CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-360

CORRESPONDENCE

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation 4

FACSIMILE TRANSMITTAL SHEET

DATE: 08/06/01

To: Robert W. Babilon, Associate Director, Regulatory Affairs	**From:** Virginia L. Yoerg
Company: DuPont Pharmaceuticals Company	Division of Antiviral Drug Products
Fax number: 302 892 0712	**Fax number:** 301 827 2523
Phone number: 302 892 7099	**Phone number:** 301 827 2335

Subject: Clinical request for information

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ✓ NO

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: **August 6, 2001**

To: **Robert W. Babilon, Associate Director, Regulatory Affairs**

Address: **DuPont Pharmaceuticals Company**
Chestnut Run Plaza, MR 2204
974 Centre Road
Wilmington, DE 19805

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

Through: **Stanka Kukich, M.D., Medical Team Leader, HFD-530**
Harry Haverkos, M.D., Medical Officer, HFD-530

NDA: **21-360**

Subject: **Clinical request for information**

This comment is being conveyed on behalf of Harry Haverkos, M.D., and is directed towards your NDA 21-360, dated March 30, 2001.

- Please provide more detailed information to justify development of the 300 mg tablet. How does the development of the two 300 mg tablets daily improve compliance compared to one 600 mg tablet daily?

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

/S/

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

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation 4

FACSIMILE TRANSMITTAL SHEET

DATE: 09/05/01

To: Damaris Degraft-Johnson, CMC Reg Affairs and Robert W. Babilon, Associate Director, Regulatory Affairs	**From:** Virginia L. Yoerg
Company: DuPont Pharmaceuticals Company	Division of Antiviral Drug Products
Fax number: 302 892 0712	**Fax number:** 301 827 2523
Phone number: 302 892 7099	**Phone number:** 301 827 2335

Subject: Chemistry comments and questions

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ✓ NO

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: **September 5, 2001**

To: **Damaris Degraft-Johnson, Senior Director, WW CMC Regulatory Affairs**
Robert W. Babilon, Associate Director, Regulatory Affairs

Address: **DuPont Pharmaceuticals Company**
Chestnut Run Plaza, MR 2204
974 Centre Road
Wilmington, DE 19805

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

Through: **Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530**
Dan Boring, R.Ph., Ph.D., Chemistry Reviewer, HFD-530

NDA: **21-360**

Subject: **Chemistry questions and comments regarding Sustiva tablets**

These comments are being conveyed on behalf of Dan Boring, R.Ph., Ph.D., and are directed towards your NDA 21-360, dated March 30, 2001.

1. Will DuPont be updating the existing stability information sometime during the review cycle and, if so, when will that be submitted?

2. Will a statistical analysis of the updated stability information be provided?

3. What is the proposed expiration dating period for the Sustiva tablets? What strategy will DuPont be using to set the expiration dating period? From the proposed data filing and assuming that a statistical analysis of the 12-month data becomes available during the review cycle and is satisfactory, three options may be viable.

   a) Seek a ——— expiration dating period based on a statistical analysis of the 12-month data and contingent upon a commitment to provide satisfactory ——— real-time stability data in the next annual report.

   b) Seek an ——— expiration based on a statistical analysis of the 12-month data and seek an extension to longer periods by prior approval supplement supported by full-term stability data from the NDA registration batches.

   c) Our decision on the expiration dating period (——————) will be based upon the behavior of the stability data that is available during the review.

4. Please provide the stability update in the Excel format we have used previously so that I can verify your statistical analysis.

5. From the submitted information, the child-resistant status of your blister presentation is unclear. Can the blisters be marked directly with their child resistance status?

   Please consider adding a "Place Pharmacy Label Here" segment to your immediate container label, well away from the red Alert box to further encourage not covering up the Alert box with a pharmacy label.

7. The How Supplied section of the package insert does not list the ——— bottles of either the 300 or 600-mg strength. Please revise to correct this omission.

