



ANDA 76-969/S-002, S-003

Sandoz Inc.  
Attention: Dietrich Bartel  
Director, Regulatory Affairs  
4700 Sandoz Drive  
Wilson, NC 27893

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 18, 2003, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Metoprolol Succinate Extended-release Tablets USP, 25 mg, 50 mg, 100 mg and 200 mg.

Reference is made to our letter dated July 31, 2006, granting final approval to your Metoprolol Succinate Extended-release Tablets USP, 25 mg and granting tentative approval to your Metoprolol Succinate Extended-release Tablets USP, 50 mg, 100 mg, and 200 mg. We acknowledge receipt of your supplemental new drug applications dated May 1, 2007, (S-002 and S-003) providing for final approval of your Metoprolol Succinate Extended-release Tablets USP, 50 mg. We acknowledge receipt of your amendment dated May 17, 2007, to these supplemental applications.

The supplemental applications were submitted as "Prior Approval Supplements".

We have completed the review of these supplemental applications and have concluded that your Metoprolol Succinate Extended-release Tablets USP, 50 mg, are safe and effective for use as recommended in the submitted labeling. Therefore, your Metoprolol Succinate Extended-release Tablets USP, 50 mg, are approved. Your Metoprolol Succinate Extended-release Tablets USP, 100 mg and 200 mg, remain tentatively approved and will not be eligible for final approval until the 180-day generic drug exclusivity period associated with these strengths has expired.

The referenced listed drug (RLD) upon which you have based your ANDA, Toprol-XL Extended-Release Tablets of AstraZeneca LP (AstraZeneca), is subject to periods of patent protection. The following patents and expiration dates (with pediatric exclusivity added) are currently listed in the Agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
4,927,640 (the '640 patent)	November 22, 2007
4,957,745 (the '745 patent)	March 18, 2008
5,001,161 (the '161 patent)	March 18, 2008
5,081,154 (the '154 patent)	March 18, 2008

To each of these patents your supplemental application contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Metoprolol Succinate Extended-release Tablets USP, under this supplemental application. You have notified the agency that Sandoz complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '161 and '154 patents was initiated against Sandoz in the United States District Court for the District of Delaware, then transferred and consolidated in the Eastern District of Missouri [Astrazeneca AB, Aktiebolaget Hassle & AstraZeneca LP, v Eon Labs Inc., Civil Action No. 04-CV-0205]. You have also notified the agency that the court decided that the '161 and '154 patents are invalid and unenforceable.

Furthermore, we acknowledge receipt of a letter dated May 1, 2007, from Andrx Pharmaceuticals LLC relinquishing its claim, with respect to the 50 mg strength, to 180-day generic drug exclusivity under section 505(j)(5)(B)(iv) of the Act. Therefore, under section 505(j)(5)(B)(iii) of the Act your supplemental applications are eligible for final approval.

**Approval of Metoprolol Succinate Extended-release Tablets USP, 50 mg**

The Division of Bioequivalence has determined your Metoprolol Succinate Extended-release Tablets USP, 50 mg, to be bioequivalent and, therefore, therapeutically equivalent to the

RLD, Toprol-XL Extended-release Tablets, 50 mg, of AstraZeneca, LP.

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA. The "interim" dissolution specifications are as follows:

Apparatus:	2 (paddle)
Speed:	50 RPM
Medium:	Acetate buffer, pH 4.5
Volume:	500 mL

Dissolution Specifications:

Time (hours)	Percent Dissolved
1	NMT --
4	-----
8	-----
20	NLT --

The "interim" dissolution test(s) 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" (CBE-30) when there are no revisions to be made to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information 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 ANDA require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this supplemental application is 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 Metoprolol Succinate Extended release Tablets USP, 50 mg.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in

draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705

**Tentative Approval of Metoprolol Succinate Extended-release Tablets USP, 100 mg and 200 mg.**

We remain unable to grant final approval to your Metoprolol Succinate Extended-release Tablets USP, 100 mg and 200 mg, at this time because another ANDA providing for these two strengths and containing paragraph IV certifications to the patents listed in the "Orange Book" were submitted to the agency prior to the submission of your ANDA. This other ANDA, therefore, is entitled to 180-day generic drug exclusivity for Metoprolol Succinate Extended-release Tablets USP 100 mg and 200 mg. Accordingly, your Metoprolol Succinate Extended-release Tablets USP, 100 mg and 200 mg will be eligible for final approval on the date that is 180 days after the agency receives notice, with respect to the other ANDA, of the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv) of the Act.

This tentative approval is based upon information currently available to the agency, i.e., data in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product. This decision is subject to change on the basis of new information that may come to our attention.

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 with a completed Form FDA 2253 at the time of their initial use.

To reactivate this ANDA to provide for final approval of the 100 mg and 200 mg strengths, please submit a "Supplemental Application - Expedited Review Requested" 90 days prior to the date you believe that these products will be eligible for final approval. Your supplement must provide a summary of the legal basis upon which you believe the ANDA should be approved, as well as:

1. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this ANDA, or
2. a statement that no such changes have been made to the ANDA since the date of tentative approval.

Any changes in the conditions outlined in this ANDA and the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the 100 mg and 200 mg strengths will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt.

In addition to the supplement requested above, the agency may request at any time prior to the final date of approval that you submit an additional supplement containing the requested information. Failure to submit either supplement may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

Your Metoprolol Succinate Extended-release Tablets USP, 100 mg and 200 mg, may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of a drug before the effective final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, the 100 mg and 200 mg strengths will not be listed in the "Orange Book."

For further information on the status of this supplemental application, or prior to submitting a supplement providing for the final approval of your Metoprolol Succinate Extended-release Tablets USP, 100 mg and 200 mg, please contact Cheryl Wiseman, Project Manager, at 301-827-5806.

Sincerely yours,

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

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Robert L. West  
5/18/2007 11:11:49 AM  
for Gary Buehler