NDA 21-036

Glaxo Wellcome Inc.
Attention: Sherman N. Alfors
Project Director Regulatory Affairs
Five Moore Drive
PO Box 13398
Research Triangle Park, North Carolina 27709-3398

Dear Mr. Alfors:

Please refer to your new drug application (NDA) dated October 26, 1998, received October 27, 1998 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Relenza^ (zanamivir for inhalation).

We acknowledge receipt of your submissions dated:

October 26, 1998
December 3, 1998 (2)
December 8, 1998
December 17, 1998 (2)
December 22, 1998
December 29, 1998
January 6, 1999
January 18, 1999
January 20, 1999
January 22, 1999
January 27, 1999
January 29, 1999
February 3, 1999
February 11, 1999 (2)
February 15, 1999 (2)
February 25, 1999
March 2, 1999
March 3, 1999
March 4, 1999
March 15, 1999
April 2, 1999 (2)
April 7, 1999
April 9, 1999
April 21, 1999
April 23, 1999
April 29, 1999
April 30, 1999
May 6, 1999
May 7, 1999
May 10, 1999
May 19, 1999
May 21, 1999
June 2, 1999
June 4, 1999
June 15, 1999
June 18, 1999
June 24, 1999
July 8, 1999
July 13, 1999
July 15, 1999
July 23, 1999
July 26, 1999 (2)

This new drug application provides for the use of Relenza^ (zanamivir for inhalation) for treatment of uncomplicated acute illness due to influenza virus in adults and adolescents twelve years and older who have been symptomatic for no more than two days. This indication is based on studies in which the predominant influenza infections were influenza A, and a limited number of patients with influenza B were also enrolled.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that Relenza^ (zanamivir for inhalation) is safe and effective for use as recommended in the draft labeling (package insert submitted July 26, 1999, patient package insert (patient instructions for use) submitted July 8, 1999). Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient instructions for use), including the agreed upon placement of the section on **Patients with Underlying Respiratory Disease** to precede the section on **Prevention of Influenza**, under the **Precautions** section, as discussed during a teleconference on July 26, 1999. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit twenty copies and one diskette that includes a PDF version of the FPL as soon as it is available, in no case 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 "FINAL PRINTED LABELING" for approved NDA 21-036." Approval of this submission by FDA is not required before the labeling is used.

In addition, we note the following Phase 4 commitments, specified in your submission dated July 26, 1999. These commitments include:

1. Provide more information on use of the Diskhaler device and improvement of instructions. This will include the following activities:
    a. Develop, conduct, and report (complete data, as well as summary and analysis) a study of use of patient instructions, improvement of patient instructions, and assessment of outcomes using improved instructions, in an appropriate population (North American, acutely ill with naturally acquired influenza virus infection).
    b. Propose and implement an active program for detecting consumer problems with the drug/Diskhaler delivery system in the potentially broader, though less systematically monitored, population of patients using the Diskhaler as actually marketed. It is expected that this information would be reported and used where appropriate in further revisions to the labeling to improve clarity of instructions and enhance effective use.

2. Provide further safety and efficacy information in patients with underlying respiratory disease. This will include the following activities:
    a. Completion of the ongoing treatment study (NAI30008) in patients with underlying respiratory disease, and submission of study report.
    b. Propose, conduct, and report a study of the acute effects of zanamivir on pulmonary function in patients with influenza and underlying respiratory disease of specified gradations of severity.
    c. Provide a proposal for a post-marketing surveillance program to optimize detection and reporting of respiratory adverse events (including, but not limited to, bronchospasm in

asthmatic patients). This should include exploration of means of actively obtaining additional information beyond what is available from usual spontaneous reporting and from ongoing or planned clinical trials (for one possible example, a proposal for an epidemiologic study). It is expected that this information would be used where appropriate in further label revisions.

3. Provide further information on safety and efficacy in high-risk patient groups, including the elderly and those with high-risk underlying medical conditions. This information will include completion and submission of study reports from any applicable ongoing studies.

4. Provide further information on the safety and efficacy of zanamivir in pediatric patients. This will include completion of the ongoing treatment study in pediatric patients and submission of study report.

5. Collect and report information pertinent to safety and efficacy of zanamivir when used for re-treatment or treatment of multiple episodes of influenza in the same patient.

6. Provide further information on the safety and efficacy of zanamivir in North American patients. This will include completion of the ongoing study of workplace treatment and submission of a study report, and presentation of results in North American subpopulations of other ongoing studies with sufficient North American enrollment.

7. Provide information on the safety and efficacy of zanamivir for interruption of influenza virus transmission, including completion and reporting of the ongoing family transmission study.

8. Provide further information on the safety and efficacy of prophylactic use of zanamivir to prevent influenza A or B, including submission of study reports for all completed and ongoing prophylaxis studies.

9. Provide additional information on the safety and efficacy of zanamivir in treatment and prevention of influenza B, as well as influenza A, and comparisons between types and subtypes where applicable.

10. Provide additional information on viral shedding during and after therapy or prophylactic use in different treatment groups, using the proposed marketed formulation of zanamivir, as well as any other formulations under development.

11. Provide plans and proposals for proactively exploring the development of a useful cell-culture-based assay for viral susceptibility and resistance to zanamivir; for developing alternative approaches (in addition to enzyme activity assays) to assessment of emergence of resistance to zanamivir if an acceptable, reliable cell-culture-based assay is not feasible; and for exploring and characterizing the relationship between enzyme activity assays and viral resistance.

12. Provide a detailed plan and timeline for development and implementation of a resistance surveillance program. This program will include the following elements:
    a. Use of other complementary approaches (such as cell-culture-based assays and proposals for other alternative approaches if a useful cell-culture-based assay is not available) in addition to enzyme-activity assays, and analysis of results to explore the relationship between enzyme activity assays and viral resistance and susceptibility.
    b. Examination of any isolates available after prolonged, as well as brief, zanamivir exposure.
    c. Assessment of antigenic variation of clinical isolates and relationship of this variation to zanamivir exposure.
    d. Exploration of clinical implications of zanamivir-induced and zanamivir-dependent variants.
    e. Provisions for storing viral isolates for additional study when improved assays are developed.

13. Complete and report nonclinical immunotoxicology and juvenile inhalation toxicology studies in a timely manner.

14. Provide an update of data after manufacture of ten batches of Relenza^ post-approval or after one year (whichever comes first) and evaluate tightening the specification of [ ].

15. Include [ ], which is to be performed as an in-process test, in the release specification table. Data will be collected after the manufacture of ten batches post-approval or after one year (whichever comes first). After this period, propose a specification based on [ ]and standard deviation, if appropriate.

16. Develop and present a plan for providing materials to educate healthcare providers regarding the appropriate use of the drug/device/delivery system and the importance of direct patient instruction, and to facilitate appropriate instruction of patients by healthcare providers.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

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 deficiencies that may occur.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that at this time you have not fulfilled all the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until December 31, 2000.

We also remind you that 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 (pediatric exclusivity). You should refer to our Pediatric Written Request letter dated December 29, 1998.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please 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-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Sylvia D. Lynche, Pharm.D., at 301 827-2335.

Sincerely,

Dianne Murphy, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research