CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-007
21-039

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

GlaxoWellcome

October 26, 1998

Mellon Bank
Food and Drug Administration
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

Re: NDA 21-039; AGENERASE™ (amprenavir) Oral Solution
User Fee # 3579

Please find enclosed Glaxo Wellcome check number [redacted] in the amount of [redacted] This payment is 100% of the application fee for the New Drug Application for AGENERASE™ (amprenavir) Oral Solution for the treatment of HIV infection.

Reference is made to NDA 21-007 AGENERASE™ (amprenavir) Capsules submitted to the FDA on October 15, 1998. The liquid formulation that is the subject of NDA 21-039 was developed for use in pediatric patients. As agreed between Mr. Anthony Zeccola of the Division of Antiviral Drug Products and Mr. Robert Watson of Glaxo Wellcome, a **full supplemental fee** is being paid for this application.

Below please find requested information regarding this application

Type of Application:	New Drug Application with Clinical Data	X
	New Drug Application without Clinical Data	
	Supplemental New Drug Application with Clinical Data	

Should you have any questions, please contact me at (919) 483-6972. Thank you.

Sincerely,

Robert S. Watson

Robert S. Watson
Product Director
Regulatory Affairs

Glaxo Wellcome Research and Development
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709
Telephone
919 483 2100
A Division of
Glaxo Wellcome Inc.

GlaxoWellcome

April 13, 1999

DESK COPY

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 21-007; AGENERASE™ Capsules (amprenavir capsules)
NDA 21-039; AGENERASE™ (amprenavir) Oral Solution
Phase IV Commitments

Dear Dr. Jolson:

Reference is made to NDAs 21-007 and 21-039 for Agenerase (amprenavir) Capsules and Agenerase (amprenavir) Oral Solution, i.e., applications under active review in your Division. Please also refer to the fax of April 6, 1999 from Ms. Melissa Truffa that listed several recommendations for Phase IV activities with these products. In view of the Division's recommendations, the purpose of this letter is to provide a statement of our commitment to Phase IV activities with amprenavir.

Background Information

This letter provides a straightforward list of Phase IV activities, recognizing the need for such a list that can be quoted in the action letter. The latter part of the letter provides expanded information on each Phase IV activity; this expanded information enables us to summarize some work that is already ongoing and to explicitly state our understanding of key operational aspects of the activities. Please note that our intent is to keep FDA informed on a regular basis of our progress toward completion of these activities. Specifically, we intend to include a progress report on these Phase IV activities in our Annual Reports to NDA 21-007 and NDA 21-039.

We believe it is important to assure a shared understanding of the nature of these Phase IV activities. Glaxo Wellcome is committed to conducting these activities as a logical extension of our historical significant investment in this important field. Glaxo Wellcome's understanding is that our Phase IV activities are subject to the

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919 248 2100

NDA Annual Reporting requirement [21 CFR 314.81(b)(2)], but are not subject to any special reporting requirements under Section 130 ("*Reports of Postmarketing Approval Studies*") of the FDA Modernization Act. As you know, a proposed regulation to implement Section 130 has not yet been issued by FDA; therefore, in the absence of such a regulation, we believe it is helpful to explicitly state Glaxo Wellcome's view in the interest of assuring a shared understanding.

List of Phase IV Activities

1. Glaxo Wellcome will continue to study and report the safety and efficacy of amprenavir used in combination with other antiretroviral agents to demonstrate the utility of amprenavir in various patient populations, including protease-inhibitor experienced and advanced HIV-infected (salvage) patients, by initiating or completing the following clinical trials:

   - ACTG 398: Phase 2 randomized trial of amprenavir in combination with abacavir, efavirenz, and ————————
   - ACTG 400: Phase 2 open-label trial of antiviral therapy (efavirenz plus 2 NRTIs plus at least one new protease inhibitor) for nelfinavir failures,
   - PRO20005: Phase 2 open-label trial for treatment of HIV infection in subjects who have failed initial combination therapy with regimens containing indinavir or nelfinavir. This study assesses combination therapy with amprenavir, 3TC, and abacavir plus either nelfinavir or indinavir for 48 weeks,
   - CNAA2007: A Phase 2 study evaluating the safety and antiviral activity of combination therapy with amprenavir, abacavir, and efavirenz in HIV-1 infected subjects with detectable plasma HIV-1 RNA despite treatment with a protease inhibitor-containing regimen for 48 weeks, and
   - Safety data for patients with CD4 cell count < 100 at entry will be provided from ACTG398, ACTG400, PRO20005, CNAA2007, and the Agenerase Early Access program. In addition, Glaxo Wellcome commits to submit for review by the Division of Antiviral Drug Products a plan for studying patients with advanced HIV infection.

