CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-183

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA 21-183
Date Submitted: 1/17/2000
Date Approved: 10/31/2000

Group Leader's Memorandum
NDA 21-183
VIDEX EC for the treatment of adults with HIV

This Group Leader's Memorandum is written in support of the approval of NDA 21-183 for VIDEX EC, an enteric coated formulation of an already marketed nucleoside reverse transcriptase inhibitor for the treatment of adults with HIV. This decision is supported by the safety, efficacy, and clinical pharmacology data contained in the NDA, as reviewed by Russell Fleischer, P.A., M.P.H., Robert Kumi, Ph.D and Greg Soon, Ph.D.

The following issues were addressed in the review of NDA 21-183 for once daily dosing of VIDEX EC in the treatment of HIV-infected adults:

1. **Elimination of significant drug interactions**

   With the enteric coated formulation, VIDEX EC, can now be administered concomitantly with the following three drugs commonly used by HIV-infected subjects: indinavir, a protease inhibitor, ketoconazole, an anti-fungal agent, and ciprofloxacin, an antibiotic. This will greatly enhance treatment options for patients.

2. **Lack of bioequivalence between VIDEX EC and VIDEX, as didanosine buffered tablet**

   VIDEX, as didanosine buffered tablet, was approved in 1991. Recent studies were performed to assess the pharmacokinetics of both formulations to determine bioequivalence. In both healthy and HIV-infected populations, results of bioequivalance testing showed that although AUC's for both products were comparable, the Cmax of VIDEX EC was about 40% lower than the buffered tablets and didanosine Tmax was prolonged for the EC formulation. Clinical trials, 152 and 158 were implemented to ensure that the two preparations, VIDEX EC and the marketed tablets produced clinically similar results.

3. **Once-daily dosing of VIDEX and Clinical Implications**

   Once-daily dosing of didanosine, as the buffered formulation, VIDEX, was studied in trial 148 where VIDEX, as part of a regimen containing stavudine and nelfinivir was compared to zidovudine, lamivudine and nelfinivir. Twenty-four week outcomes, based on the proportion of patients with HIV RNA levels less than the limit of

APPEARS THIS WAY
ON ORIGINAL

quantification of the viral load assay were comparable between regimens. Based on this 24-week data, VIDEX was labeled for once-daily dosing. However, when the results from the 48-week continuation phase of the trial were submitted for review, they showed that once-daily dosing with VIDEX was inferior to the comparator arm. Per Dr. Kumi's review, the inferiority of the once-daily dosing of VIDEX at 48 weeks could possibly be explained by the short plasma half-life of didanosine which could lead to the presence of low plasma concentrations of didanosine for a significant portion of the day, when dosed once daily.

Based on study 148, the VIDEX labeling was revised to include wording that once-daily dosing of VIDEX should be limited to those patients whose management was dependent upon once daily dosing because, although the once-daily dosing regimen was inferior to the comparator at 48 weeks, it was determined that didanosine was contributing to the antiviral activity of the regimen (For purposes of an historical comparison, only 11% of patients receiving stavudine and nelfinivir, in combination, achieved HIV RNA < 400 c/ml, as compared to a rate of 50% in study 148 when didanosine was added to stavudine and nelfinivir.)

Approval of once-daily dosing of VIDEX EC

The applicant only studied VIDEX EC as a once-daily dosing option, in an attempt to reduce the pill burden for patients and to parallel study 148, prior to knowing the final results of the 48-week data. Once-daily VIDEX EC, as part of an antiretroviral regimen containing stavudine and nelfinivir was compared to zidovudine , lamivudine, and nelfinivir in study 152. In this ongoing study, results from two-thirds of the patients revealed that both regimens produced similar antiretroviral results with 52% of patients receiving VIDEX EC reaching the primary endpoint, i.e., a viral load < 400 copies/ml compared to 57% of patients in the comparator arm.

The applicant also studied VIDEX EC in study 158 where two formulations of didanosine were directly compared. Due to the high dropout rate, the results of this study cannot be interpreted.

Conclusion

The applicant has submitted adequate data to support the approval of once-daily dosing of a new formulation of didanosine, VIDEX EC. Approval of this formulation would allow access to a new and improved formulation without the complication of significant drug interactions. Specifically, VIDEX EC can be given with indinavir, ketoconazole and ciprofloxacin. Once-daily dosing with VIDEX EC would also help to increase adherence to an antiretroviral drug regimen by limiting the pill burden; patient tolerability should also be improved, given that buffers have been removed. Although safety and efficacy of once-daily dosing of VIDEX EC were demonstrated in studies 148 and 152,

APPEARS THIS WAY
ON ORIGINAL

VIDEX EC should be studied as a bid regimen in an attempt to improve upon the results from the current studies. The applicant has agreed to this phase 4 commitment.

Debra Birnkrant, M.D.
Deputy Director, DAVDP

Cc: HFD-530/Division Director/HJolson

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-183 /SE____ - _____

Drug VIDEX EC Applicant Bristol-Myers Squibb

RPM Destry Sillivan Phone (301) 827-2335

☒505(b)(1)
☐505(b)(2) Reference listed drug _____

☐Fast Track ☐Rolling Review Review priority: ☐ S ☒P

Pivotal IND(s) [ ] _____

Application classifications:
Chem Class _____
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary Oct 31, 2000
Secondary _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☒ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☒AP ☐ AE ☐NA

- Labeling & Labels
  FDA revised labeling and reviews..... Included
  Original proposed labeling (package insert, patient package insert) ..... Included
  Other labeling in class (most recent 3) or class labeling..... Included 2 most recent
  Has DDMAC reviewed the labeling? ..... ☒ Yes (include review) ☐ No
  Immediate container and carton labels ..... _____
  Nomenclature review ..... _____

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☐ is not on the AIP.
  Exception for review (Center Director's memo)..... _____
  OC Clearance for approval..... _____

APPEARS THIS WAY
ON ORIGINAL

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☒ Materials requested in AP letter

- Post-marketing Commitments
  - Agency request for Phase 4 Commitments..... In AP letter
  - Copy of Applicant's commitments ..... In Ap letter

- Was Press Office notified of action (for approval action only)?..... ☒ Yes ☐ No
  - Copy of Press Release or Talk Paper.....

- Patent
  - Information [505(b)(1)] .....
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....

- Exclusivity Summary ..... Included

- Debarment Statement ..... Included

- Financial Disclosure
  - No disclosable information .....
  - Disclosable information – indicate where review is located .....

- Correspondence/Memoranda/Faxes ..... Included

- Minutes of Meetings ..... Included
  - Date of EOP2 Meeting N/A
  - Date of pre NDA Meeting
  - Date of pre-AP Safety Conference

- Advisory Committee Meeting ..... N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....

- Federal Register Notices, DESI documents .....

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X

- Clinical review(s) and memoranda X

APPEARS THIS WAY
ON ORIGINAL

Continued ⇨

- Safety Update review(s) ..... N/A

- Pediatric Information
  ☑ Waiver/partial waiver (Indicate location of rationale for waiver) ☒ Deferred
  Pediatric Page..... Included in AP letter
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable Med. Review

- Statistical review(s) and memoranda X

- Biopharmaceutical review(s) and memoranda..... X

- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling .....

- Microbiology (efficacy) review(s) and memoranda X

- DSI Audits ..... N/A
  ☐Clinical studies ☐ bioequivalence studies .....

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda X

- Statistics review(s) and memoranda regarding dissolution and/or stability X

- DMF review(s) .....

- Environmental Assessment review/FONSI/Categorical exemption ..... N/A

- Micro (validation of sterilization) review(s) and memoranda X

- Facilities Inspection (include EES report)
  Date completed _____ ..... ☒ Acceptable ☐ Not Acceptable

- Methods Validation ..... ☒ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda X

- Memo from DSI regarding GLP inspection (if any) ..... N/A

APPEARS THIS WAY
ON ORIGINAL

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... _____
- CAC/ECAC report X

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

APPLICANT'S NAME AND ADDRESS

Randall D. Curtiss
Bristol-Myers Squibb Company
P.O. Box 5400
Princeton, NJ 08543

3. PRODUCT NAME
VIDEX® EC (didanosine) Capsules

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

- [X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
- [ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

*** Third Submission of a Rolling NDA. User Fee Included with First Submission of Rolling NDA Submitted 9/29/99**

2. TELEPHONE NUMBER *(Include Area Code)*
(609) 818-5220

5. USER FEE I.D. NUMBER
3802

6. LICENSE NUMBER / NDA NUMBER
NDA 21-183

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- [ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*
- [ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*
- [ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*
- [ ] THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*
- [ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

- [ ] WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
- [ ] A CRUDE ALLERGENIC EXTRACT PRODUCT
- [ ] AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY
- [ ] AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
- [ ] BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [ ] NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Cynthia F. Piccillo	Associate Director Regulatory Science	January 31, 2000

FORM FDA 3397 (5/98)

APPEARS THIS WAY ON ORIGINAL

Created by Electronic Document Services/USDHHS (301) 443-3454 EF

CERTIFICATION: DEBARRED PERSONS

Bristol-Myers Squibb Company certifies that it has not used and will not use the services of any person listed as debarred as of the September 28, 1998 Debarment List under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 355 (a) or (b)] in any capacity in connection with this Application for VIDEX® EC (didanosine) Capsules.