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

/S/

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

APPEARS THIS WAY ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation 4

FACSIMILE TRANSMITTAL SHEET

DATE: 12/19/01

To: Cindy Piccirillo, Regulatory Affairs	**From:** Virginia L. Yoerg
Company: Bristol Myers-Squibb Pharma Company	Division of Antiviral Drug Products
Fax number: 203 677 7867	**Fax number:** 301 827 2523
Phone number: 203 677 7625	**Phone number:** 301 827 2335

Subject: NDA 21-360 labeling recommendations

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ✓ NO

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: December 19, 2001

To: Cindy Piccirillo, Associate Director, Global Regulatory Science

Address: Bristol Myers-Squibb Pharma Company
Chestnut Run Plaza, Maple Run
974 Centre Road
Wilmington, DE 19805

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

Through: Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530
Dan Boring, R.Ph., Ph.D., Chemistry Reviewer, HFD-530
Stanka Kukich, M.D., Medical Team Leader, HFD-530
Harry Haverkos, M.D., Medical Officer, HFD-530

NDA: 21-360

Subject: Labeling recommendations for Sustiva™ tablets

These comments are being conveyed on behalf of Dan Boring, R.Ph., Ph.D., and are directed towards your NDA 21-360, dated March 30, 2001.

1. 21CFR§201.55 provides for a statement of the recommended or usual dose on labels of prescription drugs. Compliance with this requirement, when an informative or useful statement cannot be presented, would be met by a statement such as "See package insert for dosage information" or "See package insert." We recommend that the immediate container label be revised to use this language.

2. In FDA's "Guidance for Industry, Implementation of Section 126 of the Food and Drug Modernization Act of 1997—Elimination of Certain Labeling Requirements, Procedural Guidance #3," it is stated that the Agency prefers the "Rx Only" statement to appear on the main panel of container and carton labels. Please revise your immediate container label to relocate the "Rx Only" statement to the main panel.

3. Please be advised that our Division of Drug Marketing, Advertising and Communications considers the word "new" to be valid for only six months when used in labeling. Therefore, the "New Strength" statement on the Sustiva™ carton and container labels should not appear any longer than six months. Please revise your next label printing to remove "New Strength" from your cartons and containers.

4. We recommend that you print the strength (300 and 600) on one or both sides of the tablet, as you did with your capsule product, to permit easier identification of the tablets.

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

/S/

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

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation 4

FACSIMILE TRANSMITTAL SHEET

DATE: 01/08/02

To: Cindy Piccirillo, Regulatory Affairs	**From:** Virginia L. Yoerg
Company: Bristol Myers-Squibb Pharma Company	Division of Antiviral Drug Products
Fax number: 203 677 7867	**Fax number:** 301 827 2523
Phone number: 203 677 7625	**Phone number:** 301 827 2335

Subject: NDA 21-360 labeling (PI and PPI)

Total no. of pages including cover: 26

Comments:

Document to be mailed: ☐ YES ✓ NO

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: **January 8, 2002**

To: **Cindy Piccirillo, Associate Director, Global Regulatory Science**

Address: **Bristol Myers-Squibb Pharma Company**
5 Research Parkway, 2CW-1038
Wallingford, CT 06492

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

NDA: **21-360**

Subject: **Labeling for Sustiva™ tablets**

The attached labeling is being conveyed on behalf of the Division of Antiviral Drug Products (for NDA 21-360, dated March 30, 2001).

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

/S/

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

APPEARS THIS WAY
ON ORIGINAL

Yoerg, Virginia L

From: Yoerg, Virginia L
Sent: Friday, January 25, 2002 3:32 PM
To: Cynthia F Piccirillo (E-mail)
Cc: Kukich, Stanka; Haverkos, Harry W; Reynolds, Kellie S; DiGiacinto, Jennifer; Boring, Daniel L; Yoerg, Virginia L
Subject: Sustiva tablets PI and PPI

Cindy,

Please confirm receipt, since we aren't faxing these documents.
Here are the PI and PPI. [FYI to all, I purposefully did NOT delete the blister pack information since BMS is still considering the change.]

Attachment 1: annotated PI
Attachment 2: clean PI
Attachment 3: annotated PPI
Attachment 4: clean PPI

I do need a few documents from you. I don't have an electronic (Word) copy of the original PI and PPI submitted by DuPont. I need them to do my final comparison, old suggested labeling versus final agreed upon labeling.

Virginia L. Yoerg
Regulatory Project Manager
Food and Drug Administration

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 FDA/INDUSTRY Meeting

IND: ——

Date: **February 12, 2001**

Drug: **Sustiva™ (efavirenz) Tablets- 300 mg and 600 mg**

Sponsor: **DuPont Pharmaceuticals Company**

Meeting: **Type B: Pre-NDA Meeting**

BETWEEN: **Representatives of DuPont Pharmaceuticals Company**
Joseph Meschino, Ph.D. Acting Director, Regulatory Affairs
Laura Bessen, Executive Director, Worldwide Medical Affairs, Virology
David Kornhauser, M.D. Executive Medical Director, Clinical Pharmacology
William Fiske, Ph.D. Senior Investigator, Drug Metabolism and Pharmacokinetics
D. Degraft-Johnson, R.Ph., M.Sc., Med. Chem. Senior Director, Worldwide CMC Regulatory Affairs
Chester Andruskiewicz, Ph.D., Director, Project Management
Irma Benedeck, Ph.D., Director, Clinical Pharmacology
Robert Babilon, Associate Director, Regulatory Affairs
Munir Hussain, Ph.D., Director, Pharmaceutical R&D
Eda Montgomery, Ph.D., Analytical R&D
John Taylor, Ph.D., Director, Scientific Affairs
Zhihui Gao, Ph.D., Principal Research Scientist
Vivian Gray, Senior Research Scientist

AND: **Representatives of DAVDP**
Debra Birnkrant, M.D., Acting Division Director, DAVDP
Stanka Kukich, M.D., Medical Team Leader
Harry Haverkos, M.D., Medical Reviewer
Stephen Miller, Ph.D., Chemistry Team Leader
Dan Boring, R.Ph., Ph.D., Chemistry Reviewer
Robert Kumi, Ph.D., Acting Pharmacokinetics Team Leader
Jennifer DiGiacinto, Pharm.D., Pharmacokinetics Reviewer
Anthony DeCicco, R.Ph., Chief, Project Management
Virginia Yoerg, Regulatory Project Manager

SUBJECT: Pre-NDA meeting for Sustiva™ (efavirenz) 300 mg and 600 mg tablets

Background:

In a correspondence to the Agency dated December 7, 2000 (SN451), the sponsor stated their intent to submit an NDA for Sustiva™ 300 mg and 600 mg tablets, and requested a pre-NDA meeting with DAVDP. The background information package was submitted to the Agency on December 27, 2000 (SN454).

Discussion:

DAVDP inquired as to the expected submission date of this NDA. *The sponsor verified that the target submission date is March 31, 2001, as indicated in the background package.*

Pharmacokinetics

DAVDP noted that the sponsor has not yet responded to faxed comments sent on January 31, 2001 and February 2, 2001.

❖ **Dissolution Discussion**

DAVDP asked the sponsor to respond to the questions dealing with the dissolution study. Two questions addressed the differences in dissolution methodology (volume of media and amount of sodium lauryl sulfate or SLS) used for the 200 mg capsule compared to the 300 mg tablet and 600 mg tablet. *The sponsor stated that the purpose was to maintain sink conditions.* DAVDP asked if the sponsor had documentation of the drug's solubility profile in the presence and absence of SLS. *The sponsor indicated that the data were available, and provided a brief summary of the data.*

DAVDP asked why sinkers were used during the dissolution study with the newly formulated 300-mg and 600-mg tablets. *The sponsor replied that it was to decrease the variability in dissolution results. The newly formulated tablets were sticking to the side of the vessel during the dissolution studies, affecting drug dissolution. The sinkers prevented the formulation from sticking to the vessel.*

❖ **Food Effect Discussion**

DAVDP asked the sponsor to explain their plans for addressing the food effect with the new 300 mg and 600 mg tablet formulations. *The sponsor replied that they are not planning to conduct any food-effect studies, since the 300 mg and 600 mg tablets were bioequivalent to the current marketed formulation 200 mg capsule. The sponsor further went on to discuss their population pharmacokinetic analysis for CNS side effects, which showed no correlation between CNS adverse event occurrence and AUC [The sponsor referred to their pending labeling supplement (SLR 007) for NDA 20-972].* DAVDP responded that the population pharmacokinetic analysis did not consider the severity of the CNS side effects.

The sponsor inquired if a food effect study could be conducted as a Phase 4 commitment, or if results should be submitted with the NDA. If so, what protocol design should be utilized? DAVDP stated that this issue would be discussed internally. DAVDP would suggest an appropriate study design if a food-effect study is required. [Addendum: DAVDP faxed comments to the sponsor on February 16, 2001, and suggested an appropriate study design]. *The*

sponsor asked if the Agency recommends a high-fat/high-calorie meal or a reduced-fat/reduced-calorie meal if they conduct a food effect study? DAVDP would respond to their inquiry within one week to indicate whether a high-fat/high-calorie or reduced-fat/reduced-calorie meal or both meals should be included in the study. [Addendum: DAVDP faxed comments to the sponsor on February 16, 2001, and suggested an appropriate study design].

Chemistry

DAVDP inquired as to the size and shape of the proposed 300 mg and 600 mg tablets. *The sponsor replied that the dimensions of the 300 mg tablet (capsular shape) are ——— and the 600 mg tablet (modified capsular shape) are ——— They are film-coated tablets shaped like caplets.*

DAVDP asked when the 12-month stability data and the statistical analyses would be submitted to the Agency. *The sponsor stated that the data and analyses would be submitted by September/October, 2001.* [Note: If the NDA is submitted on March 31, 2001, the stability data and analyses will be coming in approximately seven months into the NDA review cycle.]

DAVDP asked for clarification of the intent for marketing the 300 mg tablet. The sponsor stated that some physicians recommend that patients split their daily Sustiva™ dose, which may help alleviate some nervous system side effects.

Conclusions/Actions:

- The sponsor will submit as much of the Chemistry section of the NDA electronically (in PDF) as possible.
- The sponsor will submit the 12-month stability data by September/October, 2001.
- DAVDP will advise the sponsor on an appropriate design for a food effect study.

/s/

Tony DeCicco
3/14/01 04:38:52 PM

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 INTERNAL MEETING

Date of Meeting: **May 18, 2001**

NDA: **NDA 21-360**

Drug: **Sustiva™ (efavirenz) tablets**

Applicant: **DuPont Pharmaceuticals Company**

Indication: **Treatment of HIV**

Participants:
Debra B. Birnkrant, M.D., Acting DAVDP Director
Stanka Kukich, M.D., Medical Team Leader
Harry Haverkos, M.D., Medical Officer
Stephen Miller, Ph.D., Chemistry Team Leader
Kellie S. Reynolds, Pharm.D., Biopharmaceutics Team Leader
Jennifer DiGiacinto, Pharm.D., Biopharmaceutics Reviewer
Kuei-Meng Wu, Ph.D., Pharmacology/Toxicology Reviewer
Lalji Mishra, Ph.D., Microbiology Team Leader/Reviewer
Anthony DeCicco, R.Ph., Chief, Project Management Staff
Virginia L. Yoerg, Regulatory Project Manager

Type of Meeting: Filing Meeting

Related Documents: IND —— and NDA 20-972

Background: DuPont Pharmaceuticals Company submitted this NDA on March 30, 2001, received April 2, 2001 and has paid the half user fee in full. The internal action goal date for this NDA is January 18, 2002; the PDUFA date is February 2, 2002. The original NDA for Sustiva™ 50, 100, and 200 mg capsules was approved on September 17, 1998, and received traditional approval on February 9, 2000. This NDA is for Sustiva™ tablets in 300 mg and 600 mg strengths (new dosage form and strengths). This meeting was held to determine whether the application is filable.

Discussion

1. Pharmacology/Toxicology

The applicant referenced the original NDA since no new Pharmacology/Toxicology information was submitted with this NDA.

2. Microbiology

Dr. Mishra stated that there are no filing issues, since no Microbiology information was submitted in this NDA.

3. Chemistry

Dr. Miller stated that there are no filing issues. He noted that DuPont plans to market the 300 mg and 600 mg tablets in bottles and blister packs. Most of the —— manufacturing sites were acceptable on profile, as they have passed recent inspections. DAVDP has already submitted an Establishment Inspection Request for all the manufacturing sites.

4. Biopharmaceutics/Clinical Pharmacokinetics

Dr. DiGiacinto concluded that there are no filing issues. The applicant indicated in this NDA that the results from the food effect study should be submitted to FDA in November, 2001. The results from this study are not required for NDA approval, but are important for an accurate label.

5. Clinical

Dr. Haverkos stated that there are no filing issues, and therefore the application is filable.

6. Standard or Priority Review

The applicant did not request a priority review. DAVDP will grant this application a standard review.

7. Pediatric Rule

The Pediatric Rule is automatically triggered with this NDA. —— Therefore, DAVDP may grant the waiver requested by the applicant in this NDA.

Conclusions

- The review team concluded that NDA 21-360 is filable, and is designated as a standard review (ten month clock).

Action Item

- A consult will be sent to OPDRA to review the trade name and accompanying label.