2. Glaxo Wellcome will prepare and submit a supplemental NDA for traditional approval of Agenerase products. This application will include an exploration of any gender-related differences in safety and efficacy outcome measures.

3. Glaxo Wellcome will provide data on HIV-infected pediatric patients as agreed in the Written Request dated April 7, 1999. Glaxo Wellcome will have further discussions with the Division of appropriate preclinical toxicology evaluations that would support administration of amprenavir to neonates.

4. Glaxo Wellcome will propose and conduct a prospective study of (a) the tolerability of amprenavir in patients with a known history of sulfonamide allergy and (b) the tolerability of sulfonamide therapy ——— after patients have been treated with amprenavir.

5. Glaxo Wellcome will propose and conduct an evaluation of the safety of chronic, high-dose Vitamin E administration in adults and pediatric patients receiving amprenavir long-term, including the evaluation of vitamin E levels.

6. Glaxo Wellcome agrees to submit reports of completed carcinogenicity studies in a timely manner.

7. Glaxo Wellcome agrees to initiate or complete drug-drug interaction studies of amprenavir with each of the following drugs: ritonavir, efavirenz, nevirapine, methadone, and a representative female hormonal contraceptive product.

8. Glaxo Wellcome agrees to evaluate resistance to amprenavir and cross-resistance to other protease inhibitors in sequential HIV isolates from patients maintained on amprenavir in clinical trials. This evaluation will include:

- determination of *in vitro* susceptibility of HIV isolates to amprenavir
- assessment of the potential genotype basis of drug susceptibility attributable to the viral target genes and extragenic sites (such as the protease cleavage sites)
- assessment of cross-resistance of amprenavir-resistant variants to other protease inhibitors and vice versa.

9. Glaxo Wellcome will investigate lipid metabolic pathways through *in vitro* studies. We also agree to investigate the possible mechanisms for the development of fat redistribution in patients receiving amprenavir; the incidence of this event; and the potential for long-term consequences. In addition, ongoing and future clinical trials will provide appropriate monitoring for these events and for any lipid-related disorders.

10. Glaxo Wellcome agrees to complete and submit a report of the results of the experiments ———

11.

Our understanding is that this list of eleven items will be quoted in the action letter. Expanded information on each of these Phase IV activities is provided in the following section.

Expanded Information on Phase IV Activities

1. Glaxo Wellcome will continue to study and report the safety and efficacy of amprenavir used in combination with other antiretroviral agents to demonstrate the utility of amprenavir in patient populations, including protease-inhibitor experienced and advanced HIV-infected (salvage) patients. This will be accomplished by initiating or completing the following clinical trials:

   - ACTG 398 Phase 2 randomized trial of amprenavir in combination with abacavir, efavirenz, and ————

We will commit to be diligent in our collaboration on ACTG 398, recognizing that it is being conducted under ———— in conjunction with another sponsor, and that we do not control the decisions of the overall Protocol Team. We commit to submit the Executive Summary report from this study to the Division in a timely manner after it is provided to us by the ACTG.

   - ACTG 400 Phase 2 open-label trial of antiviral therapy (efavirenz plus 2 NRTIs plus at least one new protease inhibitor) for nelfinavir failures

We will commit to be diligent in our collaboration on ACTG 400 that is being conducted under an ———— and in conjunction with another sponsor. We shall submit the Executive Summary report from this study to the Division in a timely manner after it is provided to us by the ACTG.