Cynthia J. Piccirillo — 1/26/00

Cynthia Piccirillo
Associate Director, Regulatory Science
Bristol-Myers Squibb Company
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-1996
(203) 677-7625

Date

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

BEST POSSIBLE COPY

PATENT INFORMATION

1)	Patent No./Expiration:	U.S. Patent 4,861,759; expires August 29, 2006
	Type of Patent:	Method of use
	Patent Owner:	United States of America represented by Department of Human Services
2)	Patent No./Expiration:	U.S. Patent 5,254,539; expires August 29, 2006
	Type of Patent:	Method of use
	Patent Owner:	United States of America represented by Department of Human Services
3)	Patent No./Expiration:	U.S. Patent 5,616,566; expires August 29, 2006
	Type of Patent:	Method of use
	Patent Owner:	United States of America represented by Department of Human Services

Bristol-Myers Squibb Company is the exclusive licensee of U.S. Patents 4,861,759, 5,254,539 and 5,616,566 by virtue of an agreement with NTIS dated February 1, 1988.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

DECLARATION

The undersigned declares that U.S. Patents 4,861,759; 5,254,539; and 5,616,566 cover the use of 2',3'-dideoxyinosine (ddI) which is the subject of the present Supplemental New Drug Application.

Signature of Authorized Person

Samuel J. DuBoff
Name of Authorized Person

Patent Counsel - International
Title of Authorized Person

8/26/95
Date

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

EXCLUSIVITY SUMMARY for NDA # 21-183 **SUPPL #** _____

Trade Name VIDEX EC **Generic Name** didanosine

Applicant Name Bristol-Myers Squibb **HFD-** 530

Approval Date _____

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 questions 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:

      _____

      _____

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

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?

Three

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 9.

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 9.

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 9 (even if a study was required for the upgrade).

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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 /X/ NO /___/

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

NDA # 20-154 VIDEX (didanosine) Chewable/Dispersible Tablets

NDA # 20-155 VIDEX (didanosine) Buffered Powder for Oral Soln.

NDA # 20-156 VIDEX (didanosine) Pediatric Powder for Oral Soln.

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/

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /_X_/ 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 9:**

_____

_____

(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 /_X_/ 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 /_X_/

If yes, explain: _____

_____

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

(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:

Investigation #1, Study # AIA54-152

Investigation #2, Study # AIA54-158

Investigation #3, Study # _____

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 /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 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:

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #1, Study # AI454-152

Investigation #2, Study # AI454-158

Investigation #__, Study # _____

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.

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

(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 /X/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # ——— YES /X/	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 _____
_____	_____
_____	_____

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

(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 /X/

If yes, explain: _____

/S/ 10/27/00

Signature of Preparer Date
Title: Regulatory Project Manager

/S/ 10/29/00

Signature of Office of Division Director Date

CC:
Archival NDA
HFD-530 /Division File
HFD-530 /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

APPEARS THIS WAY
ON ORIGINAL

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

BEST POSSIBLE COPY

VIDEX® EC Capsules: Request for Exclusivity-

In accordance with 21 CFR 314.50 (j), Bristol-Myers Squibb Company ("the Applicant") believes the clinical investigations contained in this NDA are "essential for approval" of a change in the formulation to an encapsulated enteric-coated beadlets formulation as required by the US FDA. The Applicant certifies that the studies were conducted and sponsored by BMS, under IND ——— didanosine (BMY-40900, ddI) and meets the definition of a "new clinical investigation" set forth in section 314.108(a).

Further to the requirements of 21 CFR 314.50 (j), attached is a literature search of clinical studies investigating the use of VIDEX® EC Capsules to certify the information publicly available do not provide a sufficient basis for the approval of this NDA. The Applicant certifies that there have not been any clinical studies to date which demonstrate the endpoints of the registrational studies, AI454-152 and AI454-158, and are required by the Agency for this NDA.

Therefore, under the provisions of 21 CFR 314.108 (b)(4), the Applicant hereby claims three (3) years marketing exclusivity for VIDEX® EC Capsules upon approval of this New Drug Application, during which time no person may submit a 505 (b)(2) application or abbreviated new drug application under Section 505 (j) of the Act for a drug containing the same active moiety.

Cynthia F. Piccirillo

Cynthia F. Piccirillo
Associate Director
Regulatory Science
Bristol-Myers Squibb Company

1/26/00
Date

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

FDA Links Tracking Links Check Lists Searches Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

NDA Number:	021183	**Trade Name:**	VIDEX EC(DIDANOSINE)125/200/250/400MG EC
Supplement Number:	000	**Generic Name:**	DIDANOSINE
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	AP	**COMIS Indication:**	TREATMENT OF ADULT PATIENTS WITH HIV
Action Date:	~~11/14/00~~ 10/31/00		

Indication # 1 This new drug application provides for the use of VIDEX EC (didanosine) Delayed-Release Capsules, in combination with other antiretroviral agents, for the treatment of HIV infection in adults whose management requires once-daily administration of didanosine or an alternative didanosine formulation.

Label Adequacy: Other - See Comments

Forumulation Needed: NEW FORMULATION developed with this submission

Comments (if any): The safety and efficacy of VIDEX EC in pediatric patients have not been established.

Lower Range	Upper Range	Status	Date
6 years	18 years	Deferred	9/30/02

Comments: We are waiving the requirement for studies in children less than six years of age, and we are deferring submission of your pediatric studies for children older than six years of age until September 30, 2002.

This page was last edited on 11/21/00

Signature [signature]

11/21/00
Date

APPEARS THIS WAY
ON ORIGINAL

HFD-530

/S/

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 19, 1999

To: Cynthia Piccirillo
Associate Director, Regulatory Affairs

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Destry M. Sillivan, M.S., Regulatory Management Officer, HFD-530

Through: Russell Fleischer, PA-C, M.P.H., Medical Officer, HFD-530 1/24/00
Greg Soon, Ph.D., Statistical Reviewer, HFD-530 11/27/00
Girish Aras, Ph.D., Statistical Team Leader, HFD-530 1/24/00
Therese Cvetkovich, M.D., Medical Team Leader, HFD-530 1/24/00

Subject: The September 29, 1999 proposal for submission of clinical and statistical technical sections of NDA 21-183 for VIDEX® (EC) Beadlet Capsules.

The following requests/comments are made on behalf of Russell Fleischer, and Dr. Greg Soon:

Clinical:

1) Your proposal to submit NDA 21-183 for VIDEX EC Capsules as a rolling NDA is acceptable. As you have correctly noted, the review period will commence with the submission of the Clinical and Statistical Sections of the NDA.

2) Your proposal ——— It would be acceptable for you to submit the 24-week analysis of study 158 in May 2000, as previously agreed to. For study 152, DAVDP would expect you to submit a safety update, as well as any additional efficacy data on any additional patients who had completed 24 weeks of treatment, at the same time that the 24-week analysis of study 158 is submitted.

3) We acknowledge that once-daily dosing of ddI is an approved option.

4) We agree to waive the pre-clinical data requirements for the EC formulation NDA.

APPEARS THIS WAY ON ORIGINAL

5) Your plan to request a deferral for pediatric studies using the EC formulation is generally acceptable. However, we expect you to provide us with your pediatric development plans for the EC formulation as part of the deferral request.

Statistical:

6) Analyses based on all-randomized subjects will be considered primary and the as-treated analyses will be considered supportive. In the analysis of the proportion below the detection limit, subjects who never initiated study drug should be regarded as above the detection limit. Analysis of TAD using all available data to the time of interest should also be provided.

7) The analyses should be stratified by the factors restricting the randomization, including the investigator site. If an adaptive randomization procedure was used in assigning subjects, then re-randomization based test and confidence intervals should be used for the primary endpoints.

8) DAVDP prefers that the confidence intervals be generated in a way consistent with the testing statistics used. In addition to the confidence intervals based on normal approximations for the mean and median and the confidence interval based on the repeated measures model, it is recommended that the confidence interval for TAD be generated using an inversion of the stratified Wilcoxon test.

9) It is not clear how subjects who withdraw or who are lost to follow-up are handled in the calculation of TAD. Sensitivity analyses should be conducted to investigate the impact of various ways of analyzing these missing data.

10) A time to relapse analysis should be provided for Week 24 and 48 using all available data. Kaplan-Meier curve should be plotted and compared. The following algorithm is recommended for this analysis:

   a) Subjects who were randomized but failed to take any medication are assigned relapse time 0.

   b) Subjects who never achieved [redacted] while on the randomized treatment are assigned relapse time 0.

   c) For subjects who had a confirmed CDC Class C event but did not achieve [redacted] below [redacted] before the CDC event, the relapse time is 0

   d) For subjects who achieved [redacted] below [redacted] while on the randomized treatment without prior confirmed CDC Class C event:

   e) Regarding all visits at or after a confirmed CDC Class C event or death as [redacted]

      i) Regarding all visits at or after discontinuation of the randomized therapy as [redacted]

APPEARS THIS WAY
ON ORIGINAL

ii) Disregard all other missing values.

iii) When two consecutive viral loads are [redacted] after achieving [redacted], relapse is considered to have occurred (no confirmation needed if the last scheduled visit is the first time the viral load is above [redacted]). The relapse time is the average of the time of first [redacted] and the visit prior to this relapse.

