DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: **February 11, 2000**

To: **Sherman N. Alfors, Project Director, Regulatory Affairs**

Address: **Glaxo Wellcome Inc.**
Five Moore Drive
Research Triangle Park, NC 27709

From: **Virginia L. Yoerg, Regulatory Project Manager, HFD-530**

Through: **Kellie Reynolds, Pharm.D., Biopharmaceutics Team Leader, HFD-530** KR 2/10/00
Sandra Suarez, Ph.D., Biopharmaceutics Reviewer, HFD-530 ESO 2/10/00

sNDA: 21-036/S-001

Subject: **Request for information: Biopharmaceutics**

Please refer to your Supplemental New Drug Application (sNDA) for the use of Relenza® for the treatment of influenza A and B in pediatric patients ages 5 through 11 years. The following requests for information are being conveyed on behalf of Sandra Suarez, Ph.D., and are directed toward document number RDI998/01189/00 and Study Report/Protocol NAIA1009: *"Pharmacokinetics of zanamivir following inhaled administration in pediatric subjects with signs and symptoms of respiratory illness."*

1. Please provide pre-study validation data and statistical analysis to lower the limit of quantification from ———— L for analysis of zanamivir in human serum.

2. Please provide in-study intra-day accuracy and precision data for analysis of zanamivir in human serum data presented in document number RDI998/01189/00.

3. Please include the statistics describing the fit of the standard curves used for analysis of zanamivir in human serum data presented in document number RDI998/01189/00.

4. Please provide information regarding potential analytical interference of zanamivir with the concomitant drugs taken by the pediatric patients during study NAIA1009.

5. Please provide documentation (all standard curve data and statistical analysis) for in-study validation of the data generated during analysis of urine samples in study NAIA1009.

6. Please provide final individual inhalation profiles generated in study NAIA1009 for all patients. Appendix 11 of Volume 2 (NDA-21-036) includes preliminary data for some patients.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Virginia L. Yoerg
Regulatory Project Manager
Division of Antiviral Drug Products

Concurrence:
HFD-530/MO/Styrt BAS 2/10/00
HFD-530/MO/Baylor ESO 2/10/00
HFD-530/RPM/Yoerg-02/10/00

cc:
Original NDA 21-036/S-001
Division File
HFD-530/RPM/Yoerg
HFD-530/MO/Baylor
NDA 21-036/S-001

Facsimile

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

02/11/00 11:38
ID=DAVDP

DATE	[illegible]	DISTANT STATION ID	MODE	PAGES	RESULT	
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02/11/00 11:3[illegible] [illegible] 919194835756 NO.707 D01

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Sherman N. Alfors, Project Director, Regulatory Affairs

Fax Number: (919) 483-5756

Date: February 11, 2000

Company: Glaxo Wellcome Inc.

No. of pages (excluding cover): 2

Message: Comments regarding NDA 21-036/S-001: Requests for Information: BioPharm

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: **February 15, 2000**

To: **Sherman N. Alfors**

Address: **Glaxo Wellcome Inc.**
Five Moore Drive
Research Triangle Park, NC 27709

From: **Virginia L. Yoerg, Regulatory Project Manager, HFD-530**

Through: **Stanka Kukich, M.D., Medical Team Leader, HFD-530** SK 2/15/00
Barbara Styrt, M.D., M.P.H., Medical Reviewer, HFD-530 BS 2/15/00
Melisse Baylor, M.D., Medical Reviewer, HFD-530 MSB 2/15/00

NDA: **21-036 and 21-036/S-001**

Subject: **Relenza pediatric supplement and safety labeling issues**

The following request is being conveyed on behalf of DAVDP regarding the Relenza pediatric sNDA and safety labeling issues.

We have received a serious adverse event report for a six year old child through the adverse event reporting system (GW case number A0110476A). Please provide more information regarding this event.

Please provide a summary update of adverse event reports you have received for pediatric and adolescent subjects subsequent to those included in the pediatric supplement to the NDA. This update should include postmarketing reports as well as events from clinical studies.

Please provide a response within two weeks. Adverse event reports from any source clearly may affect the risk/benefit evaluation of zanamivir for pediatric patients.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Virginia L. Yoerg
Regulatory Project Manager
Division of Antiviral Drug Products

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 21-036 and sNDA 21-036/S-001
Division File
HFD-530/MO/Styrt
HFD-530/RPM/Yoerg-02/14/00

NDA 21-036

Facsimile

MESSAGE CONFIRMATION

02/15/00 13:21
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DATE	[illegible]	DISTANT STATION ID	MODE	PAGES	RESULT	
02/15	[illegible]	919 990 5756	CALLING	03	OK	0000

02/15/00 13:19 [illegible] - 919834835756 NO.719 P01

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Sherman N. Alfors, Project Director, Regulatory Affairs

Fax Number: (919) 483-5756

Date: February 15, 2000

Company: Glaxo Wellcome Inc.

No. of pages (excluding cover): 2

Message: Relenza pediatric supplement and safety labeling issues.

YOERG

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 6, 2000

To: Sherman N. Alfors, Project Director, Regulatory Affairs

Address: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

From: Virginia L. Yoerg, Regulatory Project Manager, HFD-530 VLY 3/3/00

Through: Kellie Reynolds, Pharm.D., Biopharmaceutics Team Leader, HFD-530 KSR 3/5 pm
Sandra Suarez, Ph.D., Biopharmaceutics Reviewer, HFD-530 ESO 3/3/00

sNDA: 21-036/S-001

Subject: Additional requests for information

Please refer to your Supplemental New Drug Application (sNDA) for the use of Relenza® for the treatment of influenza A and B in pediatric patients ages 5 through 11 years. Please also refer to your Study Report/Protocol NAIA1009: *"Pharmacokinetics of zanamivir following inhaled administration in pediatric subjects with signs and symptoms of respiratory illness."*

1. Please provide the following information for the analysis of zanamivir in urine samples from study NAIA1009:
   a) Analytical method used for analyzing zanamivir.
   b) Example chromatograms for blank, QCs and test sample
   c) Calibration curve plot
   d) Statistical analysis for QCs

2. Please indicate the procedure used for the generation of the PIFR in children (page 8, and pages 10 to 15 of your submission dated February 18, 2000). Please also refer to Volume 2 of sNDA 21-036/S-001, pages 5 and 162: for subjects at least 5 years of age, zanamivir was inhaled from the ROTADISK blisters using a DISKHALER, and the inhalation profile was recorded.

3. Please indicate which flow rate values were used to generate the in-vitro particle size distribution. Also, provide the percentage of dose deposited on the different stages of the cascade impactor.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Virginia L. Yoerg
Regulatory Project Manager
Division of Antiviral Drug Products

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 21-036/S-001
Division File
HFD-530/BioPharm/Suarez
HFD-530/RPM/Yoerg

Facsimile

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APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

03/06/00 10:20
ID=DAVDP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
03/06	00'53"	919 990 5756	CALLING	03	OK	0000

03/06/00 10:19 DAVDP → 919194835756 NO.780 P01

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Sherman N. Alfors, Project Director, Regulatory Affairs

Fax Number: (919) 483-5756

Date: March 6, 2000

Company: **Glaxo Wellcome Inc.**

No. of pages (excluding cover): 2

Message: sNDA 21-036/S001
Additional requests for information: BioPharm

Yoerg

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 14, 2000

To: Sherman N. Alfors

Address: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

From: Virginia L. Yoerg, Regulatory Project Manager, HFD-530

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530 3/14/00
Barbara Styrt, M.D., M.P.H., Medical Reviewer, HFD-530 3/14/00
Melisse Baylor, M.D., Medical Reviewer, HFD-530 MSB 3/14/00

NDA: 21-036 and 21-036/S-001

Subject: Relenza pediatric supplement

Attached are comments regarding your draft Relenza labeling dated March 6, 2000. Please note the points below, also related to this labeling process. Additional comments may follow.

Please refer to your statement under Tab 6, page 2, in your quarterly report dated February 24, 2000, for Relenza, NDA 21-036, covering the period from November 1, 1999, through January 31, 2000: "The following foreign actions have been effected during this reporting period: The International Core Text for RELENZA was revised under the Posology and Method of Administration, Special Warnings and Precautions for Use, Undesirable Effects, and Pharmacodynamic Properties sections." Please provide a copy of the current International Core Text and specify the changes made during this reporting period.

Please refer to our facsimile of February 25, 2000, and in particular to the sentence therein "In addition, we request that you re-examine all information that could clarify the possibility of cardiac adverse events, and provide a summary assessment with appropriate provisions for dissemination of information." Please also refer to the teleconference of March 1, 2000, in which you asked on what specific category of cardiac adverse events this examination should focus, and the DAVDP response that we are interested in an examination of all data available to you – not limited to postmarketing reports – that could clarify the issue of whether there is or is not a drug relationship to any of the range of reports received in which a cardiac event occurred or may have occurred, and your summary and analysis of any pertinent data. Please also refer to your submission dated March 6, 2000, which quotes the February 25, 2000 fax request and states "Please reference our separate

letter to this NDA also dated March 6, 2000, in which we provide a full response to this proposal." We received one other submission dated March 6, 2000, headed "General Correspondence: Safety Reporting," which outlines your proposal to mail selected individual adverse event reports and indicates that you will not submit summaries. Please indicate whether this is your full response to our request for an analysis of potential cardiac adverse events or whether there was yet a third submission dated March 6, 2000. We consider the requested re-examination and summary assessment of such events to be important to the current discussion of label language and the design of ongoing safety monitoring.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/ for

Virginia L. Yoerg
Regulatory Project Manager
Division of Antiviral Drug Products

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 21-036 and sNDA 21-036/S-001
Division File
HFD-530/MO/Styrt
HFD-530/RPM/Yoerg-02/14/00

NDA 21-036

Facsimile

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4. In addressing your existing Phase 4 commitments for detection and analysis of viral resistance, please indicate your proposals for improving culture yield and increasing the number of isolates examined from both clinical trials and postmarketing surveillance. In addition, provide a plan to examine cross-resistance of influenza virus isolated during the clinical use of zanamivir to the range of other available anti-influenza drugs.

5. Within one month of approval of this supplement, provide your proposal for a letter to health professionals describing safety issues noted with the use of zanamivir and your proposal for dissemination of this letter. This letter should address the safety-related modifications to the package insert, including but not limited to reports of serious respiratory adverse events in patients with and without underlying respiratory disease, should remind health care professionals to also consider bacterial etiologies when patients present with influenza-like illnesses, and should address the change in pregnancy category. Following Division review of your proposal and agreement on content and mode of dissemination, such a letter should be distributed within one month (and before the drug is marketed for pediatric use). A second letter should be sent out just prior to the next influenza season (fall 2000); please provide this for review in advance so that any needed updates can be made.

