.[5] Usually, a generic applicant establishes the

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2 FDC Act § 505(j)(2)(A)(i).

3 Id. at § 505(j)(2)(A)(v)

4 Id.

5 See id. at § 505(j)(2)(A)(i)-(v).

sameness of labeling by including a copy of the "currently approved labeling for the listed drug" in its ANDA.[6] To the extent that a generic applicant's product labeling differs from the listed drug's current labeling, FDA requires the ANDA applicant to state and explain such differences. In certain circumstances, FDA's regulations permit differences between the labeling of a generic and innovator product:

> [D]ifferences between the [ANDA] applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, *or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity* under section 505(j)(4)(D)[7] of the [Food, Drug, and Cosmetic] Act.[8]

The italicized language above specifically acknowledges the possibility that "other" differences or "omissions" between generic and innovator labeling protected by patent or exclusivity, but not specifically identified by FDA in § 314.94(a)(8)(iv), may exist, provided those labeling differences do not render the product less safe or effective. Thus, § 314.94(a)(8)(iv) is not, nor was it intended to be, an exhaustive list of the ways in which generic labeling may differ from an innovator product's labeling.

Section 314.94(a)(8)(iv) expressly applies when there is an "omission" of an aspect of labeling protected by patent or exclusivity. A generic applicant who "omits" an aspect of the innovator's revised labeling satisfies the regulation. While an ANDA that references the discontinued labeling of a listed drug gives the *appearance of including* an aspect of labeling that is different from the brand name drug labeling rather than "omitting" an aspect of labeling, such is not the case. Rather, an ANDA that references an aspect of a listed drug's discontinued labeling is simply identifying an aspect of the labeling that is no longer in the innovator's current labeling – that is, the generic applicant is not adding to the labeling, but rather, is retaining an aspect of the listed drug's discontinued labeling. There is no principle relevant to the statutory scheme or FDA's

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6 21 C.F.R. § 314.94(a)(8).

7 While the regulation cites § 505(j)(4)(D) of the FDC Act, the Food and Drug Administration Modernization Act of 1997 renumbered this provision so that it is now § 505(j)(5)(D).

8 21 C.F.R. § 314.94(a)(8)(iv) (labeling - comparison of approved and proposed labeling) (emphasis added). See also 21 C.F.R. § 314.127(a)(7) ("Information submitted in the [ANDA] is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the [ANDA] *except for* changes required . . . because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug . . . .") (emphasis added).

implementing regulations that distinguishes between the retention of an aspect of labeling on the one hand, and the "omission" of an aspect of labeling on the other. Thus, an "omission," whether defined as the retention or deletion of an aspect of labeling, and provided the "omission" does not render the product less safe or effective than the listed drug, is a permissible difference due to patent or exclusivity protection that satisfies the regulation.

Permitting generic applicants to reference discontinued labeling in their ANDAs is appropriately included within the "other" differences or "omissions" between generic and innovator labeling protected by patent or exclusivity but not specifically identified in § 314.94(a)(8)(iv). Indeed, FDA recognized as much in 1992 in the preamble to its final ANDA regulations when it agreed to revise proposed § 314.94(a)(8)(iv) to include broad, non-specific language rather than its proposed narrow, specific language. In the proposed ANDA regulations, promulgated in July 1989, FDA proposed the following language relevant to this Comment:

> [D]ifferences between the applicant's proposed labeling and labeling approved for the reference listed drug may include all differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, *or omission of an indication protected by patent or accorded exclusivity* under section 505(j)(4)(D) of the act.[9]

Pursuant to a comment that suggested § 314.94(a)(8)(iv) be revised to "protect ANDA applicants from 'a possible claim of inducement or infringement where a nonapproved, but patented, method of administration is discussed in the innovator's label' or the labeling refers to more than one method of use and 'some but fewer than all of the methods of use are entitled to nonpatent exclusivity,'" FDA agreed to amend proposed § 314.94(a)(8)(iv) to state that differences between generic and innovator labeling may include omissions of an indication "or other aspect of labeling protected by patent or accorded exclusivity . . . ."[10] Thus, FDA recognized that not only the omission of an "indication" or "method of use" were allowable differences between a generic and innovator's labeling, but that "other" differences not specifically identified in the regulation were foreseeable.

The FDA correctly identifies in the Guidance Document the problem facing ANDA applicants: when an innovator (NDA holder) receives approval and market protection for a change to a drug product that removes unprotected information from its labeling, there is no current complete labeling that an ANDA applicant may reference.[11] Thus, some brand name companies might argue the ANDA applicant is blocked from referencing the innovator's old labeling, and is ultimately prevented from introducing its product to the market, because the current labeling

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9 54 Fed. Reg. 28872, 28923 (July 10, 1989) (emphasis added).