   - PRO20005 Phase 2 open-label trial for treatment of HIV infection in subjects who have failed initial combination therapy with regimens containing indinavir or nelfinavir. This study assesses combination therapy with amprenavir, 3TC, and abacavir plus either nelfinavir or indinavir for 48 weeks.

This study is being conducted under the amprenavir —— and a study report will be submitted as an amendment to ——— This study will provide data from protease-inhibitor experienced patients.

   - CNAA2007 A Phase 2 study evaluating the safety and antiviral activity of combination therapy with amprenavir, abacavir, and efavirenz in HIV-1 infected subjects with detectable plasma HIV-1 RNA despite treatment with a protease-inhibitor containing regimen for 48 weeks.

This study also is being conducted under ——————— and the results will be reported via —— amendment. This study will provide long term data on advanced HIV-infected (salvage) patients.

- Safety data for patients with CD4 cell count < 100 at entry will be provided from ACTG398, ACTG400, PRO20005, CNAA2007, and the Agenerase Early Access program. In addition, Glaxo Wellcome commits to submit for review by the Division plans for studying patients with advanced HIV infection.

Safety data for patients with CD4 cell count < 100 at entry from these studies will be provided to ——— as each study completes. A summary report of all available safety data for all patients with CD4 cell count < 100 across these studies will be prepared and submitted to FDA. Glaxo Wellcome also commits to submit for review by the Division plans for studying patients with advanced HIV infection.

2. Glaxo Wellcome will prepare and submit a supplemental NDA for traditional approval of Agenerase. This application will include an exploration of any gender-related differences in safety and efficacy outcome measures.

The content and format of the sNDA for traditional approval will be discussed and agreed with the Division. As part of the application, we commit to perform appropriate exploration of any gender-related differences in safety and efficacy outcome measures.

3. Glaxo Wellcome will provide data on HIV-infected pediatric patients as agreed in the Written Request dated April 7, 1999. Glaxo Wellcome will have further discussions with the Division of appropriate preclinical toxicology evaluations that would support administration of amprenavir to neonates.

The Written Request of April 7 requests that information be submitted for HIV-infected patients ——————— The necessary steps to take to fulfill the Written Request will be discussed and agreed with the Division.

4. Glaxo Wellcome will propose and conduct a prospective study of (a) the tolerability of amprenavir in patients with a known history of sulfonamide allergy and (b) the tolerability of sulfonamide therapy ——————— after patients have been treated with amprenavir.

We propose to collect and report safety data to DAVDP from a prospective study in approximately 50-100 patients with a known history of sulfonamide allergy to assess tolerability of subsequent treatment with amprenavir or patients who receive sulfonamide therapy either after treatment with amprenavir or concurrently with treatment with amprenavir.

5. Glaxo Wellcome will propose and conduct an evaluation of the safety of chronic, high-dose Vitamin E administration in adults and pediatric patients receiving amprenavir long-term including the evaluation of vitamin E levels.

Glaxo Wellcome will determine plasma Vitamin E concentrations in stored frozen samples from a representative group of adult patients, that were enrolled in a randomized comparison of NRTIs plus either amprenavir or indinavir (PROAB3006). This will allow an analysis of associations of vitamin E concentrations with baseline variables (e.g. weight, age, CD4 cell count, HIVRNA, etc) and their potential changes over time compared to a randomized HIV infected population.

We will evaluate and submit reports on the safety of 48 week administration of Agenerase, using capsule formulations containing 109 IU Vitamin E/capsule (16 capsules/day) in adults (studies PROAB3001 and 3006) and an oral solution formulation containing 46 IU Vitamin E/mL in pediatric patients (PROAB3004 and PROB2004).
Glaxo Wellcome will follow a cohort of patients on Agenerase from these studies for two years to monitor Vitamin E concentrations and safety.

6. Glaxo Wellcome agrees to submit reports of completed carcinogenicity studies in a timely manner.

Reports of two 104 week studies (rat and mouse) will be submitted in 2001.

7. Glaxo Wellcome agrees to initiate or complete drug-drug interaction studies of amprenavir with each of the following drugs: ritonavir, efavirenz, nevirapine, methadone, and a representative female hormonal contraceptive product.

