DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-453

Bristol-Myers Squibb Company
Attention: Marie-Laure Papi
Senior Regulatory Associate
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

Dear Ms. Papi:

Please refer to your new drug application (NDA) dated December 10, 2001, received December 10, 2001, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zerit XR® Extended-Release, (stavudine) 37.5 mg, 50 mg, 75 mg, and 100 mg Capsules.

We acknowledge receipt of your submission(s) dated:

March 14, 2002	October 2, 2002	December 20, 2002
March 15, 2002	October 10, 2002	December 23, 2002
May 30, 2002 (2)	October 22, 2002	December 24, 2002
May 31, 2002	October 25, 2002	December 27, 2002
July 11, 2002 (4)	November 25, 2002	
August 13, 2002	December 4, 2002	
August 16, 2002	December 6, 2002	
September 23, 2002	December 12, 2002	
September 24, 2002	December 16, 2002	

This new drug application provides for the use of Zerit XR® Extended-Release (stavudine) 37.5 mg, 50 mg, 75 mg, and 100 mg Capsules, a new formulation of stavudine, for the treatment of HIV-1 infection in adults as part of a combination regimen.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the agreed-upon labeling (text for the package insert, text for the patient package insert, and immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and unapproved.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed.

Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "**FPL for approved NDA 21-453**." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments as agreed to in your submission dated **December 24, 2002**. These commitments are listed below:

1. Please elucidate the complete metabolic fate of stavudine in humans. This was a Phase IV commitment for the original stavudine NDA. Final report due: **4Q 2005.**

2. Please conduct and submit the results of studies or simulations in patients with impaired renal function based on the known pharmacokinetic information of both stavudine immediate and extended release formulations, if Zerit XR® is to be used in this population. Final report due: **2Q 2003.**

3. Please continue to assess genotypes and phenotypes of pre-therapy and post-therapy HIV-1 isolates from a large number of patients failing stavudine therapy. Final report due: **4Q 2004.**

4. Please evaluate the cross-resistance of stavudine resistant HIV-1 isolates to all approved NRTIs, and the efficacy of d4T against HIV-1 isolates resistant to all approved NRTIs. Final report due: **4Q 2004.**

5. Please determine the *in vitro* combination activity relationships of stavudine with all approved NRTIs and determine the effect of ribavirin on anti-HIV-1 activity of stavudine *in vitro.* Final report due: **2Q 2003.**

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we

hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Antiviral Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sylvia D. Lynche, Pharm.D., Regulatory Management Officer, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Debra B. Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV

Enclosure: Revised Labeling (PI and PPI) dated 12/27/2002

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

/s/

Jeffrey Murray
12/31/02 12:00:20 PM