6. Provide a plan to continue to study and submit reports on serious adverse events such as those involving the respiratory and cardiovascular systems, allergic and allergic-like reactions, and all fatalities. This should include but not be limited to:
   a) continued submission of 15-day reports for all serious adverse events, including events mentioned in the label;
   b) additional follow-up efforts to obtain more information about the circumstances surrounding events in the categories listed above; and
   c) a cumulative summary report and analysis at the end of the influenza season.

   These safety reporting provisions may be re-assessed as appropriate, if agreed between the applicant and the Division of Antiviral Drug Products, after the conclusion of the 2000-2001 influenza season.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Virginia L. Yoerg
Regulatory Project Manager
Division of Antiviral Drug Products

cc:
Original NDA 21-036/S-001
Division File
HFD-530/RPM/Yoerg-03/21/00
HFD-530/MO/Styrt
HFD-530/MO/Baylor
NDA 21-036/S-001

Facsimile

MESSAGE CONFIRMATION

03/22/00 10:08
ID=DAVDP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
03/22	03'01"	919 990 5756	CALLING	03	OK	0000

03/22/00 10:05 DAVDP → 919194835756 NO.836 D01

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Sherman N. Alfors, Project Director, Regulatory Affairs

Fax Number: (919) 483-5756

Date: March 28, 2000

Company: Glaxo Wellcome Inc.

No. of pages (excluding cover): 2

Message: sNDA 21-036/S001
Phase 4 commitments

HFD 530
YOERG

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: April 14, 2000

To: Sherman N. Alfors, Project Director, Regulatory Affairs

Address: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

From: Virginia L. Yoerg, Regulatory Project Manager, HFD-530 VLY 4/14/00

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530 SK 4/14/00
Melisse Baylor, M.D., Medical Reviewer, HFD-530 MSB 4/14/00
Barbara Styrt, M.D., M.P.H., Medical Reviewer, HFD-530 BAS 4/14/00

sNDA: 21-036/S-001

Subject: Phase 4 commitments

The following are draft suggested Phase 4 commitments for NDA 21-036, supplement SE1-001, pediatric efficacy supplement. These have been revised from the previous draft taking into account the changes in proposed labeling and the comments received from Glaxo Wellcome dated April 10, 2000. These suggestions do not imply any regulatory decision and additional comments may follow. We remind you of your existing Phase 4 commitments from original NDA 21-036; the following are in addition, and do not replace or reduce any of the existing commitments.

1. In future study reports, provide subgroup analyses for efficacy and safety in pediatric age groups. *[Note to applicant: the request for additional information in younger children has been dropped on the understanding that you are not planning to seek approval for use of the drug beyond the age group supported by the present submission. Substantial additional information would be needed, and specific requirements would need further discussion, if a broader age delimitation is sought.]*

2. Develop, conduct, and report (complete data, as well as summary and analysis) a study to assess the ability of children and adolescents of various ages to use the zanamivir dry powder inhalation system based on patient or parental use of proposed package instructions. This study should identify potential obstacles to effective use by categories of potential patients arising from characteristics of the device and the instructions, and develop and test any improvements in usage instructions that may lead to more reliably effective use by the intended patients in the settings characteristic of the intended indication (primary care medical care settings, acutely ill children, need for instructions that will reliably lead to appropriate use beginning with the first dose, etc.). This study may be conducted as a

substudy within a larger study enrolling both adults and children, if enrollment and design are adequate to address the objectives.

3. Provide a plan to increase information regarding safety and efficacy in racial and ethnic minority patients. This should include subgroup analyses of Caucasian versus non-Caucasian patient subgroups for primary safety and efficacy endpoints as part of the final study report for recently completed and ongoing studies; targeted enrollment in ongoing and future studies, including studies of device use; a summary and aggregate analysis of results for different racial/ethnic populations across studies; and a review of your global adverse event reporting system for events suggestive of lactose intolerance in populations in which this condition is common.

4. In addressing your existing Phase 4 commitments for detection and analysis of viral resistance, please indicate your proposals for improving culture yield and increasing the number of isolates examined from both clinical trials and postmarketing surveillance. In addition, in view of the increasing number of anti-influenza drugs available and under development since the existing Phase 4 commitments were delineated, please provide a plan to examine cross resistance of influenza virus isolated during the clinical use of zanamivir.

5. Within one month of approval of this supplement, provide your proposal for a letter to health professionals describing safety issues noted with the use of zanamivir and your proposal for dissemination of this letter. This letter should address the safety-related modifications to the package insert, including but not limited to reports of serious respiratory adverse events in patients with and without underlying respiratory disease, should remind health care professionals to also consider bacterial etiologies when patients present with influenza-like illnesses, and should address the change in pregnancy category. Following Division review of your proposal and agreement on content and mode of dissemination, such a letter should be distributed within one month (and before the drug is marketed for pediatric use): this letter should be targeted for June or July at the latest. A second letter covering the same safety issues and any needed safety updates should be sent out just prior to the next influenza season (fall 2000; by analogy to customary timing for influenza vaccination efforts, this should be targeted for October or early November); please provide this for review in advance so that any needed updates can be made.

6. Provide a plan to continue to study and submit reports on serious adverse events such as those involving the respiratory and cardiovascular systems, allergic and allergic-like reactions, and all fatalities. This should include the following:
   a) continued submission of 15-day reports for serious respiratory, cardiac, and allergic-like events and for fatalities, even if in categories mentioned in the package insert, as well as other events covered by the regulatory definitions; and
   b) targeted efforts to obtain additional information about antecedent and concomitant circumstances for each fatal event report, in addition to usual follow-up efforts.

[Note to applicant: we are not requesting continuation of your proposal to send desk copies of selected adverse event reports to the Project Manager at the same time that you send these to the Document Room. We expect that you will continue usual practice for submitting 15-day reports, independent of and in addition to Phase 4 commitments.]

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Virginia L. Yoerg
Regulatory Project Manager
Division of Antiviral Drug Products

APPEARS THIS WAY ON ORIGINAL

DAVDP/HFD-530 • 5600 Fishers Lane • Rockville, MD 20857 • (301) 827-2335 • Fax: (301) 827-2523

cc:
sNDA 21-036/S-001
Division File
HFD-530/RPM/Yoerg
HFD-530/MO/Styrt
HFD-530/MO/Baylor
NDA 21-036/S-001

Facsimile

Correspondence to original NDA 21-036 relevant to sNDA 21-036/SE1-001

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 28, 2000

To: Sherman N. Alfors

Address: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

From: Virginia L. Yoerg, Regulatory Project Manager, HFD-530

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530 1/28/00
Barbara Styrt, M.D., M.P.H., Medical Reviewer, HFD-530 1/28/00

NDA: 21-036

Subject: Relenza safety reports and labeling issues

The following are comments related to the Relenza safety issues recently discussed with you, including our teleconference of January 4, 2000, and telephone facsimile comments of January 5, 2000, and your submission dated January 20, 2000.

We request that you continue to track and inform us of respiratory adverse events and deaths (whether or not associated with respiratory manifestations) reported in patients receiving Relenza. Please alert the Division to such reports directly as well as submitting them through the standard adverse event reporting procedure (for example, we note that you have transmitted two reports to us by fax while your surveillance department was sending them to the FDA Central Document Room, and you may wish to continue using similar means of maintaining prompt communications to the Division). Please continue to follow up on all deaths and respiratory adverse events: this should include contacting reporters of deaths and serious respiratory adverse events to obtain further information on circumstances surrounding these events.

Please submit options for stronger warning language than that included in your proposal dated January 20, 2000. We anticipate more detailed discussions of specific content over the next few weeks in conjunction with ongoing review of adverse event reports.

Given the prospect of substantial new label contents, we suggest that you plan a Dear Health Professional letter providing updated information, to be sent after final labeling language has been agreed upon. This may also include a description and explanation of pregnancy labeling changes.

Progress on these issues is likely to be relevant to the currently proceeding review of the pediatric supplement to this NDA. Therefore, we suggest that safety-related labeling changes be incorporated into the label revisions currently under discussion in connection with this supplement. This should not delay your responses to the comments we have made regarding labeling related to the pediatric supplement: you may send those responses, and follow with additional proposals for safety-related changes as soon as possible.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Virginia L. Yoerg
Regulatory Project Manager
Division of Antiviral Drug Products

**APPEARS THIS WAY
ON ORIGINAL**

DAVDP/HFD-530 • 5600 Fishers Lane • Rockville, MD 20857 • (301) 827-2335 • Fax: (301) 827-2523

cc:
Original NDA 21-036
Division File _
HFD-530/MO/Styrt
HFD-530/RPM/Yoerg-01/28/00

NDA 21-036

Facsimile

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

01/28/00 14:50
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01/28 00 14:48 [illegible] +19194835756 NO.648 P01

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Sherman N. Alfors, Project Director, Regulatory Affairs

Fax Number: (919) 483-5756

Date: January 28, 2000

Company: Glaxo Wellcome Inc.

No. of pages (excluding cover): 2

Message: Clinical comments regarding NDA 21-036

Yoerg

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: February 25, 2000

To: Sherman N. Alfors

Address: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

From: Virginia L. Yoerg, Regulatory Project Manager, HFD-530 VLY 2/25/00

Through: Barbara Styrt, M.D., M.P.H., Medical Reviewer, HFD-530 BS 2/25/00

NDA: 21-036

Subject: Relenza label

The following comments are in response to your submission dated February 7, 2000, to NDA 21-036, including your Response to Request for Information and Proposed Content of SPECIAL SUPPLEMENT: CHANGES BEING EFFECTED.

We have noted your proposal for a bimonthly report to this Division regarding selected adverse events. We agree that it is advisable to plan frequent updated summaries; however, in addition to these summaries, we again request that you monitor your adverse event reports for cases of particular importance in the context of those already discussed, and convey such reports immediately to this Division in addition to submitting them to the Central Document Room according to standard 15-day report procedure. We consider the clarification of safety information for this drug to be important and assume that you will be able to prioritize your resource allocations appropriately.

As previously requested, please continue to obtain additional information on the circumstances surrounding all reports of serious respiratory adverse events, and all reports of fatalities whether or not classified as respiratory. In addition, we request that you re-examine all information that could clarify the possibility of cardiac adverse events, and provide a summary assessment with appropriate provisions for dissemination of information.

Our comments regarding the safety language proposed in your "Proposed Content of SPECIAL SUPPLEMENT: CHANGES BEING EFFECTED" dated February 7, 2000, are enclosed. These reflect ongoing review of adverse event reports as well as previous discussions. Additional comments may follow as more information becomes available. Note that in addition to changes in the package insert, we request that you submit concomitant changes for the Patient Instructional Leaflet.