10 57 Fed. Reg. 17950, 17962 (Apr. 28, 1992).

11 See Guidance Document at lines 51-66.

information is protected and all previous labeling information has been removed. Therefore, provided that the innovator's previous labeling was not withdrawn for reasons of safety and effectiveness, and omission of the protected information from the innovator's new labeling in the generic product's labeling does not render the drug unsafe or less effective, it is only logical for FDA to conclude that "in certain circumstances an ANDA [applicant] should be permitted to reference discontinued labeling for a listed drug," and that a generic applicant's use of discontinued labeling is one of the "other" acceptable differences in labeling encompassed by § 314.94(a)(8)(iv).[12] A more restrictive interpretation would discourage the development and marketing of low-cost generic drugs and frustrate the purpose and spirit of the Hatch-Waxman Act.

C. The Guidance Document Provides A Sensible Framework for FDA to Determine When to Permit the Use of Discontinued Labeling.

The Guidance Document provides a sensible framework for FDA to determine if a change in labeling should be permitted. Specifically, the Guidance Document permits FDA to exercise its expertise to deal with safety and effectiveness issues on a product-by-product basis to cope with the various labeling issues that may arise when generic applicants reference discontinued labeling. In addition, the Guidance Document allows FDA to ensure the safety of each generic drug that is the subject of an ANDA through a review of labeling, as required as part of the Agency's safety and effectiveness determination. It is a well established principle that "[t]hreshold questions within the peculiar expertise of an administrative agency are appropriately routed to the agency . . . ."[13] Questions about the safety and effectiveness of a generic drug that is the subject of an ANDA are certainly "threshold questions," and are well within FDA's "peculiar expertise." FDA recognizes this principle in the Guidance Document when it states that the Agency may determine the safety and effectiveness of a generic product.[14] FDA's recognition in the Guidance Document of its authority to make product-specific safety or effectiveness determinations is sensible, because it permits the Agency to quickly resolve safety and effectiveness concerns. In turn, this will result in the timely introduction of safe, effective, and low-cost generic drugs to the market.

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12 Id. at lines 85-86.

13 Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 654 (1973); see also Serono Laboratories, Inc. v. Shalala, 158 F.3d 1313, 332 (D.C.Cir. 1998) ("The FDA's determination of what is required to establish 'sameness' for purposes of the Act rests on the '[A]gency's evaluations of scientific data within its area of expertise,' and hence is entitled to a 'high level of deference' . . . ." (quoting A.L. Pharma, Inc. v. Shalala, 62 F.3d 1484, 1490 (D.C.Cir.1995); Schering Corp. v. FDA, 51 F.3d 390, 399 (3d Cir.1995) (FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs falls squarely within the ambit of the FDA's expertise and merit deference . . . .").

14 See Guidance Document at lines 222-223 ("The Agency will determine whether the labeling [of a listed drug] was discontinued for reasons of safety or effectiveness."); id. at lines 216-218 ("FDA also may, on its own initiative, . . . determine[] whether labeling was discontinued for reasons of safety or effectiveness.").

The Guidance Document, by requiring a review of labeling, ensures the safety of each generic drug that is the subject of an ANDA. While parties opposed to FDA's approach of allowing ANDAs to reference discontinued labeling might argue that confusion will result from different innovator and generic labeling, this argument does not hold merit. Each drug FDA approves, whether through the New Drug Application approval process or the ANDA approval process, is held to the same rigorous safety and effectiveness standards. The Guidance Document recognizes that FDA is in the best position to determine whether any differences between innovator and generic labeling raise issues of safety or effectiveness, and further, requires FDA to undertake such an evaluation.[15] In addition, FDA's process for determining the safety and effectiveness of a product that is the subject of an ANDA that references discontinued labeling is no different than the process FDA uses to evaluate ANDAs that omit an "indication or other aspect of labeling protected by patent or accorded exclusivity."[16] The important question is, and since 1984 has always been, whether the generic product is safe and effective. If FDA determines that the product is safe and effective, and provided relevant market protections have expired, then the ANDA should be approved, regardless of whether differences between the generic and innovator labeling exist from referencing discontinued labeling or the omission of some other aspect of labeling. In this respect, the Guidance Document is consistent with FDA's safety and effectiveness standards, because the safety of each generic drug that is the subject of an ANDA is ensured by a review of the product's labeling.

II. The FDA's Proposed Approach Furthers the Purpose and Spirit of the Hatch-Waxman Act by Promoting the Prompt Development and Marketing of Low-Cost Generic Drugs.

The Guidance Document suggests an approach for generic applicants to reference discontinued labeling that fairly interprets current law and FDA's regulations. First, application of the Guidance Document would allow the introduction of more low-cost generic drugs to the United States marketplace. Second, by allowing generic applicants to reference discontinued labeling in their ANDAs, the Guidance Document removes any incentive for innovator companies to subvert the purpose of the Hatch-Waxman Act by changing their drug labeling to prevent generic competition.

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15 See id. at lines 222-226 ("The Agency will determine whether the labeling was discontinued for reasons of safety or effectiveness. If the labeling was discontinued for reasons of safety or effectiveness, it cannot be referred to by the ANDA applicant. Such a determination will be based on the same factors and information FDA considers when determining whether a product withdrawn entirely from the market was withdrawn for reasons of safety or effectiveness.").

16 21 C.F.R. § 314.94(a)(8)(iv).

Both Congress and the Courts have stated that the purpose of the Hatch-Waxman Act was, and is, to strike a balance between innovator and generic manufacturers by providing an incentive for innovator companies to produce new drugs while offering an expeditious route for approval of low-cost generic drugs. The Supreme Court has stated that the Hatch-Waxman Act was designed "to enable new drugs to be marketed more cheaply and quickly."[17] Similarly, Congress has indicated that a major impetus behind the passage of Hatch-Waxman was to "to make available more low cost generic drugs."[18] Because the ability to reference discontinued labeling will promote the prompt marketing of low-cost generic drugs, the Guidance Document will fulfill the purpose and spirit of the Hatch-Waxman Act and should be adopted.

Currently, generic drugs become available to the public once the patent and exclusivity protections covering an innovator's product have expired and FDA has approved an ANDA for a generic product. During the period when an innovator's drug is marketed, the product may undergo changes, including the addition of new indications, changes in dosing regimens or other conditions of use, and the addition or removal of aspects of its labeling. Most labeling changes require the innovator to submit to FDA an NDA Supplement and obtain approval. Approval of a Supplement may result in additional marketing protections for the product if clinical studies are essential to support the change. When an innovator removes any aspect of its labeling and replaces it with a new, protected version, however, there is arguably no labeling to which an ANDA applicant can refer to meet the FDC Act's requirements for approval. FDA has recognized this potential barrier to marketing generic drugs, and proposes to prevent its occurrence. The Guidance Document proposes an approach for ANDA applicants to reference discontinued labeling that upholds FDA's strict standards of safety and effectiveness, comports squarely with the language of the statute and its ANDA regulations, and supports the approval and introduction of generic drugs into the marketplace.

The Guidance Document eliminates the ability of innovator companies to subvert the purpose of the Hatch-Waxman Act in one important respect. There is a significant temptation for an innovator to perpetuate the market power it has by virtue of its patent and or exclusivity protection for the drug in question by substituting protected labeling for unprotected labeling. Indeed, FDA recognizes as much in the Guidance Document when it states that in suggesting an approach for generic applicants to reference discontinued labeling, it hopes to prevent "what could be a growing practice among innovator sponsors of substituting protected labeling for unprotected labeling."[19] FDA's proposed approach of allowing ANDA applicants to reference discontinued labeling preserves and perpetuates the spirit and purpose of the Hatch-Waxman Act by promoting the availability of low-cost generic drugs, and is consistent with the idea that labeling changes should not result in insulation from generic competition.

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17 Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 676 (1990).

18 H.R. Rep. No. 98-857, pt. I, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2647-48.

19 Guidance Document at lines 178-180.

III. FDA Should Promptly Implement the Guidance Document

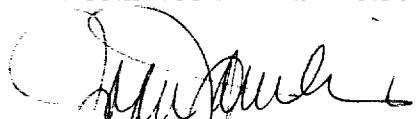
FDA should issue a final version of the Guidance Document in as expeditious manner as possible. Prompt implementation of the Guidance Document will serve to clarify FDA's ANDA regulations, provide a mechanism for generic applicants to reference discontinued labeling, and prevent innovator companies from delaying the introduction of low-cost generic drugs to consumers by substituting protected labeling for unprotected labeling.

Conclusion

Purepac fully supports FDA's effort to allow ANDA applicants to reference discontinued labeling in their ANDAs. In submitting these comments, Purepac hopes to assist FDA in achieving swift resolution of this issue. The Guidance Document is consistent with the FDC Act, fairly interprets FDA's ANDA regulations, and maintains the purpose and spirit of the Hatch-Waxman Act. To that end, Purepac also respectfully requests that FDA immediately adopt its Guidance Document.

Sincerely,

PUREPAC PHARMACEUTICAL CO.



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