DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

ANDA 76-269

JUN 18 2004

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454-1090

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated November 13, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Metformin Hydrochloride Extended-release Tablets, 500 mg.

Reference is also made to the Tentative Approval letters issued by this office on March 25, and November 3, 2003, and to your amendments dated April 16, and April 26, 2004. We also refer to your correspondence dated January 12, March 19, and June 17, 2004.

The listed drug product (RLD) referenced in your application, Glucophage XR Extended-release Tablets, 500 mg, of Bristol Myers Squibb Company, is subject to periods of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book), U.S. patents 6,475,521 (the '521 patent) and 6,660,300 (the '300 patent) are each scheduled to expire on March 19, 2018.

Your application contains a paragraph IV certification under Section 505(j)(2)(A)(vii)(IV) of the Act to the '521 patent stating that this patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Metformin Hydrochloride Extended-release Tablets, 500 mg, under this ANDA. Section 505(j)(5)(B)(iii)[1] of the Act provides that approval of an ANDA shall be made effective immediately unless an action is brought against TEVA Pharmaceuticals USA (TEVA) for infringement of the '521 patent which was the subject of the paragraph IV certification. This action must be brought before the expiration

[1] Because information on the '521 patent was submitted before August 18, 2003, this reference is to a section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) was enacted. See MMA § 1101(c)(3).

of 45 days from the date the notice you provided under paragraph (2)(B)(i) was received by the NDA/patent holder(s). You have notified the agency that TEVA complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for infringement of the '521 patent was brought against TEVA within the statutory 45 day period.

Subsequently, on December 24, 2003, the '300 patent was listed in the "Orange Book". You amended this application to contain a paragraph IV certification under Section 505(j)(2)(A)(vii)(IV) of the Act to the '300 patent stating that the '300 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Metformin Hydrochloride Extended-release Tablets, 500 mg, under this ANDA. You have notified the agency that TEVA Pharmaceuticals USA (TEVA) complied with the requirements of section 505(j)(2)(B)[2] of the Act with respect to the '300 patent and that no action for patent infringement was brought against TEVA within the statutory 45-day period.

Please note that your ANDA was not the first ANDA to be submitted to the agency for Metformin Hydrochloride Extended-release Tablets, 500 mg, containing paragraph IV certifications to the listed patents. Thus, the Act provides that approval of an ANDA that contains a paragraph IV certification, and that provides for approval of the same drug product as that for which another ANDA containing a paragraph IV certification was previously received, shall be made effective not earlier than 180 days after certain events occur.

With respect to Metformin Hydrochloride Extended-release Tablets, 500 mg, and the '521 patent, the agency has concluded that all claims to 180-day generic drug exclusivity have expired. With respect to the '300 patent, the agency has received amendments to one or more ANDAs containing a paragraph IV certification to the '300 patent prior to the receipt of TEVA's amendment providing a paragraph IV certification. Accordingly, with respect to the '300 patent, your application would have been eligible for final approval beginning 180 days after either the first commercial marketing of the drug by one of these applicants, or the date of a court decision finding the '300 patent invalid or not infringed, whichever occurred first.

[2] Because information on the '300 patent was submitted *after* August 18, 2003, this reference is to a section of the Act as in effect after December 8, 2003, when the MMA was enacted. See MMA § 1101 (c) (2).

However, we are able to grant final approval to your application based upon your letter dated June 17, 2004, and information submitted in conjunction with that correspondence, indicating that Andrx Laboratories, Inc. (Andrx) commercially launched its Metformin Hydrochloride Extended-release Tablets, 500 mg, under its approved ANDA on June 17, 2004. The agency has concluded that this launch served to trigger the 180-day generic drug exclusivity for this drug product with respect to the '300 patent. In addition, the agency was informed that (b)(4) (b)(4) selectively waived the 180-day generic drug exclusivity to which (b)(4) is entitled with respect to the '300 patent to TEVA. Thus, with the receipt of this waiver, the agency is permitted to grant final approval to your application for Metformin Hydrochloride Extended-release Tablets, 500 mg.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Metformin Hydrochloride Extended-release Tablets, 500 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Glucophage XR Extended-release Tablets, 500 mg, of Bristol Myers Squibb Company). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

The dissolution testing should be conducted in (b)(4) of (b)(4) (b)(4) The test product should meet the following "interim" dissolution specifications:

Time (hours)	Percent Dissolved
1	(b)(4)
2	
6	
10	

The "interim" dissolution tests and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement - Changes Being Effected" if no revisions are to be proposed to the "interim" specifications, or when the final specifications are tighter than the "interim" specifications. In all other instances, the data should be submitted in the form of a "Prior Approval Supplement."

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy, which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

(b)(6)

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research