As you are aware, we have also requested that you provide an update on pediatric adverse event reports. Please indicate when you anticipate this will be provided, as it may affect both the safety wording referenced in this communication and the review process for the pediatric efficacy supplement (NDA 21-036, S-001). Additional comments regarding S-001 and pregnancy labeling are being conveyed separately.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Virginia L. Yoerg
Regulatory Project Manager
Division of Antiviral Drug Products

**APPEARS THIS WAY
ON ORIGINAL**

MESSAGE CONFIRMATION

02/25/00 16:55
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DATE	TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
02/25	16:55	919 990 5756	CALLING	13	OK	0000

02/25/00 16:44 IN IP - 919194835756 NO.751 001

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Shermon N. Affors, Project Director, Regulatory Affairs

Fax Number: 919 483-5756

Date: January 28, 2000

Company: Glaxo Wellcome Inc.

No. of pages (excluding cover): 12

Message: Relenza label (NDA 21-036)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Record of Teleconference

NDA: **21-036**

Date: **September 21, 1999**

Drug: **Relenza (Zanamivir)**

Applicant: **Glaxo Wellcome, Inc.**

BETWEEN: **Representatives of Glaxo Wellcome (GW)**
Marc Rubin, M.D., VP, Therapeutic Development and Product Strategy
Mike Elliott, M.D., Project Team Leader
Janet Hammond, M.D., Ph.D., Medical Project Leader
Patti Szymborski, Clinical Research Project Manager
Nancy Flack, Clinical Research Project Manager
David Cocchetto, Ph.D., VP, Regulatory Affairs
Sherman Alfors, Project Director, Regulatory Affairs

AND: **Representatives of the Division of Antiviral Drug Products (DAVDP)**
Heidi Jolson, M.D., M.P.H. Division Director
Debra Birnkrant, M.D., Deputy Director
Stanka Kukich, M.D., Medical Team Leader
Barbara Styrt. M.D., M.P.H., Medical Reviewer
Melisse Baylor, M.D., Medical Officer
Girish Aras, Ph.D., Statistics Team Leader
K.M. Wu, Ph.D., Pharmacology/Toxicology Reviewer
Narayana Battula, Ph.D., Acting Microbiology Team Leader
Virginia Yoerg, Regulatory Project Manager

SUBJECT: Clinical comments regarding NDA 21-036 pediatric and prophylaxis proposals.

Background:

This teleconference was scheduled in response to the applicant's proposals and requests in their submissions to NDA 21-036 dated August 4, 1999, "Pre-sNDA Briefing Information (Pediatric Supplement)" and submission dated August 19, 1999, titled "General Correspondence: Pre-sNDA Briefing Information (Prophylaxis Supplement)" (in effect, covers some pre-sNDA meeting type issues). Questions from the applicant in the submissions, responses to these questions from DAVDP during the teleconference, and DAVDP comments on specific points in the proposal are summarized below. Responses and comments from the applicant during the teleconference, and additional discussion during the teleconference, are summarized in italics.

Discussion:

DAVDP stated that it would try to briefly cover their questions and some of the principal proposals from both of these submissions, first for the pediatric supplement and then for the prophylaxis supplement. It should be understood that some open issues may remain for subsequent discussions. *Applicant indicated they plan to have both applications ready for submission in late October.*

Pediatric supplement proposal

DAVDP began with the applicant's "Questions/Issues for Discussion" and general responses, followed by some specific comments on other parts of the submission, and concluded with comments on the applicant's Pediatric Written Request Letter status summary.

Dr. Melisse Baylor was introduced as the anticipated primary medical reviewer for the pediatric supplement.

"Questions/Issues for Discussion":

1. Does DAVDP agree that GW has proposed a reasonable basis for preparing and submitting a Supplemental NDA on pediatric use of Relenza?

   As the applicant is aware, DAVDP is willing to review a pediatric supplement based on a single efficacy study with appropriate supporting information. Other pediatric information has been requested and is anticipated from other ongoing and future studies.

2. The proposed format and content of the sNDA are straightforward, given that the information in the sNDA comes from one controlled clinical trial for treatment of pediatric patients (NAI30009) and relevant safety data from a second study in the same pediatric age group (NAI30010). Does DAVDP accept the proposed Table of Contents (content and format) for this sNDA?

   Please see the comments on specific parts of the submission. For format of the Table of Contents, the major issue is that it should be possible readily to locate appropriate information during review; items of content will be commented on separately.

3. The Data Analysis Plan reflects approaches used in the original NDA, as well as lessons learned from previous discussions with DAVDP. Does DAVDP accept this proposed Data Analysis Plan?

   We will have some comments on specific parts of the Data Analysis Plan to be outlined in succeeding parts of the teleconference. Additional comments, evaluations, and requests may also be made during the review process.

Additional DAVDP comments:

Submission of electronic data: We request that both efficacy and safety data be made available electronically. Please also provide the SAS programs needed for replication of the principal analyses. As the applicant is aware, requests for additional electronic data and/or analyses may be made during the review process. *Applicant asked whether these requests apply only to study*

NAI30009. DAVDP indicated these requests apply to all information from NAI30009 and the supporting information that is proposed for submission from NAI30010.

Proposal for priority review: This proposal has been noted, will be considered, and a decision will be made after the submission is received. We will be particularly interested in seeing the influenza B data as these constitute a major part of the basis for the priority review request but are not included in the preliminary summary. *Applicant indicated the influenza B efficacy results are "quite positive" and slightly better than influenza A.*

Preclinical data: It will be important to see as much virology information as can be made available from all sampling times. In addition, information should be presented regarding relationships between treatment group and specific means of diagnosing influenza (this will be expanded in comments on Analyses to follow). Please provide an additional copy of the Clinical Virology part of the submission directed to the Clinical reviewer. *Applicant indicated they will prepare an integrated report which will be directed to the Clinical reviewer as well as the Microbiology reviewer.* [The following Pharm/Tox and Chemistry issues may not be crucial to the submission of the pediatric supplement itself but it seems appropriate to issue a reminder as they may directly affect additional pediatric development plans.] Please also indicate your timeline for performance of the additional preclinical studies (juvenile inhalation toxicology and immunotoxicity) agreed to in the NDA 21-036 Phase 4 commitments. *Applicant indicated they are "in discussion" regarding timing.* Also note with respect to any anticipated formulation for nebulized use in younger children (as suggested by one of their recent submissions [redacted]), there may be major Chemistry issues for review including device-specific issues & we suggest they take this into account when planning the timing of their protocol or draft protocol submission. *Applicant indicated they will prepare both CMC and clinical information to be submitted for protocol review, understand this will be device-specific, and have tobramycin and pentamidine submissions available as models.*

Safety data: For the supplemental safety data from NAI30010, we request that data be submitted for contacts as well as index cases in the appropriate age ranges, as these constitute another population receiving study drug that should be available and relevant. Similarly for the supplement including the full study report and data from NAI30010 we would expect complete safety data from that study to be included. We recognize that this may result in data from some of the same subjects being included in two separate supplements: the submission should indicate which parts of the data are duplicates of data included in other previous or planned supplements. This duplication will be appropriately taken into account and is preferable to omitting relevant data from any of the submissions. For all safety and efficacy data, please also provide breakouts by high-risk underlying disease. *Applicant indicated agreement. For the portion of NAI30010 safety data to be included in the pediatric supplement, it was agreed this will encompass all 5- to 11-year-olds whether index or contact subjects, while all safety data from NAI30010 will be included in the submission in which the NAI30010 complete study report is submitted, with an indication of which part is a duplicate of information in the pediatric supplement.*

With regard to the Safety Update, as the applicant is aware, additional requests may be made during the review period if concerns arise.

Analyses: In addition to those described, we would appreciate seeing analyses incorporating any return of symptoms after the primary endpoint (which they are presumably aware could be a salient concern based on pediatric studies w [redacted]) *[applicant asked whether analyses similar to*

those submitted during the review period of the original NDA would be acceptable, and were informed these would be fine to submit and additional requests might be made as needed]; analyses incorporating comparison of treatment groups over time throughout the period of symptom recording; graphical representations of treatment group comparisons for time to primary endpoint and for comparison of symptoms (and temperature) at sequential points over time. In addition, for any planned analyses of specific symptoms over days 2 through 5 (which are considered subsidiary), analyses should also be provided that take the entire symptom recording period into account. In the analysis of the protocol-defined primary endpoint and other analogous analyses, in addition to the primary analysis in the data analysis plan, please provide results using the Hodges-Lehmann estimator of treatment effect. Please also provide results of comparison of mean times to the primary endpoint and secondary endpoint, with t-test results. These may be presented as part of the planned sensitivity analyses. *[Applicant asked what should be done with subjects reaching primary endpoint after the end of symptom recording, and were informed they could follow their practice in previous submissions of considering these as having alleviation after the end of symptom recording and indicate how many of these there were and discuss any other representation that might be appropriate. Applicant also reiterated that the Hodges-Lehmann estimator makes an assumption of a constant shift in outcomes that may not be justified, and were informed that this is understood, that DAVDP does wish to see these analyses and will consider them as secondary analyses and does not propose that they will replace the applicant's protocol-defined primary analysis using bootstrap analysis.]* Also among additional subsidiary analyses, we would appreciate receiving as much virologic information as possible from baseline, day 3 samples (including characteristics of subjects from whom samples were obtained and how they were selected), day 6 samples, and any others that might be available. Please also include in your analyses sufficient information on different methods of influenza diagnosis to permit evaluation of any relationship to treatment effect. This should include (but need not be limited to) separate consideration of subjects with positive rapid direct tests for influenza according to the specific test used and according to whether culture or serologic confirmation is available; tabulation by treatment group of proportion of subjects with positive baseline cultures, proportion with acute and convalescent serologic samples obtained, proportion of all subjects and of culture-positive subjects who seroconvert. Both efficacy and safety data should also be presented with breakdowns according to high-risk diagnoses. We also expect to see analyses of efficacy and safety results broken down by influenza type (A and B), and by geographic area (North America and other). *Applicant agreed with all of the above.*

"By-variable listings": DAVDP will need to see how these are actually sent to determine whether additional information, or information in additional formats, will be needed.

Case report forms: In addition to those subjects discontinuing the study prematurely, we would like to receive case report forms for those discontinuing medication prematurely even if still on study. Please also provide case report forms for a 5% random sample of the enrolled subjects. We would also like to receive a sampling of photocopies of actual diary cards. *Applicant asked how large a sampling and should these be distributed between North America and other. DAVDP agreed with a sampling of both North America and other and indicated 2-3% of diary cards could be considered, or if the volume of material is large, 1% may be adequate.*

Comments on GW comments addressing pediatric request letter:

We acknowledge that this attachment does not constitute, and is not presented as, a complete response to the Pediatric Written Request Letter issued by the Office of Drug Evaluation IV, dated

December 29, 1998. Therefore, it is not appropriate to make any determination regarding pediatric exclusivity at this time and there is no pre-specified timeframe for doing so based on the information received to date. Informal interim comments from DAVDP regarding this "Pediatric Written Request Status Information" are being conveyed to ensure ongoing communication and understanding of the status of plans for addressing points in the request letter.