The draft protocols for each Glaxo Wellcome sponsored study has been or will be submitted to the Division for review and comment prior to initiation. Results will be reported as supplemental applications to support labeling changes.

8. Glaxo Wellcome agrees to evaluate resistance to amprenavir and cross-resistance to other protease inhibitors in sequential HIV isolates from patients maintained on amprenavir in clinical trials. This evaluation will include:

- determination of *in vitro* susceptibility of HIV isolates to amprenavir
- assessment of the potential genotype basis of drug susceptibility attributable to the viral target genes and extragenic sites (such as the protease cleavage sites)
- assessment of cross-resistance of amprenavir-resistant variants to other protease inhibitors and vice versa.

We intend to perform these evaluations on viral isolates collected in the following ongoing clinical studies: PROA3001, PROA3006, CNAA2007, and PRO20005. In addition, we will collaborate with the ACTG to encourage conduct of these assessments in studies ACTG 398 and ACTG 400.

9. Glaxo Wellcome will investigate lipid metabolic pathways through *in vitro* studies. The applicant also agrees to investigate the possible mechanisms for the development of fat redistribution in patients receiving amprenavir; the incidence of this event; and the potential for long-term consequences. In addition, ongoing and future clinical trials should provide appropriate monitoring for these events and for any lipid-related disorders.

We will incorporate appropriate monitoring for fat redistribution and abnormalities of serum lipids in future GW-sponsored clinical trials of amprenavir under [redacted] Further, we will advise our collaborators (e.g., ACTG, ICC) that it is appropriate to build such monitoring into studies of amprenavir conducted under their sponsorship. We also commit to investigate the possible mechanisms for development of fat distribution and the frequency of this event with amprenavir. If a sufficient frequency of this event is observed with amprenavir, we will examine ways to follow the potential long-term consequences of this event in a cohort of patients.

The following commitments have been agreed with the reviewing Chemist at DAVDP.

10. Glaxo Wellcome agrees to complete and submit a report of the results of the experiments [redacted]

[ ]

This letter is submitted in duplicate. Seven desk copies have been provided directly to Ms. Truffa for use by the review team. Please contact me at (919)-483-6972 for any matters regarding these applications. Thank you.

Sincerely,

Robert S. Watson
Director
Regulatory Affairs

Lynn Smiley, M.D.
Vice President
HIV and Opportunistic Infections
Clinical Development

APPEARS THIS WAY
ON ORIGINAL

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 13, 1999
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)*:
Five Moore Drive
Research Triangle Park, NC 27709

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-007

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME (*trade name*) IF ANY
Amprenavir Capsules	Agenerase™ (Amprenavir) Capsules

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
(3S)-tetrahydro-3-furyl N-((1S, 2R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl) carbamate

CODE NAME (If any)
141W94

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsules	50 mg, 150 mg	oral

(PROPOSED) INDICATION(S) FOR USE
Treatment of HIV Infection

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
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)


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) **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
Robert S. Watson	**Robert S. Watson** **Director, Regulatory Affairs**	**April 13, 1999**

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
Five Moore Drive **Research Triangle Park, NC 27709**	**(919) 483-6972**

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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

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

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)

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Five Moore Drive Research Triangle Park, NC 27709	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-039

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Amprenavir Oral Solution	Agenerase™ (Amprenavir) Oral Solution

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME (If any)
(3S)-tetrahydro-3-furyl N-((1S, 2R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl) carbamate	141W94

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	15mg/ml	oral

(PROPOSED) INDICATION(S) FOR USE
Treatment of HIV Infection

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
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

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Robert S Watson	**Robert S. Watson** **Director, Regulatory Affairs**	**April 13, 1999**

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
Five Moore Drive **Research Triangle Park, NC 27709**	**(919) 483-6972**

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Paperwork Reduction Project (0910-0338)
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GlaxoWellcome

DESK COPY

February 18, 1999

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 21-007; AGENERASE™ Capsules (amprenavir capsules)
General Correspondence; Traditional Approval

Dear Dr. Jolson:

Reference is made to NDA 21-007 for Agenerase (amprenavir) capsules for the treatment of HIV infection submitted on October 15, 1998. Reference is also made to subsequent communications with the Division of Antiviral Drug Products regarding this application, specifically, reports from the two pivotal studies containing 24 week data submitted on October 28, 1998. This NDA is under review for accelerated approval in accordance with the regulations in 21 CFR 314, Subpart H.