11) In view of the increased importance of the ultrasensitive assay, it is recommended that measurements for HIV RNA levels using the ultrasensitive assay be obtained for all the samples, not just for those with the [redacted] results below [redacted] At a minimum, the ultrasensitive assay should be conducted on samples obtained at weeks 24 and 48.

12) The equivalence deltas of 12% for the proportions below [redacted] and $0.5\log_{10}$ for the TAD are for the sample size calculations only. The deltas used for regulatory review may be different.

13) For Study 152, the week 24 interim analysis will be used for making the regulatory decision.

14) In Study 152 a single combined drug (Combivir) is substituted with two drugs (ddI+d4T). Please note that it will be difficult to characterize the contribution of ddI to the treatment regimen, given this study design.

15) For Study 158, proportion below [redacted] will be regarded as the primary endpoint for week 24 analysis.

16) TAD will be regarded as secondary. Please modify your proposed electronic data submission, dated January 17, 2000 to reflect the comments above.

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/

Destry M. Sillivan, MS
Regulatory Management Officer
Division of Antiviral Drug Products

APPEARS THIS WAY
ON ORIGINAL

Concurrence:
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/SR/Soon
HFD-530/STL/Aras
HFD-530/RPM/Sillivan

cc:
Original NDA 21-183
Division File NDA 21-183
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/SR/Soon
HFD-530/STL/Aras
HFD-530/RPM/Sillivan

NDA 21-183

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

RECORD OF INDUSTRY MEETING

Meeting Date: September 15, 1999 **Time:** 1:30 p.m.

IND: [redacted]

Drug: [redacted]

Indication: Treatment of HIV-1

Sponsor: Bristol-Myers Squibb Company

Type of Meeting: Biopharmaceutics: Senior FDA staff/Senior BMS Staff

FDA Participants:
Murray Lumpkin, M.D., Deputy Center Director, Office of Review Management
Robert Temple, M.D., Director, Office of Drug Evaluation I
Rodger Williams, M.D., Deputy Center Director, Office of Pharmaceutical Science
Heidi Jolsen, M.D., Director, DAVDP
Debra Birnkrant, M.D., Deputy Director, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP
Russell Fleischer, PA-C, M.P.H., Medical Officer, DAVDP
Steve Miller, Ph.D., Chemistry Team Leader, DAVDP
John Lazor, Pharm.D., Director, Division of Pharmaceutical Evaluation III
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, DAVDP
Robert Kumi, Ph.D., Clinical Pharmacology Reviewer, DAVDP
Destry Sillivan, M.S., Regulatory Project Manager, DAVDP
Melissa Truffa, R.Ph., Regulatory Project Manager, DAVDP

External Constituents:
Laurie Smaldone, M.D., Sr. Vice President, Worldwide Regulatory Affairs
Anthony Santopolo, M.D., Vice President, Worldwide Regulatory Affairs
Roger Echols, M.D., Vice President, Infectious Diseases Clinical Research
Rashmi Barbhaiya, Ph.D., Vice President, Metabolism and Pharmacokinetics
Catherine Knupp, D.V.M., M.S., Director, Metabolism and Pharmacokinetics
[redacted]
Sherry Konrad, Regulatory Manager

Background:

Bristol-Myers Squibb (BMS) requested a meeting to discuss the submission of an application for a new enteric-coated beadlet capsule (EC) formulation of VIDEX . BMS's position is that because the Area Under the Curve (AUC) of the EC formulation is equivalent to the AUC of the currently approved formulation, approval of the EC formulation should be allowed under FDAMA 1997

APPEARS THIS WAY
ON ORIGINAL

(November 1997), the "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" II.C.1 (May 1998), and 21 CFR 312.23(b). However, since the Cmax of the two formulations are not equivalent, DAVDP has requested on multiple occasions that BMS demonstrate that the difference in Cmax does not adversely effect safety or efficacy of the EC formulation. DAVDP has requested that this be demonstrated through the conduct of a clinical study.

Discussion Points:
BMS:

VIDEX EC approval should be on the basis of pharmacokinetic data alone for the following reasons:

1. The AUC's of VIDEX EC and the currently approved formulation are equivalent.

2. Although Cmax is not equivalent, AUC is the relevant pharmacokinetic parameter for assessing equivalence between VIDEX EC and the currently approved formulation.

3. There is a great medical need for VIDEX EC because of its assumed improved tolerability and elimination of the need for a buffer in the formulation, which may eliminate many drug-drug interactions.

BMS conclusions:

1. The safety and efficacy of EC is assured by pharmacokinetic data and clinical data from trials that used the reduced mass tablet formulation.

2. The medical need for EC warrants its approval

3. Agreement by the Agency would allow filing of the new NDA by late September 1999.

Discussion:

BMS:

1. The rate of absorption does not appear to be critical in determining the activity of nucleoside reverse transcriptase inhibitors (NRTIs). Thus, the reduced Cmax does not impact HIV-1 viral load suppression after treatment with VIDEX EC.

2. The studies currently enrolled are underpowered to address the Agency's concerns regarding the impact of a reduced Cmax on efficacy when VIDEX EC is compared with the approved formulation.

3. The requirement that BMS provide clinical data to create a link between the two parameters (Cmax and AUC) would unacceptably delay the filing of this NDA. Additionally, BMS believes that it would be unethical to conduct large, fully powered trials necessary to satisfy the Agency's questions regarding a change in formulation.

APPEARS THIS WAY
ON ORIGINAL

4. BMS has evaluated other metrics (Cmax/AUC, partial AUCs) to evaluate the bioequivalence of the two formulations (VIDEX EC and the VIDEX reduced mass tablet); lack of equivalence was observed, as it was with Cmax.

5. BMS believes that the intracellular concentration of didanosine plays the primary role in the reduction of HIV-1 viral load, and exposure to the drug is secondary.

6. There are no clinical data on the presumed increased tolerability of VIDEX EC because attribution of the adverse events in a combination trial would not be feasible.

7. There are many literature citations that state that AUC is the most important factor in determining bioequivalence for VIDEX. There is only one which states that it is not, but it does not suggest that Cmax is the most important.

8. BMS should be allowed to pre-submit CMC and biopharmaceutic data as it becomes available prior to submitting the full NDA.

FDA:

1. BMS has not provided any data to show conclusively that the difference in Cmax would not affect clinical outcomes.

2. Filing and approval of a NDA would need to be based on the submission of clinical data. Data from the two ongoing studies (studies 152 and 158, already under enrollment) should be sufficient to satisfy the Agency's concerns regarding the safety and efficacy of the two formulations. A clinical link is necessary.

3. BMS should research methods that may allow a correlation between pharmacokinetics and efficacy.

4. The Agency's Office of Clinical Pharmacology and Biopharmaceutics would be willing to aid in the evaluation of any data that BMS may submit.

5. Pre-submission of ~~non~~-clinical data is acceptable, and may aid in the review; however, the review clock will not begin until the submission of clinical data. Sixteen weeks of clinical data will be acceptable for submission, provided we have a commitment from BMS that 24 week clinical data be submitted during the review period. Twenty-four week data will be used for labeling purposes.

Conclusions/Agreements:

1. The NDA for VIDEX EC would require supporting clinical data, and would not be filable without such data.

2. The clinical data from study 158 should be sufficient to address the Agency's concerns with respect to comparable activity, safety, and efficacy of VIDEX EC when compared with the currently approved formulation.

APPEARS THIS WAY
ON ORIGINAL

3. BMS has agreed to submit a proposal for the contents of a clinical package. DAVDP has agreed to review this proposal and respond in a timely manner.

4. Pre-submission of non-clinical data is acceptable to DAVDP. Submission of clinical data will start the review clock for the proposed NDA for VIDEX EC.

5. BMS may make an argument for a priority review for the proposed NDA for VIDEX EC.

APPEARS THIS WAY
ON ORIGINAL

Signature, minutes prepared by:_____ Date: _____

APPEARS THIS WAY
ON ORIGINAL

Concurrence:
Murray Lumpkin/Dep.Cen.Dir, Office of Review Management
Robert Temple/Dir/ODE1
HFD-530/Dir/Jolson
HFD-530/DepDir/Birnkrant
HFD-530/AssocDir/Dempsey
HFD-530/MOTL/Cvetkovich
HFD-530/MO/Fleischer
HFD-530/ChemTL/Miller
HFD-530/Chem/Lo
HFD-530/BPHTL/Reynolds, K
HFD-530/BioPharm/Kumi, R
HFD-880/Dir/Div. Pharm Eval III/Lazor
HFD-530/CPMS/Decicco
HFD-530/RPM/Sillivan

cc:
Original IND
Division File
HFD-530/Dir/Jolson
HFD-530/DepDir/Birnkrant
HFD-530/AssocDir/Dempsey
HFD-530/MOTL/Cvetkovich
HFD-530/MO/Fleischer
HFD-530/ChemTL/Miller
HFD-530/Chem/Lo
HFD-530/BPHTL/Reynolds, K
HFD-530/BioPharm/R. Kumi
HFD-530/CPMS/Decicco
HFD-530/RPM/Sillivan
HFD-530/RPM/Truffa

RECORD OF MEETING

Location:

APPEARS THIS WAY
ON ORIGINAL

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: Cynthia Piccirillo

Fax Number: (203) 677-7867

Date: January 27, 2000

Company: Bristol-Myers Squibb

No. of pages (excluding cover): 3

Message:

Comments on Clinical and Statistical sections of VIDEX EC proposal.