Studies 1 and 2: we expect the forthcoming studies (NAI30009 and NAI30010) ought to be relevant and look forward to the opportunity to assess the actual reports before any determination of whether these parts of the request are satisfied.

Study 3: The Pediatric Written Request specifies an adequate and well-controlled study of zanamivir efficacy and safety in treatment of adolescents with underlying chronic respiratory disease. We are a little confused by the applicant's status summary which indicates that this information was included in original NDA 21-036; no specific citation is provided for the location in NDA 21-036 of such information and it's not clear what they are referring to as addressing the Written Request. *Applicant stated they were referring to the fact that the general population phase 3 studies enrolled some adolescents.* DAVDP: There was not any information that could be considered to constitute an adequate and well-controlled study of zanamivir efficacy or safety in treatment of adolescents with underlying chronic respiratory disease in the original NDA submission. In any case, as the applicant is aware from discussions in connection with other drugs, any study included in the original NDA submission could not also be used as a response to the subsequent pediatric request letter. Therefore, for multiple reasons, this part of the pediatric request letter has definitely not been fulfilled, and we assume the applicant would want to be reminded of this because trying to use this assertion in the final response to the Written Request would likely result in a denial of pediatric exclusivity. We were under the impression that there was an ongoing study more likely to provide information responding to this request (that is, the ongoing study of influenza treatment in patients with underlying respiratory disease might meet this part of the request if an adequate number of adolescents are enrolled and if an appropriate subgroup analysis is provided), and again it would be determined after assessment of the study report whether the report would adequately respond to the Written Pediatric Request Letter. *Applicant stated they appreciated this information.*

Study 4: We look forward to seeing a protocol for evaluation of ability of children to use the device and instructions and for exploring ways of improving these. We are pleased that the applicant has also been carrying out some assessments of ability of patients in the pediatric studies to use the device. Because evaluation in the course of such a study may contribute to identification of problems with use, any information available from such studies should be submitted as part of the response to this request, but will not provide more than a subsidiary contribution to fulfillment of this part of the request. As has previously been discussed, it is not possible to evaluate the extent of ability of an age group to use the device/delivery system in a study which required ability to use the device/delivery system as a condition of enrollment.

Other comments regarding pediatric exclusivity:

It appears that the applicant intends to submit parts of the response to the request letter within the next few months and other parts over a more prolonged timeline. There is no objection to that as long as overall timelines are met, and we encourage the submission of available parts of the information as soon as feasible. The applicant is reminded that when submitting the last part of their information responding to the request, they should refer to all prior submissions containing

information responding to the request and indicate exactly where each part of the response is located, so that the eligibility of their response for according pediatric exclusivity can be determined at that time.

Prophylaxis supplement proposal

1. Does DAVDP agree that GW has proposed a reasonable basis for preparing and submitting a Supplemental NDA on the prophylaxis of influenza with Relenza?

   As the applicant acknowledges in their proposal of August 19, 1999, important expectations for a prophylaxis supplement were discussed at the pre-NDA meeting for NDA 21-036. As they note, at that time the applicant was informed that more studies would be needed than the completed community prophylaxis study to justify a prophylaxis indication, and that the population of greatest concern for documenting efficacy was high-risk patients particularly elderly nursing home residents. The family transmission study, while it may provide some interesting information for review, was not proposed as the second principal study for a prophylaxis indication and it is extremely difficult to see how it could fulfill this function. In addition to the fact that it is not likely to provide any substantial amount of information regarding the high-risk population agreed upon as critically important, this study does not appear likely to provide information concerning the benefit of prophylactic drug administration for an individual that could be separated from effects of treating the active case that is a potential source of infection for that individual: the entire family was both the unit of randomization and treatment, and the unit of analysis. In addition, it appears that study of the elderly nursing home population is actually at an advanced stage, such that efficacy information from this population should be available in the near future: this is another reason why it is highly preferable to plan a coordinated package containing efficacy information from this population as well as the information in healthy young adults, all to be included in the supplement submitted for a prophylaxis indication. We invite the applicant to provide additional information on their anticipated timeline for availability of efficacy information for this critical subpopulation and to consider how this can be incorporated into their timeline for preparation of a prophylaxis efficacy supplement.

2. The proposed format and content of the sNDA are based on the two study reports NAIA3005 and NAI30010. Does DAVDP accept the proposed Table of Contents (content and format) for this sNDA?

   See combined response to questions 2 and 3.

3. The Data Analysis Plan reflects approaches used in the original NDA, as well as lessons learned from previous discussions with DAVDP. Does DAVDP accept this proposed Data Analysis Plan?

   It does not appear appropriate to provide extensive comments on specific points of content, format, and data analysis until there has been clarification of the studies to be included in a prophylaxis supplement. During consideration of this issue, we also remind the applicant that the supplement in its final form should include complete information (including complete safety and efficacy information and electronic datasets as appropriate) for all studies contributing to consideration of the proposed indication. As a particularly essential example, the dataset and

SAS programs for principal analyses should be submitted for NAIA3005 even if previously submitted in another context. The supplement should indicate which parts of the data are duplicates of data included in other previous or planned submissions. This duplication will be appropriately taken into account and is preferable to omitting relevant data from any of the submissions. Additional comments on specific points of content, format, and data analysis will be provided following clarification of the studies to be included in a prophylaxis supplement, considering that this may involve development of a revised version of the planned table of contents and data analysis plan, to which comments may be more appropriately addressed.

The following is a summary of points from the ensuing discussion:

The applicant indicated that their two nursing home prophylaxis studies "did not complete last winter" and they expect to recruit during the next flu season and "depending on the vagaries of the influenza season" to have data by April or May. They indicated they wish to submit a supplement containing the community prophylaxis study and the family transmission study. They stated the design of the family transmission study was based on input from their expert consultants after review of the alternatives (including "mix and match treatment of index cases and contacts") and they stated they believe the Advisory Committee wanted to see results of a study of transmission in families.

DAVDP indicated that the Advisory Committee expressed strongly the need for efficacy data in high-risk populations who are considered in greatest need of treatment or prophylaxis (such as the elderly); there is interest in seeing results from the family transmission study but it is difficult to see how it could be used to write a general prophylaxis indication considering that the effects of therapeutic and prophylactic drug use cannot be distinguished (e.g. given treatment of the index case, it is impossible to tell whether prescribing prophylactic drug to contacts enhances prevention of transmission). It was strongly recommended that the applicant consider how and when they could make efficacy information from their well-advanced studies in the important elderly population available as part of their package to submit for a prophylaxis indication.

The applicant indicated they would like to submit a supplement containing the community prophylaxis study and the family transmission study. They would then propose to submit the elderly nursing home prophylaxis studies in a later supplement. The supplement containing the community prophylaxis study and the family transmission study would not be for a general prophylaxis indication, but just to describe the results of these studies in the Description of Clinical Studies section of the label. They propose that these studies constitute two adequate and well-controlled studies. They acknowledge that it is not possible to separate the effect of index case treatment from contact prophylaxis in the family transmission study but suggest that this study "may provide some useful information." They acknowledge it was agreed at the NDA 21-036 pre-NDA meeting that data from elderly subjects were extremely important; they will have interim safety data in more elderly subjects than they had at that time.

DAVDP indicated that at the pre-NDA meeting it was clarified that description of efficacy results from a study in the label cannot be separated from consideration of the indication implied by that description; that it is difficult to see how the family transmission study could be used to write a prophylaxis indication when it is agreed that the effects of prophylactic drug cannot be separately evaluated from this study; that both the Division and the Advisory Committee have previously emphasized the importance of efficacy data in the populations most likely to be targeted for use, specifically the high-risk populations for prophylaxis which are to some extent addressed by ongoing

studies that should have data available in the near future; that there is room for question as to whether a submission for a prophylaxis indication with no high-risk efficacy data and with a principal study that does not permit evaluation of prophylactic use would be filable. It was recommended that the applicant review their possibilities for extent and timeframe of making efficacy data from high-risk target populations available and how this could be incorporated into a package for submitting a prophylaxis efficacy supplement, and submit a revised proposal for review and further discussion as appropriate, given that any proposal made at this point (including the applicant's initial proposal) would at the earliest address the possibility of approval for the influenza season beginning in the autumn of the year 2000, and that a more complete package might put them in a better position to make a case for a priority review.

The understanding at the end of the teleconference was that the applicant will work on preparing a pediatric supplement for submission in late October, incorporating material to address the comments from DAVDP made during the teleconference; and that the applicant will re-evaluate their plans regarding prophylaxis and submit a proposal for additional DAVDP review and discussion.

concurrence:
HFD-530/DivDir/Jolson 12/14/99
HFD-530/DepDir/Birnkrant 12/13/99
HFD-530/MOTL/Kukich SK 12/13/99
HFD-530/MO/Styrt 12/6/99
HFD-530/MO/Baylor 12/8/99
HFD-530/StatsATL/Aras 12/12/99
HFD-530/PharmTox/Wu 12/8/99
HFD-530/MicroATL/Battula 12/13/99
HFD-530/RPM/Yoerg – 12/06/99

cc:
Original NDA 21-036
Division File
HFD-530/MOTL/Kukich
HFD-530/MO/Styrt
HFD-530/MO/Baylor
HFD-530/PharmTox/Wu
HFD-725/Stats/Aras
HFD-530/Micro/Battula
HFD-530/RPM/Yoerg

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Record of Teleconference

NDA: **21-036 and sNDA 21-036/S-001 (pediatric supplement)**

Date: **December 9, 1999**

Drug: **Relenza® (zanamivir for inhalation)**

Applicant: **Glaxo Wellcome, Inc.**

BETWEEN: **Representatives of Glaxo Wellcome, Inc. (GW)**
Mike Elliott, M.D., Project Team Leader, Clinical Research
David Cocchetto, Ph.D., VP, Regulatory Affairs
Sherman Alfors, Project Director, Regulatory Affairs
Stephen Sharp, Statistics
Oliver Keene, Statistics
Derek Newall, Ph.D., Toxicology
Gill Dines, Toxicology
Meg Parkinson, Toxicology
Mick Daniel, Biometrics

AND: **Representatives of the Division of Antiviral Drug Products (DAVDP)**
Barbara Styrt, M.D., M.P.H., Medical Reviewer
Melisse Baylor, M.D., Medical Reviewer
Jim Farrelly, Ph.D., Pharmacology/Toxicology Team Leader
K.M. Wu, Ph.D., Pharmacology/Toxicology Reviewer
Virginia Yoerg, Regulatory Project Manager

SUBJECT: Pregnancy Category Change from B to C, and FDA requests sent via 12/6/99 fax

Background:

This teleconference was held at the request of DAVDP to discuss the initial comments from reviewers of NDA 21-036, supplement S-001, raised at the filing meeting. These comments were provided to the applicant by telephone facsimile on December 6, 1999, as an agenda for the teleconference. In addition to items in S-001 itself, these requests included a request for a response to the DAVDP request (via facsimile sent November 23, 1999) that the sponsor change the pregnancy category for Relenza® (NDA 21-036) from B to C. This request was made based on information submitted by the sponsor (serial submission 082, dated October 13, 1999 to IND [redacted]. Items from the facsimile of December 6, 1999 are listed below, followed by a summary of discussion. Note that summaries of sponsor responses are in boldface type.