As agreed at the April 27, 1998, preNDA meeting, results from clinical trials assessing the durability of antiviral effect of amprenavir will be used as a basis for traditional approval of Agenerase. Forty-eight week data from the two primary clinical trials used for accelerated approval will be submitted in a supplemental NDA. The two phase 3 clinical trials are PROAB3001, a prospective, double-blind, randomized, placebo-controlled trial in the treatment of naïve adult patients, and PROAB3006, a trial comparing amprenavir to indinavir in treatment experienced adult patients, both in combination with other nucleoside reverse transcriptase inhibitors.

The content and format of the supplemental NDA for traditional approval are being proposed in the draft table of contents provided in Attachment 1. The analysis plans for both clinical trials are also provided (Attachment 2). The proposed analyses are based on discussion of this subject with the FDA statisticians during the December 22, 1998, teleconference.

APPEARS THIS WAY
ON ORIGINAL

Glaxo Wellcome Research and Development
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

A Division of
Glaxo Wellcome Inc.

We would very much appreciate receiving comments on our proposals. We would be happy to discuss this via teleconference if you would like. This submission is provided in duplicate with four additional desk copies being provided directly to Ms. Melissa Truffa. If there are any questions, please contact me at 919-483-6972. Thank you.

Sincerely,

Robert S. Watson
Product Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages

Number of Pages Redacted 55

❖❖❖

Draft Labeling
(not releasable

TIME SENSITIVE PATENT INFORMATION

pursuant to 21 C.F.R. § 314.53
for

AGENERASE™ (amprenavir) Oral Solution
NDA 21-039

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	Agenerase™
Active Ingredient(s):	amprenavir
Strength(s):	15 mg/mL
Dosage Form:	Oral Solution

Applicable Patent Numbers and Expiration Dates:

Patent No.	5,585,397
Expires:	December 17, 2013
Owner:	Vertex Pharmaceuticals Inc. Licensed to Glaxo Wellcome Inc.
Type:	Drug Substance Drug Product Composition Formulation

Patent No.	5,723,490
Expires:	March 3, 2015
Owner:	Vertex Pharmaceuticals Inc. Licensed to Glaxo Wellcome Inc.
Type:	Method of Use

Patent No.	5,646,180
Expires:	July 8, 2014
Owner:	Vertex Pharmaceuticals Inc. Licensed to Glaxo Wellcome Inc.
Type:	Method of Use

The undersigned declares that U.S. Patent 5,585,397 covers the composition, formulation and/or method of use of AGENERASE™ (amprenavir) Oral Solution. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

The undersigned declares that U.S. Patent 5,723,490 covers the composition, formulation and/or method of use of AGENERASE™ (amprenavir) Oral Solution. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

The undersigned declares that U.S. Patent 5,646,180 covers the composition, formulation and/or method of use of AGENERASE™ (amprenavir) Oral Solution. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Please address all communications to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Intellectual Property Department
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709
(919)483-2723

Respectfully submitted,

April 26, 1999
Date

Karen L. Prus, Ph.D.
Registered Patent Attorney
Glaxo Wellcome Inc.

Exclusivity Summary Form

EXCLUSIVITY SUMMARY FOR NDA # 21-039

Trade Name: Agenerase™ Oral Solution 15mg/mL **Generic Name:** amprenavir

Applicant Name: Glaxo Wellcome Inc. **HFD #** 530

Approval Date If Known: _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /__/

b) Is it an effectiveness supplement?

YES /__/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES / X / NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /__/ NO /X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES /___/ NO / X /

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing

the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /__/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available

data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a

previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency,

or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature: /S/ *Date:* 3/22/99
Title: Regulatory Project Manager

Signature of Office/Division Director
Signature: /S/ *Date:* 4/6/99

cc: Original NDA Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

Market Exclusivity Under the Federal Food, Drug, and Cosmetic Act

Under sections 505(c)(3)(D)(ii) and 505(j)(4)(D)(ii), Glaxo Wellcome Inc. requests a determination of 5 years of exclusivity from the date of approval for Agenerase™ (amprenavir) oral solution.