From: Destry Sillivan, M.S.

Telephone: (301) 827- 2335

Fax Number: (301) 827-2523

Mail:
Division of Antiviral Drug Products
5600 Fishers Lane (HFD-530)
Rockville, Maryland 20857

Courier:
Division of Antiviral Drug Products
HFD-530
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail.

HFD 530

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: June 19, 2000

JUN 10 2000

To: Cynthia Piccirillo
Associate Director, Regulatory Affairs

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Destry M. Sillivan, M.S., Regulatory Management Officer, HFD-530

Through: Robert Kumi, Clinical Pharmacology Reviewer, HFD-530
Kellie Reynolds, Clinical Pharmacology Team Leader, HFD-530 6/19/2000
Therese Cvetkovich, M.D., Medical Team Leader, HFD-530 /S/ 6/20/00

Subject: NDA 21-183 for VIDEX® [redacted]
(EC) Beadlet Capsules.

The following requests/comments are made on behalf of Dr. Robert Kumi:

1. Please indicate the information and rationale used to support approval of the 125, 200, and 250 mg strength didanosine enteric coated capsules (VIDEX® EC).

2. Please provide dissolution data for individual enteric coated capsules (n ≥ 6 capsules/batch). Dissolution data should be from two or more batches for each proposed didanosine capsule strength (125, 200, 250 and 400 mg).

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/

APPEARS THIS WAY
ON ORIGINAL

Destry M. Sillivan, MS
Regulatory Project Manager
Division of Antiviral Drug Products

Concurrence:
HFD-530/MTL/Cvetkovich /S/ 6/19/2000
HFD-530/BPhTL/Reynolds
HFD-530?BPhR/Kumi, R.
HFD-530/RPM/Sillivan

cc:
Original NDA 21-183
Division File NDA 21-183
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/BPhTL/Reynolds
HFD-530?BPhR/Kumi, R.
HFD-530/RPM/Sillivan

NDA 21-183

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

45 DAY FILING MEETING MINUTES

NDA: 21-183

DATE: March 7, 2000

DRUG: VIDEX® [redacted] EC [redacted]

SPONSOR: Bristol-Myers Squibb
Pharmaceutical Research Institute

PARTICIPANTS: Heidi Jolson, M.D., M.P.H., Division Director
Walla Dempsey, Ph.D., Associate Director
Anthony DeCicco, R.Ph., Chief, Project Management Staff
Therese Cvetkovich, M.D., Medical Team Leader
Russell Fleischer, PA-C, Clinical Reviewer
Anita Bigger, Ph.D., Pharmacology/Toxicology Reviewer
Greg Soon, Ph.D., Statistical Reviewer
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader
Robert Kumi, Ph.D., Clinical Pharmacology Reviewer
Lalji Mishra, Ph.D., Microbiology Reviewer
Stephen Miller, Ph.D., Chemistry Team Leader
Ko-Yu Lo, Ph.D., Chemistry Reviewer
Destry Sillivan, MS, Regulatory Project Manager

BACKGROUND: This NDA is being made in support of a new enteric release beadlet capsule to treat HIV-infected patients, and other revisions to relevant sections of the VIDEX® package insert. Submission date February 1, 2000.

CHEMISTRY:

- This submission is filable from the Chemistry, Manufacturing and Controls perspective.
- No stability information from the Mt. Vernon site has been submitted. A complete stability package should be available by March 15, 2000.
- An environmental assessment is not required with this submission.

PHARMACOLOGY/TOXICOLOGY:

- This submission is filable from the Pharmacology/Toxicology perspective.

APPEARS THIS WAY
ON ORIGINAL

BIOPHARMACEUTICS:

- This submission is filable from the biopharmaceutics perspective.
- Three bioequivalence studies were submitted.
- New drug interactions section of the VIDEX label, allowing for coadministration of drugs previously restricted.
- There are potential dosing issues for patients with renal impairment (regarding capsule sizes).

CLINICAL:

- This submission is filable from the clinical perspective, and will be given a "P" for priority review.
- The results from two pivotal clinical trials, AI454-152 and AI454-158 have been submitted.
  - Sixteen week data is available for all patients participating in study AI454-158
  - Sixteen week activity data is available for 230 of the 430 patients enrolled in study AI454-152, with safety data available on all patients
  - The 24 week updates are due in April.
  - Requirements of the 1998 Pediatric Rule will need to be addressed.

MICROBIOLOGY:

- This submission is filable from the Microbiology perspective.

STATISTICS:

- This submission is filable from the Statistical perspective.

DISCUSSION:

- There are no filing issues; this NDA is filable
- The six month timeline is acceptable.

APPEARS THIS WAY
ON ORIGINAL

CONCURRENCE:

HFD-530/Dir/Jolson
HFD-530/DepDir/Birnkrant
HFD-530/AscDir/Dempsey
HFD-530/C-RPM/DeCicco
HFD-530/MTL/Cvetkovich
HFD-530/MO/Fleischer
HFD-530/PTTL/Farrelly
HFD-530/PTR/Bigger
HFD-530/STL/Aras
HFD-530/BPTL/Reynolds, K
HFD-530/BPR/Kumi, R
HFD-530/MicroTL/Iacono-Connors
HFD-530/MicroR/Mishra
HFD-530/CTL/Miller
HFD-530/CR/Lo
HFD-530/RPM/Sillivan

cc:

Archival NDA 21-183
Division File NDA 21-183
HFD-530/Dir/Jolson
HFD-530/DepDir/Birnkrant
HFD-530/AscDir/Dempsey
HFD-530/C-RPM/DeCicco
HFD-530/MTL/Cvetkovich
HFD-530/MO/Fleischer
HFD-530/PTTL/Farrelly
HFD-530/PTR/Bigger
HFD-530/STL/Aras
HFD-530/BPTL/Reynolds, K.
HFD-530/BPR/Kumi, R.
HFD-530/MicroTL/Iacono-Connors
HFD-530/MicroR/Mishra
HFD-530/CTL/Miller
HFD-530/CR/Lo
HFD-530/RPM/Sillivan

45 Day Filing Meeting

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

RECORD OF INDUSTRY MEETING

Meeting Date: April 26, 2000 **Time:** 11:00 a.m.

NDA 21-183

Drug: VIDEX® ([redacted]) EC

Indication: Treatment of HIV-1

Sponsor: Bristol-Myers Squibb Company

Type of Meeting: Drug Development

FDA Participants:
Heidi Jolson, M.D., Director, DAVDP
Debra Birnkrant, M.D., Deputy Director, DAVDP
Walla Dempsey, Ph.D., Associate Director, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP
Russell Fleischer, PA-C, M.P.H., Medical Officer, DAVDP
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, DAVDP
Destry Sillivan, M.S., Regulatory Project Manager, DAVDP

External Constituents:
Roger Echols, M.D., Vice President, Infectious Diseases Clinical Research
Claude Nicaise, M.D., Vice President, Regulatory Science
Larry Bell, M.D., Vice President, Regulatory Sciences, Labeling Group
David Fink, Senior Director, Commercial Affairs
Cynthia Piccirillo, Associate Director, Regulatory Science

Background:

This meeting was requested by Bristol-Myers Squibb (BMS) to discuss the impact of the results of BMS study AI454-148 on the continued review of the VIDEX EC® application. The final report of study AI454-148 was submitted on March 21, 2000, in fulfillment of a phase 4 commitment to provide 48-week data from the study that supported approval of the once-daily VIDEX® efficacy supplement approved on October 28, 1999. The 24-week data from this study supported approval of the once-daily dosing option for ddI; however, the 48-week data demonstrated that the once daily ddI-containing regimen produced inferior long-term antiviral suppression compared to the reference regimen. BMS currently has an NDA (NDA 21-183) for a new enteric-coated formulation (VIDEX EC®) under review. The purpose of the meeting was to reach agreement between BMS and DAVDP on the impact of the results of study AI454-148 and the regulatory options for the VIDEX EC® application review.

APPEARS THIS WAY
ON ORIGINAL

Specific reference is made to the DAVDP facsimile dated April 5, 2000, which outlined our concerns regarding the contribution of once daily administration of VIDEX® to a durable antiviral response, and the ability of 24-week data to predict 48-week activity results. In this facsimile, DAVDP requested that BMS provide proposals for the VIDEX EC® NDA addressing these concerns.

For each discussion topic, the sponsor's position/question is shown in regular font, followed by the FDA's response in **bold font.**

Discussion:

BMS would like to explore, and come to agreement, on a proposal which [redacted] BMS is willing to:

- Work closely with DAVDP on scheduling the submission of additional efficacy data from the ongoing VIDEX EC® clinical trials (AI454-152 and AI454-158) so that the application can be approved by August 1, 2000.
- Work out a label agreement describing the outcome of study AI454-148 as soon as possible.
- Incorporate 48-week data from studies AI454-152 and AI454-158 as part of the final VIDEX® label as a phase 4 commitment.
- Enter into phase 4 commitments for additional studies to further define the efficacy of VIDEX EC® as part of a HAART regimen.

BMS proposes to:

1. [redacted]
2.
3.

We feel that our uncertainty concerning the ability of 24-week data to predict the durability of 48-week antiviral responses is well-founded, given the 24 and 48-week results of study AI454-148. DAVDP believes that 24-week data will not be adequate to approve the VIDEX EC® application. The completion of your ongoing clinical trials for VIDEX EC® and submission of the data may clarify the uncertainty raised by the results of study AI454-148. We would be uncomfortable with the approval of a product without adequately addressing this uncertainty.

APPEARS THIS WAY
ON ORIGINAL

A regulatory action for NDA 21-183 will need to occur on or before August 1, 2000, the PDUFA date for this application. This application is under a priority review and the review classification cannot be changed from a priority to a standard review to extend the clock. An alternative that would provide additional time for submission and review of new data would be to consider the submission of the May 2000 data package as a major amendment to the NDA. This option would allow the review clock to be extended by no more than three months, allowing for a new PDUFA date of November 1, 2000.

The ability of DAVDP to approve this application will be based on the review of additional clinical data from the two ongoing studies. Decisions about how much data will be provided, and the timing of those submissions, belong to BMS.

BMS would like to fully address the results of study AI454-148 in the label prior to August 1, 2000. Could this allow for a (positive) action to be taken?

Data from study AI454-148 raises concern about the efficacy of the once daily administration of VIDEX® as part an antiretroviral dosing regimen. The 48 week results for study AI454-148 must be fully described in the VIDEX® label. This information must be included within a relatively short period of time so that clinicians and patients have information upon which to base treatment decisions.

Hypothetically, should the data from study AI454-152 closely resemble that observed in AI454-148, what would DAVDP's expectation be at that time?

Should the results of study AI454-152 closely resemble the results of study AI-454-148. we would need to question whether VIDEX EC® should be approved. The risk would be approval of an inferior regimen. Although the advantages of the improved formulation are clear, this regimen would likely be a poor first choice, and if approved, might be more applicable for patients who require a simplified dosing schedule. Again, should the results of study AI454-152 replicate the results of study AI454-148, BMS would need to propose an acceptable niche for VIDEX EC® dosed once daily for us to make a decision regarding the approvability of the VIDEX EC® formulation. To help us better understand the role of the VIDEX EC® formulation in a potent HAART regimen, DAVDP would be interested in any available twice-daily VIDEX EC® dosing information that BMS may have or could generate.

Could the study of a twice daily dosing regimen for VIDEX EC® be incorporated into a phase 4 commitment?

A phase 4 commitment to study twice daily dosing would not help patients who need treatment in the interim. This would also not obviate the observed reduced efficacy of the VIDEX® once daily dosing regimen, and DAVDP does not believe this will be solved with a phase 4 commitment.

What course of action would DAVDP like to see BMS pursue at this time?

We are willing to consider your May 2000 submission of 24 week data as a major amendment to the VIDEX EC® NDA. BMS should understand that it is DAVDP's preference that complete 48-week data from both VIDEX EC® studies be submitted. Additionally, there are no guarantees

APPEARS THIS WAY
ON ORIGINAL

that either the amount of data available by November 1, 2000 will be sufficient, or that the information submitted will be sufficient to support approval of this application.

Would all 90 days (of the extension) need to be consumed for the review process?

We cannot answer this at the present time. This application has a number of significant issues to address.

Could any approval be based on equivalence, if such is demonstrated by study AI454-152?

This cannot be fully addressed with the data that has currently been submitted, and we do not wish to speculate. We would also like to reiterate that it is our belief that BMS has not demonstrated what we believe is proper dosing with VIDEX®.

If BMS shows that VIDEX EC® is equivalent to the currently approved tablet formulation, how would DAVDP view this?

We believe that once daily VIDEX® would be best used as a second line regimen for patients who require a once daily regimen. DAVDP believes that twice daily dosing may be a better dosing regimen for VIDEX EC®. So approval of VIDEX EC® based on equivalence to what we already view as a second line regimen would not be a comfortable position.

DAVDP encourages BMS to share the results of study AI454-148 with the AIDS community.

Signature, minutes prepared by:_____ Date: _____

APPEARS THIS WAY
ON ORIGINAL

Concurrence:
HFD-530/Dir/Jolson
HFD-530/DepDir/Birnkrant
HFD-530/AssocDir/Dempsey
HFD-530/MOTL/Cvetkovich
HFD-530/MO/Fleischer
HFD-530/BPHTL/Reynolds, K
HFD-530/RPM/Sillivan

cc:
Archival NDA 21-183
Division File NDA 21-183
Division File NDAs 20-154, 20-155, 20-156
HFD-530/Dir/Jolson
HFD-530/DepDir/Birnkrant
HFD-530/AssocDir/Dempsey
HFD-530/MOTL/Cvetkovich
HFD-530/MO/Fleischer
HFD-530/ChemTL/Miller
HFD-530/Chem/Lo
HFD-530/BPHTL/Reynolds, K
HFD-530/BioPharm/R. Kumi
HFD-530/PharmToxTL/Farrelly
HFD-530/PharmToxR/Bigger
HFD-530/MicroTL/Iacono-Connors
HFD-530/MicroR/Mishra
HFD-530/StatisticsTL/Aras
HFD-530/StatisticsR/Soon
HFD-530/CPMS/Decicco
HFD-530/RPM/Sillivan

RECORD OF MEETING

APPEARS THIS WAY
ON ORIGINAL

HFD-530

/S/

NDA 21-183

MAY 23 2000

Bristol-Myers Squibb Company
Attention: Cynthia F. Piccirillo
Associate Director, Worldwide Regulatory Affairs
5 Research Parkway
Wallingford, CT 06492

Dear Ms. Piccirillo:

Please refer to the meeting between representatives of your firm and the FDA on April 26, 2000. The purpose of the meeting was to discuss the impact of the results of BMS study AI454-148 on the continued review of the VIDEX EC® application.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, Destry M. Sillivan, M.S., Regulatory Project Manager, at (301) 827-2335.

Sincerely.

/S/

Anthony W. DeCreco
Supervisory Consumer Safety Officer
Division of Antiviral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evalution and Research

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Concurrence:
HFD-530/CPMS/DeCicco
HFD-530/RPM/Sillivan

CC:

Archival NDA 21-183

HFD-530/division file/NDA 21-183
HFD-530/Dir/Jolson
HFD-530/Cvetkovich
HFD-530/Fleischer
HFD-530/CPMS/DeCicco
HFD-530/RPM/Sillivan

GENERAL CORRESPONDENCE (Minutes Sent)

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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: Cynthia Piccirillo

Fax Number: (203) 677-7867

Date: June 20, 2000

Company: Bristol-Myers Squibb

No. of pages (excluding cover): 1

Message:

Clinical Pharmacology Comments/Requests for NDA 21-183, Videx EC.

From: Destry Sillivan, M.S.

Telephone: (301) 827- 2335

Fax Number: (301) 827-2523

Mail:
Division of Antiviral Drug Products
5600 Fishers Lane (HFD-530)
Rockville, Maryland 20857

Courier:
Division of Antiviral Drug Products
HFD-530
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail.

APPEARS THIS WAY
ON ORIGINAL

HFD-530/

/S/

NDA 21-183

JUN 16 2000

Bristol-Myers Squibb Company
Attention: Cynthia F. Piccirillo
Associate Director, Worldwide Regulatory Affairs
5 Research Parkway
Wallingford, CT 06492

Dear Ms. Piccirillo:

Please refer to your January 31, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIDEX® EC (didanosine) Capsules in 125 mg, 200 mg, 250 mg, and 400 mg strengths.

On May 25, 2000, we received your May 24, 2000, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended secondary user fee goal date is October 31, 2000.

If you have any questions, please contact Destry M. Sillivan, M.S., Regulatory Project Manager at (301) 827-2335.

Sincerely yours,

/S/

Anthony W. DeCicco
Supervisory Consumer Safety Officer
Division of Antiviral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evalution and Research

APPEARS THIS WAY
ON ORIGINAL

Concurrence:
HFD-530/RPM/Sillivan

cc:
Original NDA 21-183
Division File NDA 21-183
HFD-530/SCSO/DeCicco
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/RPM/Sillivan

ACKNOWLEDGEMENT LETTER

NDA 21-183

GC

User Fee Goal Date Extension

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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: August 10, 2000

To: Cynthia Piccirillo
Associate Director, Regulatory Affairs

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Destry M. Sillivan, M.S., Regulatory Project Manager, HFD-530 /S/ 8/11/00

Through: Russell Fleischer, PA-C, M.P.H., Medical Officer, HFD-530 For
Debra Birnkrant, M.D., Deputy Division Director, HFD-530

Subject: IND —— for VIDEX® —— (EC) —— Please reference serial number 874.

The following requests/comments are made on behalf of Mr. Russell Fleischer:

We note in the protocol for study AI454-165 you describe the results of a study that demonstrated a 60% reduction in Cmax and 64% reduction in AUC when ddI was co-administered to patients receiving methadone. This appears to be a clinically significant interaction that raises important safety concerns. Therefore, please submit the following:

1. The data from the ddI-methadone interaction study (reference #9).

2. Proposed language for incorporating this information in the current VIDEX® label.

3. A time frame for revising the VIDEX® label.

Please reply to these requests by September 1, 2000.

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

APPEARS THIS WAY
ON ORIGINAL

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/

Destry M. Sullivan, MS
Regulatory Project Manager
Division of Antiviral Drug Products

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Concurrence:
HFD-530/MO/Fleischerr /S/ 8/11/00
HFD-530/DepDir/Birnkrant
HFD-530/RPM/Sillivan

cc:
Original
Division File
Original NDA 21-183
Division File NDA 21-183
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/DepDir/Birnkrant
HFD-530/RPM/Sillivan

NDA 21-183
IND

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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: Cynthia Piccirillo

Fax Number: (203) 677-7867

Date: August 29, 2000

Company: Bristol-Myers Squibb

No. of pages (excluding cover): 1

Message:

Clinical Pharmacology comments for NDA 21-183/ IND —— SN 874

From: **Destry Sillivan, M.S.**

Telephone: (301) 827- 2335

Fax Number: (301) 327-2523

Mail:
Division of Antiviral Drug Products
5600 Fishers Lane (HFD-530)
Rockville, Maryland 20857

Courier:
Division of Antiviral Drug Products
HFD-530
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail.

APPEARS THIS WAY
ON ORIGINAL

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: August 23, 2000

To: Cynthia Piccirillo
Associate Director, Regulatory Affairs

FILE COPY

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Destry M. Sillivan, M.S., Regulatory Project Manager, HFD-530

Through: Russell Fleischer, PA-C, M.P.H., Medical Officer, HFD-530
Greg Soon, Ph.D., Statistical Team Leader (Acting), HFD-530
Stanka Kukich, M.D., Medical Team Leader, HFD-530

Subject: NDA 21-183 for VIDEX® [redacted] (EC) [redacted]

The following requests/comments are made on behalf of Dr. Greg Soon:

Please conduct the analyses for the two studies in NDA 21-183 as requested below, using LOQ= [redacted]nd then LOQ= [redacted] Reference is made to the algorithm for time to virologic failure sent earlier to you during the review of study AI454-148 for NDA 20154 (SE8).

For study AI454-158, the requested analyses are identical to those requested for study AI454-158, except that item 5 is modified and item 7 is removed.

1. Calculate the time to virologic failure based on the new algorithm and plot the survival curves up until Week 48.

2. For any visit, subjects with the following events before or at the visit will be regarded as failures for that visit:
   a. Never initiated study drug
   b. Death
   c. Disease progression
   d. Discontinuation of the treatment
   e. Lost to follow up

APPEARS THIS WAY
ON ORIGINAL

f. Have not achieved confirmed <LOQ status or achieved confirmed <LOQ status but rebounded (two consecutive >LOQ copies/mL or one >LOQ copies/mL if last available visit).

Other subjects will be regarded as responders. Therefore, responders are those who have achieved confirmed viral load <LOQ before the visit of interest but have not become a virologic failure yet.

Please calculate the response rate for each visit up until Week 48 and conduct the primary analyses.

3. Plot the response rates over time and summarize the rates in tables. Graphs and tables should be provided to allow modifications by the reviewers. For example, Microsoft Word tables and Excel/Powerpoint graphs are acceptable.

4. Classify Week 48 failures into the following categories according to the primary reason for the earliest failure:

-Never treated
-Viral rebounder, or Discontinued due to viral rebound
-Never confirmed <LOQ through Week 48
-Death
-HIV disease progression
-Discontinued due to Adverse Events
-Discontinued due to other reasons, including lost to follow ups

5. Produce a table of following format based on the results in 4:
ddI EC/d4T/NLF and ddI TAB/d4T/NLF.

Week 48 Status	ddIEC/d4T/NLF N=503	ddITAB/d4T/NLF N=253
Responder*[a]	xx% (xx%)	xx% (xx%)
Virologic failure*[b]	xx% (xx%)	xx% (xx%)
Death or disease progression	xx% (xx%)	xx% (xx%)
Discontinued due to AE	xx% (xx%)	xx% (xx%)
Discontinued due to others*[c]	xx% (xx%)	xx% (xx%)
Never initiated treatment	xx% (xx%)	xx% (xx%)

*[a]: Subjects achieved virologic response (two consecutive viral load <400 (<50) copies/mL) and maintained it to Week 48.
*[b]: Includes viral rebound and failing to achieved confirmed <400 (50) copies/mL by Week 48.
*[c]: Includes not initiating treatment, lost to follow up, non-compliance, withdraw and pregnancy.

Note: For subjects who never achieved confirmed <400 (50) status and discontinued, if the discontinuation occurred before or at Week 24 they should be classified according to reasons for discontinuation, others who discontinued after Week 24 should be classified as virologic failures.

APPEARS THIS WAY
ON ORIGINAL

6. Repeat 1-5 with subjects who did not initiate the treatment removed.

7. SAS programs together with datasets should be submitted. All programs, including the ones used to derive patient status, should be submitted.

For Study AI454-152, not all subjects will have the opportunity to complete 48 weeks of therapy by the database cutoff date. Please conduct the analyses in the following two ways:

A. Conduct analyses 1-7 above. In calculating proportions for each visit, use only those subjects who would have completed that visit by the cutoff date.

B. Based on analysis 1, compute the treatment difference and its 95% confidence interval for the proportion of subjects who are not yet virologic failures at Week 48. Classify all subjects into the categories listed in item 5, with one additional category list as those subjects who were still virologic responders when censored. SAS programs should also be submitted for this analysis.

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.

Destry M. Sillivan, MS
Regulatory Project Manager
Division of Antiviral Drug Products

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Concurrence:
HFD-530/MO/Fleischerr
HFD-530/DepDir/Birnkrant
HFD-530/RPM/Sillivan

cc:
Original IND
Division File
Original NDA 21-183
Division File NDA 21-183
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/DepDir/Birnkrant
HFD-530/RPM/Sillivan

NDA 21-183
IND

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

S -530

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: August 29, 2000

To: Cynthia Piccirillo
Associate Director, Regulatory Affairs

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Destry M. Sillivan, M.S., Regulatory Project Manager, HFD-530

Through: Russell Fleischer, PA-C, M.P.H., Medical Officer, HFD-530 /s/ 8/29/00
Robert Kumi, Ph.D., Clinical Pharmacology Reviewer, HFD-530 /s/ 08/29/2000
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, HFD-530 /s/ 8/29/2000
Debra Birnkrant, M.D., Deputy Division Director, HFD-530

Subject: IND ——— for VIDEX® [redacted] (EC) [redacted]

The following requests/comments are made on behalf of Dr. Robert Kumi:

1. The study by Rainey *et al.* included a control arm which allows for an estimation of the magnitude of the drug-drug interaction. Please indicate why your proposed study does not include a suitable control arm(s). With the current study design, interpretation of the pharmacokinetic data will be complicated, due to the lack of bioequivalence between the two formulations, and provide only a relative assessment of the methadone-didanosine interaction. Furthermore, the results from this study may not be suitable for labeling statements.

2. Please indicate how you intend to analyze pharmacokinetic drug-drug interaction results with respect to methadone dose.

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/

APPEARS THIS WAY
ON ORIGINAL

Destry M. Sillivan, MS
Regulatory Project Manager
Division of Antiviral Drug Products

Concurrence:
HFD-530/MO/Fleischerr
HFD-530/BioPharmR/Kumi R
HFD-530/BioPharmTL/Reynolds, K.
HFD-530/DepDir/Birnkrant
HFD-530/RPM/Sillivan

cc:
Original IND ———
Division File IND ———
Original NDA 21-183
Division File NDA 21-183
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/DepDir/Birnkrant
HFD-530/RPM/Sillivan

NDA 21-183
IND ———

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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: Cynthia Piccirillo

Fax Number: (203) 677-7867

Date: September 13, 2000

Company: Bristol-Myers Squibb

No. of pages (excluding cover): 2

Message:

Comments concerning the September 6, 2000 submission.

From: Destry Sillivan, M.S.

Telephone: (301) 827- 2335

Fax Number: (301) 827-2523

Mail:
Division of Antiviral Drug Products
5600 Fishers Lane (HFD-530)
Rockville, Maryland 20857

Courier:
Division of Antiviral Drug Products
HFD-530
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail.

APPEARS THIS WAY
ON ORIGINAL

HFD 530

/S/

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: September 13, 2000

To: Cynthia Piccirillo
Associate Director, Regulatory Affairs

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

/S/

From: Destry M. Sillivan, M.S., Regulatory Management Officer, DAVDP FOR US 9/13/00

Through: Debra Birnkrant, MD, Deputy Director, DAVDP

IND: ——— (SN881)

Subject: September 6, 2000 Protocol and Printed Materials for Study AI454-170, Videx EC Capsules Early Access (SN881).

Please include a statement about the preferred dosing regimen for didanosine with your printed materials for the Early Access to Videx EC protocol.

The preferred dosing frequency of the FDA approved VIDEX formulations is twice daily because there is more evidence to support the effectiveness of this dosing frequency. Once-daily dosing should be considered only for adult patients whose management requires once daily dosing of VIDEX. Please note: Videx EC is an investigational formulation that has only been studied once daily in clinical trials.

If you have any questions, please feel free to call me at 301-827-2335. We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

APPEARS THIS WAY
ON ORIGINAL

cc:
Original IND ——— (SN881)
Division File
HFD-530/MO/Fleischer
HFD-530/Sillivan

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service
Drug Products
Division of Antiviral
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 26, 2000

To: Christopher Vogel
Associate Director, CMC Regulatory Science and Outcomes Research

Address: Bristol-Myers Squibb Company
P.O. Box 5400
Princton, NJ 08543-5400

From: Destry M. Sillivan, M.S., Regulatory Project Manager, HFD-530

Through: Steve Miller, Ph.D., Chemistry Team Leader, HFD-530
Ko-Yu Lo, Ph.D., Chemistry Reviewer, HFD-530

Subject: NDA 21-183, for VIDEX® [redacted] (EC) [redacted] Capsules. Chemistry, Manufacturing, and Controls (CMC) section

---

The following requests/comments address CMC issues and are made on behalf of Dr. Ko-Yu Lo. Please provide an electronic copy of your responses in addition to those submitted officially to the NDA, if possible.

1. Components/composition: Please provide the amount of ingredients per typical batch of bulk coated beadlets.

2. Manufacturing of bulk coated beadlets at Mt. Vernon facility: Please clarify for DAVDP whether the manufacturing process at Mt. Vernon site is the same as the process at the Evansville site.

APPEARS THIS WAY
ON ORIGINAL

3. In-process controls: (i) Please identify the in-process controls for the manufacturing process of uncoated beadlets, coated beadlets, and encapsulation, and (ii) please identify the hold times for bulk uncoated and coated beadlets.

4. [redacted] of bulk beadlets: Please provide [redacted] information to and from the contractor [redacted] facility.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

5. Drug product specification: Please adopt the ICH (Q3B) format for DP specification, as shown below. Only degradants (specified and unspecified) are reported in the related substances attribute.

Description
Identification
Uniformity
Assay (didanosine)
Related substances
Total degradants
[redacted]
Any unspecified (individual) degradant
Dissolution (acid and buffer stages)
Moisture
Aerobic microbial counts

4. Batch analysis of VIDEX Capsules: Please provide a summary table for all available lots of VIDEX Capsules (all strengths) manufactured with coated beadlets from the Evansville, Mt. Vernon, and [redacted] Please also report the Mean, SD, and Mean ± 3 x SD for potency, [redacted], total degradants (specified and unspecified), and moisture.

5. Statistic analysis of VIDEX Capsules: Statistical analysis of stability lots (Evansville [redacted]) was performed and prediction of potency changes and hypoxanthine changes was reported (3/17/00 amendment, pp. 311-312). Please assess whether the data from the Evansville [redacted] lots are poolable and provide a graphical display of these data sets with a linear regression and 95% confidence intervals, including the extrapolated 24 and 36 months values, for [redacted] Also, please perform additional statistical analysis on total related substances and provide a graphical display, as described above. DAVDP wishes to consider results from Items 4 and 5 when setting drug product specification.

6. Stability of 30 count packaging configuration: Stability data provided for the new 30 count packaging configuration (9/11/00 amendment) was limited. The impact of [redacted] on the long term physical stability (i.e., capsule brittleness) in this new configuration is a concern (9/21/00 teleconference with Mr. C. Vogel). Please provide additional stability data or any available data to address this issue. Additionally, we note that a nine months stability report will be available in the beginning of October 2000 (9/26/00 teleconference with Mr. C Vogel).

7. Container labels: Please provide better quality images of container and carton labels, including labels for physician samples, if applicable.

BEST POSSIBLE COPY

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.

Destry M. Sillivan, MS
Regulatory Project Manager
Division of Antiviral Drug Products

Concurrence:
HFD-530/CTL/Miller, S.
HFD-530/CR/Lo, Ko-Yu
HFD-530/RPM/Sillivan

cc:
Original NDA 21-183
Division File NDA 21-183
HFD-830/Dir/Chen, Chi-wan
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/DepDir/Birnkrant
HFD-530/CTL/Miller, S.
HFD-530/CR/Lo, Ko-Yu
HFD-530/RPM/Sillivan

NDA 21-183

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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: Christopher Vogel

Fax Number: (609) 818-5832

Date: September 27, 2000

Company: Bristol-Myers Squibb

No. of pages (excluding cover): 3

Message:

CMC comments and requests for NDA 21-183. Expedited response requested due to the limited timeframe before PDUFA date (October 31, 2000).

From: Destry Sillivan, M.S.

Telephone: (301) 827-2335

Fax Number: (301) 827-2523

Mail:
Division of Antiviral Drug Products
5600 Fishers Lane (HFD-530)
Rockville, Maryland 20857

Courier:
Division of Antiviral Drug Products
HFD-530
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail.

APPEARS THIS WAY
ON ORIGINAL

Concurrence:
HFD-530/CTL/Miller, S.
HFD-530/CR/Lo, Ko-Yu
HFD-530/RPM/Sillivan

cc:
Original NDA 21-183
Division File NDA 21-183
HFD-830/Dir/Chen, Chi-wan
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/DepDir/Birnkrant
HFD-530/CTL/Miller, S.
HFD-530/CR/Lo, Ko-Yu
HFD-530/RPM/Sillivan

NDA 21-183

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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: Cynthia Piccirillo

Fax Number: (203) 677-7867

Date: October 20, 2000

Company: Bristol-Myers Squibb

No. of pages (excluding cover): 2

Message:

Clinical Pharmacology comments for NDA 21-183, Videx EC labeling

From: Destry Sillivan, M.S.

Telephone: (301) 827- 2335

Fax Number: (301) 827-2523

Mail:
Division of Antiviral Drug Products
5600 Fishers Lane (HFD-530)
Rockville, Maryland 20857

Courier:
Division of Antiviral Drug Products
HFD-530
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-183
Div File

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: October 20, 2000

To: Cynthia Piccirillo
Associate Director, Regulatory Affairs

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Destry M. Sillivan, M.S., Regulatory Project Manager, HFD-530

Through: Russell Fleischer, PA-C, M.P.H., Medical Officer, HFD-530 10/20/00
Robert Kumi, Ph.D., Clinical Pharmacology Reviewer, HFD-530 /s/
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, HFD-530 /s/ 10/20/00
Debra Birnkrant, M.D., Deputy Division Director, HFD-530 10/20/00

Subject: NDA 21-183 for VIDEX® [redacted] (EC) [redacted] Clinical Pharmacology Label Revisions

---

The following requests/comments are made on behalf of Dr. Robert Kumi:

(1) Drug Interactions:

The following comments apply to the drug interaction results in Tables 3, 4, and 5.

(a) The symbol, ↔, should be used in place of mean AUC and C_{max} changes if they are less than 10 % and the confidence intervals should not be included (e.g. Table 5 with ritonavir results).

(b) If mean changes that are less than 10 % are considered clinically significant, the confidence interval may be included in the Tables. In these cases, please provide your rationale for concluding that the interactions are clinically significant.

(c) Include in footnotes: ↔ indicates no change, mean increase, or decrease, of less than 10 %

(2) Dosage Adjustment (Patients with renal impairment):

(a) The recommendations in Table 11 are acceptable.

APPEARS THIS WAY
ON ORIGINAL

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/

Desty M. Sillivan, MS
Regulatory Project Manager
Division of Antiviral Drug Products

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

cc:
Original IND ———
Division File IND ———
Original NDA 21-183
Division File NDA 21-183
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/DepDir/Birnkrant
HFD-530/RPM/Sillivan

NDA 21-183
IND ———

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Record of Teleconference

NDA: **21-183**

Date: **October 23, 2000**

Drug: **VIDEX® EC**

Sponsor: **Bristol-Myers Squibb Co.**

BETWEEN: **Representatives of Bristol-Myers Squibb Co.**
Chris Vogel, Associate Director, CMC Regulatory Science and Outcomes Research
Michael Burnett, Director, CMC Regulatory Science and Outcomes Research

AND: **Representatives of DAVDP**
Steve Miller, Ph.D., Chemistry Team Leader /S/ 11/21/00
Ko-Yu Lo, Ph.D. Chemistry Reviewer /S/ 11/21/00
Kellie Reynolds, PharmD., Clinical Pharmacology Team Leader 11/22/00
Destry Sillivan, MS, Regulatory Project Manager 11/22/00

SUBJECT: Chemistry, Manufacturing, and Controls Information Amendment, letter date October 16, 2000

Background:
The Bristol-Myers Squibb (BMS) submission of October 16, 2000 was made in response to a DAVDP request for information sent via facsimile, dated September 26, 2000. This teleconference was requested by BMS to discuss the appropriateness of their responses.

For each discussion topic, the sponsor's position/question is shown in regular font, followed by the FDA's response in **bold font.**

Discussion:

For the responses for DAVDP requests for information, points one through nine outlined in the DAVDP facsimile dated September 26, 2000, which points are acceptable to DAVDP?

Responses for requests one through four are acceptable to DAVDP. The response for request number five we will defer to the ICH committee for further discussion; however, the current format is acceptable to DAVDP.

Additionally, we would like to know if you want one or two (release and shelf-life) specifications for [redacted] and what Q you have proposed for the dissolution rate, [redacted] The data supports a Q of [redacted] Further, you have proposed a specification of [redacted] for aerobic microbial count. DAVDP believes this specification should be [redacted]

APPEARS THIS WAY
ON ORIGINAL

Only one specification is necessary for [redacted] (shelf-life). Additionally, with regard to the Q and the specification for aerobic microbial count, BMS [redacted] soon as possible.

DAVDP would request that you submit moisture data to support the hold time (if an extended time period is expected) prior to [redacted] DAVDP will not require a phase 4 commitment for this data. Please submit the data as it becomes available.

Additional Requests:

The 30 count bottle configuration is acceptable. Does BMS wish to market the [redacted] count bottle configuration.

The initial market configuration is only planned for the 30 count bottle.

Stability testing for VIDEX EC is only planned for 24 months. Does BMS [redacted]

BMS [redacted]

Additionally, DAVDP requires that you submit a revised container label, preferably accompanied by an electronic copy, and revised product specifications.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Concurrence:
HFD-530/CTL/Miller, S.
HFD-530/CR/Lo
HFD-530/BiopharmTL/Reynolds
HFD-530/RPM/Sillivan

cc:
Original NDA 21-183
Division File
HFD-530/CTL/Miller, S.
HFD-530/CR/Lo
HFD-530/BiopharmTL/Reynolds
HFD-530/RPM/Sillivan

Record of Teleconference

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

DIV. FILE

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: October 25, 2000

To: Cynthia Piccirillo
Associate Director, Regulatory Affairs

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Destry M. Sillivan, M.S., Regulatory Project Manager, HFD-530

Through: Russell Fleischer, PA-C, M.P.H., Medical Officer, HFD-530 /S/ 10/25/2000
Robert Kumi, Ph.D., Clinical Pharmacology Reviewer, HFD-530
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, HFD-530 10-25-00
Debra Birnkrant, M.D., Deputy Division Director, HFD-530 10/25/00

Subject: NDA 21-183 for VIDEX® [redacted] (EC) [redacted]
Phase IV commitments

The following requests for Phase IV commitments for NDA 21-183, VIDEX® EC, are made on behalf of the VIDEX EC review team, DAVDP:

1. The submission of the final report from BMS study AI454-152.

   Projected Submission Date: First quarter 2001

2. The evaluation of the safety and pharmacokinetics of VIDEX EC dosed as a twice daily regimen, and a commitment to discuss with DAVDP further clinical development of this regimen based on these results.

   Projected Submission Date: Third quarter 2002

3. The evaluation of the pharmacokinetics and safety of VIDEX EC in appropriate pediatric populations.

   Projected Submission Date: Third quarter 2002

4. The development of educational materials for patients and healthcare providers regarding information about once daily administration of VIDEX EC.

APPEARS THIS WAY
ON ORIGINAL

Projected Submission date: This should be an ongoing commitment to provide this information.

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/

Destry M. Sillivan, MS
Regulatory Project Manager
Division of Antiviral Drug Products

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

cc:
Original IND ———
Division File IND ———
Original NDA 21-183
Division File NDA 21-183
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/DepDir/Birnkrant
HFD-530/RPM/Sillivan

NDA 21-183
IND ———

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Record of Teleconference

NDA: **21-183**

Date: **October 30, 2000**

Drug: **VIDEX® EC**

Sponsor: **Bristol-Myers Squibb Co.**

BETWEEN: **Representatives of Bristol-Myers Squibb Co.**
Chris Vogel, Associate Director, CMC Regulatory Science and Outcomes Research
Michael Burnett, Director, CMC Regulatory Science and Outcomes Research

AND: **Representatives of DAVDP**
Steve Miller, Ph.D., Chemistry Team Leader
Ko-Yu Lo, Ph.D. Chemistry Reviewer
Destry Sillivan, MS, Regulatory Project Manager

SUBJECT: Chemistry, Manufacturing, and Controls Information Amendment, letter date October 30, 2000

Background:
The Bristol-Myers Squibb (BMS) submission of October 16, 2000 was made in response to a DAVDP request for information sent via facsimile, dated September 26, 2000. A teleconference was held with BMS on October 23 to discuss BMS October16 submission. A follow up submission was made on October 30, 2000 in response to issues discussed on October 23, 2000. This teleconference was requested by BMS to discuss the appropriateness of their responses, as outlined in the October 30, 2000, submission.

For each discussion topic, the sponsor's position/question is shown in regular font, followed by the FDA's response in **bold font.**

Discussion:

BMS has agreed to our recommendations, discussed on October 23, 2000, as follows:

1. **Dissolution (buffer stage) –Change from: ——————— within 45 minutes," to: "minimum —— (Q) within 45 minutes.**

2. **Microbial Count. – Change from : ——————— to: "maximum 100 cfu/gm."**

APPEARS THIS WAY
ON ORIGINAL

Concurrence:
HFD-530/CTL/Miller, S.
HFD-530/CR/Lo
HFD-530/RPM/Sillivan

cc:
Original NDA 21-183
Division File
HFD-530/CTL/Miller, S.
HFD-530/CR/Lo
HFD-530/RPM/Sillivan

Record of Teleconference

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

WITHHOLD 4 PAGE (S)

Draft Labeling

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: **October 31, 2000**

TO: **NDA 21-183** /S/

FROM: **Russell Fleischer, PA-C, MPH**
Senior Clinical Analyst, DAVDP

THROUGH: **Debra Birnkrant, MD** /s/ 10/31/00
Deputy Director, DAVDP

RE: **DSI Audit**

No DSI audits were requested for this application because:

For study AI454-152, patients were enrolled at 53 US and non-US sites. No site contributed more than 20 patients. A review of the investigators' CVs showed that all were qualified to conduct the study. Finally, there were no anomalies in the data that suggested specific problems at any of these sites. Therefore, the conduct of the study at these sites was not expected to have a substantial impact on the study conclusions.

For study AI454-158, 20 US-based investigators enrolled subjects in this study. A review of the investigators' CVs showed that all were qualified to conduct the study. Finally, there were no anomalies in the data that suggested specific problems at any of these sites. Therefore, the conduct of the study at these sites was not expected to have a substantial impact on the study conclusions.

APPEARS THIS WAY
ON ORIGINAL

HFD-530

/S/

NDA 21-183

Bristol-Myers Squibb Company
Attention: Cynthia F. Piccirillo
Associate Director, Worldwide Regulatory Affairs
5 Research Parkway
Wallingford, CT 06492

JUN 9 2000

Dear Ms. Piccirillo:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: VIDEX® EC (didanosine) Capsules in 125 mg, 200 mg, 250 mg, and 400 mg strengths

Review Priority Classification: Priority (P)

Date of Application: January 31, 2000

Date of Receipt: January 31, 2000

Our Reference Number: NDA 21-183

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 31, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 31, 2000.

Please be advised that, as of April 1, 1999, all applications of new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will

APPEARS THIS WAY
ON ORIGINAL

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

5 pages

ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for industry on Qualifying for Pediatric Exclusivity (available on our website at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days form the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as is does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530

Attention: Division Document Room,
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and
Division of Antiviral Drug Products, HFD-530
9201 Corporate Blvd
Rockville, Maryland 20850

If you have any questions, please contact Destry M. Sillivan, M.S., Regulatory Project Manager at (301) 827-2335.

Sincerely yours,

/S/

Anthony W. DeCicco
Supervisory Consumer Safety Officer
Division of Antiviral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evalution and Research

APPEARS THIS WAY
ON ORIGINAL

Concurrence:
HFD-530/RPM/Sillivan

/S/ 6/6/00

cc:
Original NDA 21-183
Division File NDA 21-183
HFD-530/SCSO/DeCicco
HFD-530/MO/Fleischer
HFD-530/MTL/Cvetkovich
HFD-530/RPM/Sillivan

ACKNOWLEDGEMENT LETTER

NDA 21-183

APPEARS THIS WAY
ON ORIGINAL