Discussion:

1. Please provide your timeline for submission of a labeling supplement to incorporate pregnancy labeling changes (refer to our fax dated November 24, 1999).

Additional explanation of the request was provided by FDA Pharmacology/Toxicology:

Additional data were submitted to ————————————), in which a pattern of toxicities were seen in rats dosed with high doses of zanamivir similar to those seen for oseltamivir in reproductive toxicology studies. The pharmacology reviewers considered the findings to be part of a syndrome of ossification delays and worthy of a Category C. Oseltamivir is pregnancy Category C because of the presence of a similar syndrome.

The sponsor felt that the findings of note were slightly higher incidences of a number of common background findings in the high dose group versus controls, but these were not significantly higher than in historic controls.

DAVDP pointed out that there were numerous instances in which the percentage of fetuses affected was higher than the upper range of the background incidence. DAVDP also recognized that there was a definite positive trend in the appearance of some of the lesions and the positive trend was reminiscent of the lesions seen in the oseltamivir studies, suggesting that the toxicity syndrome was a class effect.

The sponsor considered the findings to be unrelated in type and did not show any consistent pattern indicative of an adverse effect on a developing organ system. Moreover, they maintained that the lesions occurred at a systemic exposure (based on AUC), much higher than would be attainable in the clinical setting.

The sponsor was told that the rat study showed effects similar to those seen in the oseltamivir studies. Zanamivir showed a syndrome of effects including incomplete ossification of skull bones and sacral vertebral arches, as well as kinked ribs where an area of a rib showed a nodule of ossification. The increases in kinked ribs were seen at doses as low as 1 mg/kg tid where the systemic exposure would be no more than approximately ten fold that found during clinical use of the drug.

The overall assessment of the study showed that administering zanamivir to rats in an embryofetal development study induced a syndrome of toxic effects very similar to that induced by oseltamivir in a similar study. Since Tamiflu is, because of this syndrome of effects, pregnancy Category C, Relenza should also be changed to Category C.

The sponsor stated that they were not aware of the oseltamivir results, but under the circumstances understood our concern. They stated that they would present the explanation that was offered to their development team and provide DAVDP with comments and a proposed timeline.

The division asked that the comments be provided in a timely manner.

The sponsor asked if item 8 on the facsimile could be addressed next so that their toxicologists could leave. Item 8 was then addressed as follows:

Please provide an update on the progress of juvenile inhalation studies and immunotoxicologic studies, which were agreed to as a part of Glaxo Wellcome's Phase 4 commitments for the original NDA 21-036.

The sponsor stated that an immunotoxicology study was started as a Phase 4 commitment and has been completed. A draft copy of the results would be provided to the IND in early February. A Phase 4 inhalation study in juvenile animals is in the final stages of preparation. A draft protocol for the study will be provided for review when it is ready (probably in April).

At this point during the teleconference, Drs. Wu and Farrelly exited, and attention was turned to the remaining items in the requests sent to the sponsor by telephone facsimile on December 6, 1999.

2. Please provide a proposal for revision of the printed patient instructions.

   The sponsor agreed to provide such a proposal after agreement that this referred to changes in instructions that might be required for pediatric use.

3. Please provide an analysis of safety and efficacy data from study NAI30009 by age. We suggest both the analysis of patients by year of age and the analysis of two age groups, 5 through 7 year olds and 8 through 12 year olds.

   The sponsor agreed to the analysis by January 14, 2000.

4. Please provide a table of primary outcomes by site for the U.S. sites in study NAI30009.

   See sponsor response to #3 above.

5. Although the results of NAI30010 have been submitted primarily for safety information, the efficacy results of the index cases in this clinical trial were also mentioned in the sNDA as supporting evidence of the efficacy of Relenza in pediatric patients. Please provide complete pediatric efficacy results from index cases in NAI30010, including an analysis of results by age subgroups comparable to those analyzed for NAI30009.

   See sponsor response to #3 above.

6. Please ensure that this information from NAI30010 is included in the datasets submitted electronically, including the programs needed to generate the principal efficacy outcomes.

   The sponsor agreed to provide all of the additional analyses and data requested in the telephone facsimile, and made a comment that these were all "very fair requests."

7. The sNDA submission states that the sequencing studies of viral isolates from pediatric patients enrolled in NAI30009 are underway. Please provide your timeline for completion and for submission of these studies as well as any analysis of isolates from NAI30010. Please indicate your

proposal for providing cross-resistance information and for sequencing additional areas of the hemaglutinin gene.

The sponsor inquired if cross-resistance refers to oseltamivir. DAVDP expressed the expectation that the applicant has taken an active interest in cross-resistance to any other marketed influenza drug, especially a second marketed neuraminidase inhibitor. The sponsor agreed, and indicated they were waiting for input from their virologists and would send information before the Christmas break.

8. Please provide an update on the progress of juvenile inhalation studies and immunotoxicologic studies, which were agreed to as a part of Glaxo Wellcome's Phase 4 commitments for the original NDA 21-036.

See discussion under item 1 above.

9. Please provide a description of the actions to be taken in order to increase the reproducibility and efficiency of pulmonary delivery to pediatric patients.

The sponsor asked for clarification. DAVDP encouraged the sponsor to evaluate how to ensure consistent use and delivery of Relenza in the pediatric population, and indicated that additional requests may be sent if requested by the Biopharmaceutics reviewers. The sponsor indicated that they expect to submit an actual use protocol imminently.

Conclusions/Actions:

- The sponsor will submit their proposal regarding the pregnancy category for Relenza.
- The sponsor will respond to DAVDP requests for information (numbers 1-9 above).
- The sponsor also indicated they are working on revisions to their investigator brochure in response to the DAVDP facsimile of December 2, 1999, and expect to submit a revised version in January.

Concurrence:
HFD-530/MO/Styrt 1/11/00
HFD-530/MO/Baylor-ESO 01/09/00
HFD-530/PharmToxTL/Farrelly-ESO 01/10/00
HFD-530/PharmTox/Wu-ESO 01/07/00
HFD-530/RPM/Yoerg – 01/05/2000
Drafted: VLY 12/13/99

cc:
Original NDA 21-036
NDA 21-036/S-001
Division Files
HFD-530/MOTL/Kukich
HFD-530/MO/Styrt
HFD-530/MO/Baylor
HFD-530/PharmToxTL/Farrelly
HFD-530/PharmTox/Wu
HFD-530/RPM/Yoerg

Record of Teleconference

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTIVIRAL DRUG PRODUCTS

MEMORANDUM

DATE: February 2, 2000
TO: NDA 21-036
FROM: Medical Officer, HFD-530
SUBJECT: Zanamivir safety and labeling comments (submission dated January 20, 2000); "Proposed Content of SPECIAL SUPPLEMENT/CHANGES BEING EFFECTED"

This one-volume submission contains the applicant's responses to safety issues discussed by DAVDP in a teleconference of January 4, 2000, and summarized in telephone facsimile comments transmitted to the applicant on January 5, 2000. These issues included reports of respiratory adverse events and deaths, including deaths from bacterial sepsis, in patients receiving Relenza for presumed or documented influenza. A Public Health Advisory issued by FDA on January 12, 2000, also addressed some of these points. In the submission dated January 20, 2000, the applicant provided additional reports of respiratory adverse events and some allergic-like manifestations; indicated that they felt no additional circulation of information to health care professionals was needed, and subsequent adverse event reports would be submitted to the FDA Central Document Room according to minimum regulatory requirements; and proposed modified labeling language (principally, additions to the Precautions section beginning with a statement that influenza can produce airway hyperreactivity, and an Observed During Clinical Practice list for the Adverse Events section) to be submitted as a Changes Being Effected supplement.

Assessment: The information in this submission was discussed internally. It was concluded that ongoing monitoring should be requested, that safety wording should be stronger, and that it would be more appropriate to have dialogue between the Division and the applicant to achieve acceptable wording. In addition it was decided that it would be appropriate to incorporate the revisions of safety wording into the ongoing labeling discussions for the pediatric efficacy supplement currently under review. Accordingly, the following comments were transmitted to the applicant via telephone facsimile:

- We request that you continue to track and inform us of respiratory adverse events and deaths (whether or not associated with respiratory manifestations) reported in patients receiving Relenza. Please alert the Division to such reports directly as well as submitting them through the standard adverse event reporting procedure (for example, we note that you have transmitted two reports to us by fax while your surveillance department was sending them to the FDA Central Document Room, and you may wish to continue using similar means of

maintaining prompt communications to the Division). Please continue to follow up on all deaths and respiratory adverse events: this should include contacting reporters of deaths and serious respiratory adverse events to obtain further information on circumstances surrounding these events.

- Please submit options for stronger warning language than that included in your proposal dated January 20, 2000. We anticipate more detailed discussions of specific content over the next few weeks in conjunction with ongoing review of adverse event reports.

- Given the prospect of substantial new label contents, we suggest that you plan a Dear Health Professional letter providing updated information, to be sent after final labeling language has been agreed upon. This may also include a description and explanation of pregnancy labeling changes.

- Progress on these issues is likely to be relevant to the currently proceeding review of the pediatric supplement to this NDA. Therefore, we suggest that safety-related label changes be incorporated into the label revisions currently under discussion in connection with this supplement. This should not delay your responses to the comments we have made regarding labeling related to the pediatric supplement: you may send those responses, and follow with additional proposals for safety-related changes as soon as possible.

/S/

Barbara A. Styrt, M.D., M.P.H.
Medical Officer, DAVDP

Concurrence:
HFD-530/MTL/SKukich SK 2/15/00

cc:
HFD-530/NDA21036
HFD-530/Division File
HFD-530/Dir/HJolson
HFD-530/MTL/SKukich
HFD-530/MO/BStyrt
HFD-530/CSO/Yoerg

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Record of Teleconference

NDA: **sNDA 21-036/S-001 (pediatric supplement)**

Date: **March 2, 2000**

Drug: **Relenza® (zanamivir for inhalation)**

Applicant: **Glaxo Wellcome, Inc.**

BETWEEN: **Representatives of Glaxo Wellcome, Inc. (GW)**
Krzysztof Selinger, Ph.D., Director International Bioanalysis, US
Pat Burnell, Ph.D., Principal Scientist, Inhalation Product Development, UK
Sherman Alfors, Project Director, Regulatory Affairs

AND: **Representatives of the Division of Antiviral Drug Products (DAVDP)**
Kellie Reynolds, Pharm.D., Biopharmaceutics Team Leader
Sandra Suarez, Ph.D., Biopharmaceutics Reviewer
Virginia Yoerg, Regulatory Project Manager

SUBJECT: GW's response to FDA request for Biopharmaceutics information

Background:

This teleconference was held at the request of DAVDP to clarify issues addressed in GW's submission dated February 18, 2000, *"Response to FDA Request/Comment: Biopharmaceutics Requests from February 11, 2000."* Please note that sponsor responses are in boldface type.

Discussion:

1. For urine samples in study NAIA1009, please provide information about the following:
   - Analytical method used for analyzing zanamivir.
   - Example chromatograms for blank, quality controls (QCs) and test sample
   - Calibration curve plot
   - Statistical analysis for QCs

   The sponsor mentioned in general that the method used to analyze zanamivir was [redacted] [Note: Complete information on these points was submitted on March 3, 2000].

2. Please refer to page 8 and pages 10-15 of GW's response to the FDA telephone facsimile dated February 11, 2000, and to pages 5 and 162 in Volume 2 of sNDA 21-036/S-001. For subjects at least five years of age, zanamivir was inhaled from the rotadisk blisters using a diskhaler, and the inhalation profile was recorded. Please indicate the procedure for the generation of the peak inspiration flow rate (PIFR) in those children.

Electronic lung technique was used to determine PIFR. [Note: Detailed information on this point was submitted on March 9, 2000].

3. Please indicate if the PIFR values reported (page 8 from GW's response to the FDA telephone facsimile dated February 11, 2000) were registered prior to inhalation of the zanamivir dose used for pharmacokinetic (PK) analysis. Also, was there any lag time between inhalations for PK analysis?

   PIFR reported were part of PK study NAIA1009. There was no lag time between inhalations.

4. Please refer to page 8 of response to FDA comments from February 11, 2000. Please indicate the reason for omitting PIFR values for the following patients: 101109 (6 years old), 101117 (7 y), 101125 (12y) and 101129 (6y).

   Some PIFR were not measurable, and PIFR values were not recorded for 101129.

5. Please indicate the optimal flow rate for the DISKHALER.

   60L/min.

6. Please indicate which flow rates were used to assess the in vitro particle size distribution (refer to page 8 from response to FDA comments from February 11, 2000).

   The flow rate used was 28.3 L/min.

concurrence:
HFD-530/BioPharmTL/Reynolds KSR 4/12/00
HFD-530/BioPharm/Suarez ES 04/10/00
HFD-530/RPM/Yoerg – 04/07/00
Drafted: VLY 04/06/00

cc:
sNDA 21-036/S-001
Division Files
HFD-530/BioPharmTL/Reynolds
HFD-530/BioPharm/Suarez
HFD-530/RPM/Yoerg

Record of Teleconference

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Record of Teleconference

NDA: **sNDA 21-036/S-001 (pediatric supplement)**

Date: **March 23, 2000**

Drug: **Relenza® (zanamivir for inhalation)**

Applicant: **Glaxo Wellcome, Inc.**

BETWEEN: **Representatives of Glaxo Wellcome, Inc. (GW)**
Pat Burnell, Ph.D., Principal Scientist, Inhalation Product Development, UK
Mike Elliott, M.D., Project Team Leader
Janet Hammond, M.D., Ph.D., Medical Project Leader
David Cocchetto, Ph.D., VP, Regulatory Affairs
Sherman Alfors, Project Director, Regulatory Affairs
Michael Ossi, M.D., Clinical Research
Robert Watson, Director, Regulatory Affairs

AND: **Representatives of the Division of Antiviral Drug Products (DAVDP)**
Heidi Jolson, M.D., M.P.H., Division Director
Barbara Styrt, M.D., M.P.H., Medical Reviewer
Melisse Baylor, M.D., Medical Reviewer
Virginia Yoerg, Regulatory Project Manager

SUBJECT: Rationale for label revisions

Background:

This teleconference was in response to Glaxo Wellcome's request made in a submission dated March 21, 2000. This submission contained the applicant's responses and proposals related to DAVDP comments on labeling issues arising from the Relenza pediatric efficacy supplement and revision of safety labeling.

Discussion:

The applicant stated that they would like to focus on three major areas of concern: the change in proposed label to limit the draft proposed indication to use in children 7 years of age and older, the latest changes in the Warning Section of the label, and the efficacy statement in the latest proposed label. DAVDP responses to the sponsor's concerns raised in the teleconference and in their submission dated March 21, 2000 are summarized as follows. Applicant responses and discussion are summarized in brackets.

Age limit for proposed indication: The Division's decision to change the proposed indication of zanamivir to 7 years of age and older was made based on the results of *both* NAIA1009 and NAI30009. In NAIA1009, the pediatric PK study, serum levels of zanamivir were lower for the younger children participating in this study and peak inspiratory pressures were low or unmeasurable for these younger children. In NAI30009, the pediatric efficacy study, there was no difference between the placebo and zanamivir groups when the 5 and 6 year olds were analyzed together.

In response to the sponsor's summary of peak inspiratory flow rates given in the March 21, 2000 submission, DAVDP noted that inspiratory flow rates were performed for the children enrolled in NAIA1009 and that tracings were provided for 7 of the 8 children who were said to not have had the test done. The DAVDP requested any further information which might help accurately represent this data in the label, taking into account the children who were unable to inhale on request or otherwise unable to produce adequate inspiratory flow (which is considered to be clinically relevant to use of the product in practice).

[Applicant expressed concern about focusing on a single subgroup analysis; DAVDP reiterated that the issue was multifactorial rather than based on a single analysis: suggestions of lesser efficacy in younger children in 30009, similar results from 30010, combined with the evidence from 1009 that younger children may not be able to use the device and lack of evidence that they can do so in this clinical setting.]

Description of treatment effect: DAVDP considers overall efficacy results of NAI30009 are most accurately represented as a one day difference. Our intention was not to focus on the North American population but to best represent the data. Reasons include:

1. Since diary cards entries were made twice daily, alleviation of symptoms was reported in a unit of 0.5 days; yet the difference in median times to alleviation for the two treatment groups was given as 1.25 days. This difference in medians depends on the fact that exactly the same number of influenza-positive placebo subjects had alleviation times of 5.0 days and below or of 5.5 days and above, giving a calculated median of 5.25 days compared with 4.0 days for zanamivir subjects; no individual study subject could have an alleviation time of 5.25 days and this value actually represents an interpolated value between two measurements. Therefore it is a highly unstable derived value: moving or omitting just one subject could change the placebo median by 0.25 days, and because the treatment difference in medians is not a large multiple of this amount of change, this creates the highly unusual situation that moving or omitting one subject in a study of over 400 subjects could make a large proportional difference to the estimate of treatment effect.

2. Because of the instability of this median value, the Division looked closely at pre-agreed secondary analyses of the overall efficacy endpoint. The initial analysis was also noted to be highly sensitive to the treatment of missing values, especially because there were far more missing values for time to alleviation in the placebo group than the zanamivir group, and subjects with missing values were assigned the longest possible time to alleviation in the primary analysis. When a censored analysis was done, it was noted that there were more censored subjects in the placebo group which could have skewed the results. On censored analysis, the difference in medians between the treatment and zanamivir groups was one day. The difference in means was also close to one day. In addition, the difference in medians in several important

subgroups was one day (influenza A infected subjects, U.S. subjects, subjects treated after 24 hours, the per protocol population).

[Applicant acknowledged that one day may be a more accurate representation under the circumstances.]

Warning language: The Division strongly considers that the Warnings section of the label should clearly and adequately reflect the concern about the use in patients with underlying airways disease that has been noted both in clinical studies of zanamivir and in postmarketing surveillance. Especially because there is now another neuraminidase inhibitor available for use, the potential risks for this subpopulation are important relative to the unclear benefits. We will be glad to revisit this issue if more information becomes available in the future, but prescribers should have appropriate information conveyed to them based on currently applicable data in order to make informed choices.

Other issues from March 21, 2000, Glaxo-Wellcome submission:

DAVDP considers the information that should be made available to patients now warrants a Patient Package Insert in addition to, or in combination with, the existing instruction leaflet (which itself is under revision and for which DAVDP has recently sent fax comments). Applicant asked whether this could be designed as a tear-off addition to the package insert (as recently done for another drug) while keeping the instruction leaflet simpler, and DAVDP indicated willingness to review a submission with this format.

In response to the applicant's query regarding deletion of the sentence in PRECAUTIONS: Information for Patients that states that patients should finish the entire 5 day course of zanamivir, DAVDP indicated that adverse event reports have been received in which patients experienced a striking adverse event following a zanamivir dose but continued to take subsequent doses with recurrence of the adverse event, and there have also been reports of patients developing clinical deterioration who were not evaluated for complications until after the 5-day course was completed: these reports suggest that an incorrect message is being derived from the label statement.

With respect to the applicant's proposal for pregnancy study language, it was noted that DAVDP Pharmacology/Toxicology reviewers have observed a dose-related increase in kinked ribs not limited to the highest dose, and have discussed this with the Reproductive Toxicology Committee. Applicant indicated they will want to discuss this further.

Regarding the applicant's comment on inclusion of inspiratory flow data under PRECAUTIONS: Pediatric Use, this section of the March 21, 2000 submission is an incomplete paragraph so the specific point cannot be assessed [no comment from applicant]; DAVDP indicated clinically relevant information that clarifies the age groups with adequate safety and efficacy data is being considered for inclusion in this section.

With regard to applicant's proposal for describing lower respiratory adverse events in high risk respiratory subjects, the Division proposes that including the adverse events for these subjects in NAI30010 provides valuable information in a subgroup that is already of concern, while the similarly coded events for NAI30009 provide little clinically applicable information, especially because subjects in NAI30009 had an influenza-like illness on enrollment and such events would be reported

differently for this group. There was additional discussion (as in the March 21, 2000, submission) and DAVDP agreed to consider the applicant's proposal in further internal discussions.

It was agreed that the applicant will submit a draft patient package insert early next week, and that DAVDP will send additional labeling comments and revisions after internal consideration of the issues addressed in the teleconference.

concurrence:
HFD-530/DivDir/Jolson 4/17/00
HFD-530/MO/Styrt 4/12/00
HFD-530/MO/Baylor 4/12/00
HFD-530/RPM/Yoerg – 04/10/00
Drafted: VLY 04/07/00

cc:
sNDA 21-036/S-001
Division Files
HFD-530/DivDir/Jolson
HFD-530/MOTL/Kukich
HFD-530/MO/Styrt
HFD-530/MO/Baylor
HFD-530/RPM/Yoerg

Record of Teleconference

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Record of Teleconference

NDA: **sNDA 21-036/S-001 (pediatric supplement)**

Date: **April 17, 2000**

Drug: **Relenza® (zanamivir for inhalation)**

Applicant: **Glaxo Wellcome, Inc.**

BETWEEN: **Representatives of Glaxo Wellcome, Inc. (GW)**
Michael Elliott, M.D., Project Team Leader
Janet Hammond, M.D., Ph.D., Medical Project Leader
Patti Szymborski, Clinical Research
Michael Ossi, M.D., Clinical Research
Marc Rubin, M.D., Clinical Research
Oliver Keene, Statistics (UK)
Peter Lammers, Commercial Operations
David Cocchetto, Ph.D., Vice President, Regulatory Affairs
Sherman Alfors, Project Director, Regulatory Affairs

AND: **Representatives of the Division of Antiviral Drug Products (DAVDP)**
Heidi Jolson, M.D., M.P.H., Division Director
Stanka Kukich, M.D., Medical Team Leader
Barbara Styrt, M.D., M.P.H., Medical Reviewer
Melisse Baylor, M.D., Medical Reviewer
Virginia Yoerg, Regulatory Project Manager

SUBJECT: Labeling and Phase 4 commitments

Background:

This teleconference was requested by DAVDP in response to the applicant's submissions of April 10, 2000, and April 11, 2000, regarding Phase 4 commitments, label, patient instruction sheet, and patient package insert for the pediatric efficacy supplement (sNDA 21-036/S-001). Comments on these submissions were sent to the applicant via telephone facsimile on April 14, 2000; the teleconference was scheduled to clarify questions from the applicant and rationale for the DAVDP comments. Please note that agreements reached are italicized.

Discussion:

1. The label

The applicant stated their only remaining issue for the professional package insert is their proposal to include separate results for 7 to 12 year old children in study NAI30009 in the label. DAVDP

responded that subgroup analyses are not generally included in the label. The study was designed to evaluate efficacy in 5 to 12 year olds; this is the population that should be included in the label. In addition, the decision to restrict the indication for zanamivir to children 7 years of age and older was based on the results of three studies which enrolled pediatric patients; including the results for children from 7 to 12 years of age in the label implies that the decision was based on a subgroup analysis of NAI30009 only.

The applicant asked for specification of language that the Division of Drug Marketing, Advertising, and Communications would consider acceptable in promotional material. They were informed that such material would be expected to reflect appropriate information in the label, and that if specific questions arose, it would be acceptable to submit proposed material for discussion before it was disseminated.

2. Patient Instruction Sheet

The applicant agreed to the changes proposed by the Division in the fax dated April 14, 2000.

The applicant agreed to submit a color mock-up of the patient instruction sheet as soon as it was available. Before that time, the applicant will submit a black and white copy for review.

3. Phase 4 Commitments

The Phase 4 commitments were discussed individually by the Division and the applicant.

The applicant suggested that they thought the first Phase 4 commitment could be interpreted as too open-ended. DAVDP indicated it would be acceptable to add "where applicable" to the sentence. *The applicant agreed to this change.*

The applicant agreed to the proposed second Phase 4 commitment, and indicated they would submit a protocol proposal for review.

For the third proposed Phase 4 commitment, the applicant suggested that targeted enrollment of ethnic minorities into studies might be interpreted as meaning that ethnic minorities were to be preferentially enrolled before Caucasians who were also eligible for studies. They suggested recruiting subjects at study sites where ethnic minority patients are commonly seen for medical care. It was agreed that the word "enrollment" could be changed to "recruitment". The applicant stated that they would attempt to enroll more ethnic minority subjects in the studies of use of the drug delivery device. The applicant stated that they considered the amount of lactose included in the zanamivir was not enough to cause diarrhea in patients with lactose deficiency and so they did not consider monitoring this potential adverse event to be necessary; but acknowledged that they could readily review adverse event reports for evidence of lactose intolerance. *After further discussion the applicant accepted this Phase 4 commitment with the one-word change indicated.*

The applicant agreed to the proposed fourth Phase 4 commitment regarding resistance testing.

The applicant disagreed with the need for two letters to health professionals and proposed that instead they notify associations involved in the dissemination of drug information (i.e. Physicians Desk Reference and similar compendia) of the new label. They stated that the circulation list for a

letter regarding this drug would be larger than for HIV drugs, and that a second letter might be ignored by health care professionals. They proposed to send a letter only at the beginning of the influenza season. DAVDP indicated that it would be unusual for such extensive changes in safety labeling to be made without plans for effective dissemination of information at the time the changes are implemented, and that it would be unfortunate if there were substantial summer use of influenza drugs this year without having appropriate information disseminated to practitioners; DAVDP agreed that a letter sent in the spring would probably not be fresh in practitioners' recollection when the major seasonal use of this drug is likely to occur, so the seasonal nature of influenza creates the reason for two letters which in fact would probably be several months apart. *The applicant agreed to send two separate letters.*

The applicant suggested that the provisions in the sixth Phase 4 commitment were unique for their drug and might leave them susceptible to excess liability. The Division stated that the use of zanamivir was different from most drugs in that its use occurred almost exclusively during influenza season. If periodic reports were only made quarterly, new information would not be evaluated in time to notify health care providers during the current influenza season. The applicant was also reminded that the Division had requested this type of continued reporting of adverse events with other drugs. *The applicant will submit suggestions for alternative wording of this request to the Division within the next day.*

4. Patient Package Insert

The applicant suggested that the patient package insert include the most common adverse events plus a statement that the list is not complete and more complete information can be obtained from the patient's health care provider. DAVDP indicated that adverse events noted in the Precautions or Warnings section of the label should be specifically included in the Patient Package Insert along with more common adverse events. *It was agreed that with this consideration taken into account, the applicant could submit revised wording for review.*

5. Timing

It was noted that all disciplines in the Division will need to look over the label and related documents, that additional comments may follow after viewing the clean copy, and that an action is anticipated by April 26, 2000. *The applicant agreed to send revisions of the label, the PPI, and the patient instruction sheet to the Division by e-mail within the next few hours and to send revised Phase 4 commitments within the next day. The applicant also agreed to provide side-by-side comparison copies with revision markings showing the previously approved labeling and the changes encompassed in the proposed version.*

concurrence:
HFD-530/DivDir/Jolson 4/25/00
HFD-530/MOTL/Kukich SK 4/24/00
HFD-530/MO/Styrt BSS 4/24/00
HFD-530/MO/Baylor- ESO 04/24/00
HFD-530/RPM/Yoerg – 04/24/00
Drafted: VLY 04/18/00

cc:
sNDA 21-036/S-001
Division Files
HFD-530/DivDir/Jolson
HFD-530/MOTL/Kukich
HFD-530/MO/Styrt
HFD-530/MO/Baylor
HFD-530/RPM/Yoerg

Record of Teleconference

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Yoerg
Styrt
Baylor
Package

GlaxoWellcome

April 21, 2000

Heidi M. Jolson, M.D., M.P.H.
Director, Division of Antiviral Drug Products
Attn: Document Control Room
Food and Drug Administration
Fourth Floor, HFD-530
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-036/S-001; RELENZA® (zanamivir for inhalation); General Correspondence: Phase IV Commitments

Dear Dr. Jolson:

Reference is made to NDA 21-036/S-001 for Relenza (zanamivir for inhalation), as submitted on October 25, 1999. The purpose of this Supplemental Application was to expand the indication for Relenza to include treatment of influenza in pediatric patients. Please also refer to the fax of April 14, 2000 from Ms. Yoerg to Mr. Alfors regarding proposed Phase 4 commitments, as well as the teleconference of April 17, 2000 in which DAVDP and GW personnel discussed the proposed Phase 4 commitments. The purpose of this letter is to provide a statement of Phase IV commitments pursuant to approval of S-001; these commitments are in addition to previous commitments as stated in our letter of July 26, 1999.

Format of This Letter

We are providing this letter in a format consistent with our previous letter of Phase IV commitments on Relenza, as submitted on July 26, 1999. In the first section below, we are providing a concise statement of each Phase IV commitment (based on the format in your fax of April 14). Our understanding is that each of these statements will be repeated, verbatim, in the approval letter for S-001. We have tried to write them in a style such that you can readily "cut and paste" them into the action letter.

In the second section below, we have provided expanded information on several of the commitments. Specifically, we have summarized work that is already ongoing on each of these topics, given examples of future work that we intend to complete, and explicitly stated our understanding of key operational aspects of the activities. We are using this format to provide more specific information so that GW and DAVDP will have a common

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398
Telephone
919 483 2100

understanding of the commitments. Please note that our intent is to keep FDA informed on a regular basis of our progress toward completion of these activities by including a progress report on the original Phase IV commitments, as well as these additional Phase IV commitments, in our Annual Reports to NDA 21-036.

List of Phase IV Commitments for NDA 21-036/S-001

Glaxo Wellcome makes the following Phase IV commitments for NDA 21-036/S-001:

1. Provide subgroup analyses for efficacy and safety in pediatric age groups for reports of applicable studies with pediatric subgroups.

2. Develop, conduct, and report a study to assess the ability of children and adolescents of various ages to use the zanamivir dry powder inhalation system (Diskhaler) based on patient or parental comprehension of the proposed Instructions for Use. This study will seek to identify potential obstacles to effective use by categories of potential patients arising from characteristics of the Diskhaler and the Instructions for Use. This study will also seek to develop and test improvements in Instructions for Use that may lead to more reliably effective use by pediatric patients in the settings characteristic of the indication (i.e., primary care medical care settings, acutely ill children, need for instructions that will reliably lead to appropriate use beginning with the first dose). This study may be conducted as a substudy on pediatric subjects within a larger study enrolling both pediatric and adult subjects. Submit the draft protocol for review and comment to assure that the design of the study is adequate to address this commitment.

3. Provide a plan to increase information regarding safety and efficacy in racial and ethnic minority patients. This plan should include (a) subgroup analyses of Caucasian versus non-Caucasian patient subgroups for primary safety and efficacy endpoints as part of the final study report for recently completed and ongoing studies; (b) targeted recruitment of non-Caucasian patients in ongoing and future studies, including the labeling comprehension study on use of the Diskhaler with its Instructions for Use; (c) a summary and aggregate analysis of results for different racial/ethnic populations across studies; and (d) a review of Glaxo Wellcome's global postmarketing adverse event database for reports of lactose intolerance in non-Caucasian patients.

4. Provide a progress report (as part of the existing Phase IV commitment for detection and analysis of influenza resistance to zanamivir) on the work toward improving culture yield and increasing the number of isolates examined from both clinical trials and postmarketing surveillance. Provide the plan for examining zanamivir-resistant clinical isolates of influenza for cross-resistance.

5. Within one month of approval of S-001, provide a proposal for a letter to health care professionals describing safety issues noted with the use of zanamivir and a proposal for dissemination of this letter. This letter will (a) address the safety-related modifications to the package insert (including but not limited to reports of serious respiratory adverse events in patients with and without underlying respiratory disease), (b) remind health care professionals to also consider bacterial etiologies when patients present with influenza-like illnesses, and (c) address the change in pregnancy category. Following the Division's review of this proposal and agreement on content and mode of dissemination, this letter will be distributed within one month (most likely in June or July) and before the drug is promoted for pediatric use.

   A second letter to health care professionals (covering the same safety issues as the first letter and incorporating any needed safety updates) will be drafted and submitted to the Division for review. Following the Division's review and agreement on content and dissemination, this letter will be distributed prior to the next influenza season (i.e., mailing to be completed by end-October 2000).

6. For each postmarketing adverse drug experience with a fatal outcome, Glaxo Wellcome will make diligent efforts to obtain additional information about antecedent and concomitant medical circumstances of the fatality. These diligent efforts will include requesting that each health care professional reporter provide a copy of medical records, results of laboratory or diagnostic tests, and an autopsy report (if an autopsy was performed). Prepare and submit "15-Day Alert Reports - Follow Up" to report such information in accordance with 21 CFR 314.80 (c)(1)(ii).

7. Collect and submit specific postmarketing adverse drug experience information directly to DAVDP as follows:
   a. Submit each serious postmarketing adverse drug experience report (involving one or more of the respiratory system, cardiovascular system, allergic and allergic-like reactions) directly to DAVDP within 15 calendar days of receipt, regardless of whether the adverse drug experience is classified as expected or unexpected.
   b. Submit a report of each fatal postmarketing adverse drug experience directly to DAVDP within 15 calendar days of receipt, regardless of whether the fatality is classified as expected or unexpected, and regardless of which specific organ system is involved.

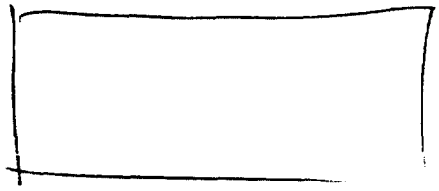
   The 15-day reports due to DAVDP each week will be collected and submitted as a batch, once a week, to DAVDP. Each such submission will be sent to NDA 21-036 as "General Correspondence: Safety Reports per Phase 4 Commitment".

   The data collected in this manner will be reviewed after the 2000-2001 influenza season using a data cut-off of end-March 2001 (and after each subsequent season that the practice continues) to assess the merits of continuing these additional expedited reporting procedures.

More Detailed Information on Glaxo Wellcome's Activities Pursuant to Phase IV Commitments for NDA 21-036

Each of the Phase IV commitments is reiterated below (in bold type), followed by additional information on specific activities to meet this commitment.

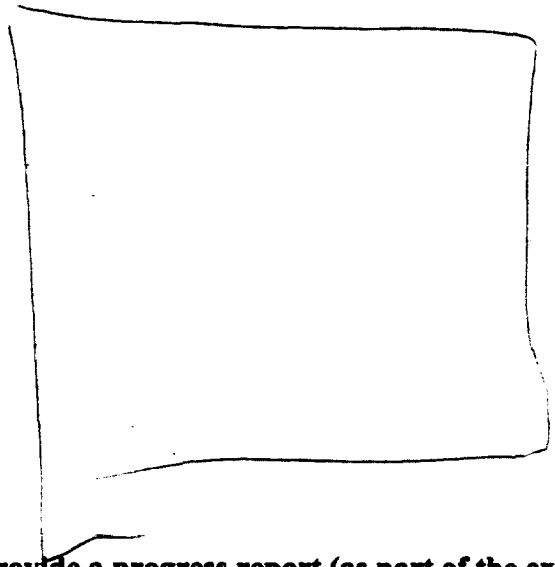
1. **Provide subgroup analyses for efficacy and safety in pediatric age groups for reports of applicable studies with pediatric subgroups.**



2. **Develop, conduct, and report a study to assess the ability of children and adolescents of various ages to use the zanamivir dry powder inhalation system (Diskhaler) based on patient or parental comprehension of the proposed Instructions for Use. This study will seek to identify potential obstacles to effective use by categories of potential patients arising from characteristics of the Diskhaler and the Instructions for Use. This study will also seek to develop and test improvements in Instructions for Use that may lead to more reliably effective use by pediatric patients in the settings characteristic of the indication (i.e., primary care medical care settings, acutely ill children, need for instructions that will reliably lead to appropriate use beginning with the first dose). This study may be conducted as a substudy on pediatric subjects within a larger study enrolling both pediatric and adult subjects. Submit the draft protocol for review and comment to assure that the design of the study is adequate to address this commitment.**

3. **Provide a plan to increase information regarding safety and efficacy in racial and ethnic minority patients. This plan should include (a) subgroup analyses of Caucasian versus non-Caucasian patient subgroups for primary safety and efficacy endpoints as part of the final study report for recently completed and ongoing studies; (b) targeted recruitment of non-Caucasian patients in ongoing and future studies, including the labeling comprehension study on use of the Diskhaler with its Instructions for Use; (c) a summary and aggregate analysis of results for different racial/ethnic populations across studies; and (d) a review of**

Glaxo Wellcome's global postmarketing adverse event database for reports of lactose intolerance in non-Caucasian patients.



4. **Provide a progress report (as part of the existing Phase IV commitment for detection and analysis of influenza resistance to zanamivir) on the work toward improving culture yield and increasing the number of isolates examined from both clinical trials and postmarketing surveillance. Provide the plan for examining zanamivir-resistant clinical isolates of influenza for cross-resistance.**

5. **Within one month of approval of S-001, we will provide a proposal for a letter to health care professionals describing safety issues noted with the use of zanamivir and a proposal for dissemination of this letter. This letter will (a) address the safety-related modifications to the package insert (including but not limited to reports of serious respiratory adverse events in patients with and without underlying respiratory disease), (b) remind health care professionals to also consider bacterial etiologies when patients present with influenza-like illnesses, and (c) address the change in pregnancy category. Following the Division's review of this proposal and agreement on content and mode of dissemination, this letter will be distributed within one month (most likely in June or July) and before the drug is promoted for pediatric use.**

A second letter to health care professionals (covering the same safety issues as the first letter and incorporating any needed safety updates) will be drafted and submitted to the Division for review. Following the Division's review and agreement on content and dissemination, this letter will be distributed prior to the next influenza season (i.e., mailing to be completed by end-October 2000).

6. **For each postmarketing adverse drug experience with a fatal outcome, Glaxo Wellcome will make diligent efforts to obtain additional information about antecedent and concomitant medical circumstances of the fatality. These diligent efforts will include requesting that each reporter provide a copy of medical records, results of laboratory or diagnostic tests, and an autopsy report (if an autopsy was performed). Prepare and submit "15-Day Alert Reports - Follow Up" to report such information in accordance with 21 CFR 314.80 (c)(1)(ii).**

7. **Collect and submit specific postmarketing adverse drug experience information directly to DAVDP as follows:**
   a. **Submit each serious postmarketing adverse drug experience report (involving one or more of the respiratory system, cardiovascular system, allergic and allergic-like reactions) directly to DAVDP within 15 calendar days of receipt, regardless of whether the adverse drug experience is classified as expected or unexpected.**
   b. **Submit a report of each fatal postmarketing adverse drug experience directly to DAVDP within 15 calendar days of receipt, regardless of whether the fatality is classified as expected or unexpected, and regardless of which specific organ system is involved.**

   The 15-day reports due to DAVDP each week will be collected and submitted as a batch, once a week, to DAVDP. Each such submission will be sent to NDA 21-036 as "General Correspondence: Safety Reports per Phase 4 Commitment".

   The data collected in this manner will be reviewed after the 2000-2001 influenza season using a data cut-off of end-March 2001 (and after each subsequent season that the practice continues) to assess the merits of continuing these additional expedited reporting procedures.

We also acknowledge the fax of April 14, 2000 from Ms. Yoerg (regarding "Phase 4 commitments") which informed us that DAVDP does not request that GW continue to submit desk copies of selected 15-Day Alert Reports directly to the Project Manager. Therefore, as of April 18, we are discontinuing the practice of providing desk copies directly to the Project Manager.

This letter is provided in duplicate. Four desk copies are being sent directly to Ms. Virginia Yoerg for distribution to the review team. Please contact me at (919)-483-5127 for any matters regarding this application. Thank you.

Sincerely,

David M. Cocchetto, Ph.D.
Vice President
Antiviral/Anti-Infective Regulatory Affairs

Michael J. Ossi, M.D.
Vice President, Infectious Disease
& Hepatitis Clinical Development

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338.
Expiration Date: April 30, 2000.
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Glaxo Wellcome Inc.	April 21, 2000
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number *(Include Area Code)***
(919) 483-2100	(919) 483-5756
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued)*:	**AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE**
Five Moore Drive Research Triangle Park, NC 27709	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued): 21-036/S-001

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME (*trade name*) IF ANY
zanamivir for inhalation	Relenza® (zanamivir for inhalation)

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: 5-(acetylamino-4-[(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid

CODE NAME (If any):

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Powder for Inhalation	5 mg	oral

(PROPOSED) INDICATION(S) FOR USE: Treatment of influenza A and B

APPLICATION INFORMATION

APPLICATION TYPE (check one): [X] NEW DRUG APPLICATION (21 CFR 314.50) [ ] ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) [ ] BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE: [X] 505 (b) (1) [ ] 505 (b) (2) [ ] 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug: Holder of Approved Application:

TYPE OF SUBMISSION (check one):
[ ] ORIGINAL APPLICATION [ ] AMENDMENT TO A PENDING APPLICATION [ ] RESUBMISSION
[ ] PRESUBMISSION [ ] ANNUAL REPORT [ ] ESTABLISHMENT DESCRIPTION SUPPLEMENT [ ] SUPAC SUPPLEMENT
[ ] EFFICACY SUPPLEMENT [ ] LABELING SUPPLEMENT [ ] CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT [X] OTHER

REASON FOR SUBMISSION: General Correspondence: Phase IV Commitments

PROPOSED MARKETING STATUS (check one): [X] PRESCRIPTION PRODUCT (Rx) [ ] OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1

THIS APPLICATION IS: [X] PAPER [ ] PAPER AND ELECTRONIC [ ] ELECTRONIC

ESTABLISHMENT INFORMATION N/A

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Please see attached list.

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods Validation Package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3) , 21 CFR 601.2)
	7. Clinical Microbiology (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b) , 21 CFR 601.2)
	10. Statistical section (21 CFR 314.50 (d) (6) , 21 CFR 601.2)
	11. Case report tabulations (21 CFR 314.50 (f) (1) , 21 CFR 601.2)
	12. Case reports forms (21 CFR 314.50 (f) (2) , 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (K) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) **General Correspondence: Phase IV Commitments**

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biologic product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
David M. Cocchetto	**David M. Cocchetto, Ph.D.** **Vice President, AV/AI Regulatory Affairs**	**April 21, 2000**

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
Five Moore Drive **Research Triangle Park, NC 27709**	**(919) 483-5127**

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DHHS. Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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FORM FDA 356h (4/97)

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application):