Glaxo Wellcome Inc. requests this determination of exclusivity because this new drug application contains the following new investigations which were conducted and sponsored by Glaxo Wellcome and which are essential to the approval of the application:

PROAB3001 A Phase III Trial to Evaluate the Safety and Antiviral Efficacy of 141W94 in Combination with RETROVIR and EPIVIR Compared to RETROVIR and EPIVIR Alone in Patients with HIV Infection

PROAB3006 A Phase III Trial to Compare the Safety and Antiviral Efficacy of 141W94 and Indinavir in Combination with Standard Nucleoside Reverse Transcriptase Inhibitor (NRTI) Therapy in NRTI Experienced, Protease Inhibitor Naïve HIV-1 Infected Patients

PROB2004 A Phase II Trial to Assess the Preliminary Antiviral Effect, Pharmacokinetics, Safety and Tolerability of Multiple Oral Doses of 141W94 Liquid Formulation in Combination with NRTIs in HIV Infected Children Below 13 Years Old

PROAB3004 A Phase III Open Label Trial to Evaluate the Safety, Antiviral Efficacy and Pharmacokinetics of 141W94 Plus Current Therapy HIV-Infected Children

These clinical investigations are "new" in that they have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of any such investigations.

Reference is made to NDA 21-007 Agenerase (amprenavir) Capsules.

Extended Market Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Submission of Reports of Clinical Studies of Amprenavir in Pediatric Patients

Glaxo Wellcome Inc. requests a determination that marketing submissions and approvals under subsections (b) (2) or (j) of Section 505 of the Federal Food, Drug, and Cosmetic Act (the "FFDCA"), for any product containing amprenavir, will be fully subject to the market exclusivity extension provisions of new Section 505A of the FFDCA (as added by Section 111 of the Food and Drug Administration Modernization Act of 1997). This request is made on the basis of Glaxo Wellcome Inc.'s submission of reports of clinical studies of amprenavir in pediatric patients, as described in the PROPOSED PEDIATRIC STUDY REQUEST submitted to [redacted] on August 18, 1998.

A copy of the request is attached.

Although the proposed "Written Request" pertaining to amprenavir has yet to be issued, Glaxo Wellcome Inc. is proceeding in good faith with the submission of NDA 21-039 (amprenavir oral solution), as we did with NDA 21-007 (amprenavir capsules), on the assumption that delayed submission would not well serve the interests of either the adult or pediatric patient populations who may benefit from therapy with the new drug. Prior communications with the Reviewing Division have given us confidence that amprenavir is considered an appropriate candidate for extended exclusivity, in light of our program of pediatric development, and that we can expect a Written Request before approval of NDA 21-007, pursuant to subsection 505A(a) of the FFDCA. The anticipated Written Request is expected to call for and can precede the submission of significant pediatric data not being submitted at this time, *viz.*, presently unavailable 48-week data from Protocols PROB2004 and PROAB3004, both open label trials of amprenavir in combination with other antiviral products in HIV-infected children. In any event, Glaxo Wellcome Inc.'s decision not to delay submission of NDAs 21-007 and 21-039 pending receipt of a Written Request should not prejudice our ability to qualify for extended exclusivity under Section 505A. Such an adverse outcome is certainly not mandated by the statute, would in fact contravene congressional intent, and would be unfair and inappropriate from a policy standpoint.

Exclusivity Summary Form

EXCLUSIVITY SUMMARY FOR NDA # 21-007

Trade Name: Agenerase™ 50mg & 150mg Capsules Generic Name: amprenavir

Applicant Name: Glaxo Wellcome Inc. HFD # 530

Approval Date If Known: _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /__/

b) Is it an effectiveness supplement?

YES /__/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/27/97
cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES / X / NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /__/ NO / X /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES /___/ NO / X /

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing

the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available

data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a

previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency,