CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-945

CORRESPONDENCE

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 25, 1999

To: Becky Welsh, Sr. Regulatory Administrator

From: Ko-Yu Lo, Ph.D., Chemistry Reviewer

Through: Stephen Miller, Ph.D., Chemistry Team Leader

NDA: 20-945

Subject: Norvir SEC Chemistry comments from June 22, 1999 Teleconference

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The following chemistry comments are from the June 22, 1999 teleconference regarding NDA 20-945 Norvir (ritonavir capsules) soft gelatin 100 mg.

1. Agreement was reached on a Phase 4 commitment to [redacted]

2. [redacted]

3. The Division agrees to use Abbott's proposed drug product acceptance criteria [redacted] provided that the statistical analysis on total related impurities will meet a "Not More Than [redacted] w/w)" limit at a projected [redacted] time point. Abbott agreed to submit the requested statistical analyses.

4. Agreement was reached on a Phase 4 commitment to [redacted]

5. [redacted]

6. The expiration dating period at approval will be [redacted] Abbott currently plans to [redacted]

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.

Sylvia Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

cc:
Original NDA 20-945
Division File
HFD-530/CSO/Lynche
HFD-530/RRO/Struble
HFD-530/CR/Lo

Facsimile

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 25, 1999

To: Becky Welch, Sr. Regulatory Administrator

Address: Abbott Laboratories

From: Ko-yu Lo, Ph.D., Chemistry Reviewer

Through: Stephen Miller, Ph.D., Chemistry Team Leader

NDA: 20-945

Subject: Phase 4 Commitments

The following is our proposed wording for the Phase 4 commitments reached in our June 22, 1999 teleconference. Please submit a correspondence indicating your agreement to these or any other phase 4 commitments.

Phase 4 Commitments:

1. [redacted]

2. [redacted]

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.

Sylvia Lynche, PharmD.
Regulatory Management Officer
Division of Antiviral Drug Products

cc:
Original NDA 20-945
Division File
HFD-530/CSO/Lynche
HFD-530/RRO/Struble
HFD-530/MO/Murray

Facsimile

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Record of Telecon

NDA: **20-945**

Date: **June 22, 1999**

Drug: **Norvir (ritonavir capsules) soft gelatin 100 mg**

Sponsor: **Abbott Laboratories**

BETWEEN: **Representative of Abbott:** **Ms. Becky Welch, Mr. John Wolfinger, Mr. Roland Catherall, Dr. Efraim Shek, Dr. Laman AlRazzak, Dr. John Morris, Dr. Soumajeet Ghosh, Dr. Eugene Sun**

AND: **Representatives of DAVDP:** **Dr. Stephen Miller, Dr. Kŏ-yu Lo, Dr. Sylvia Lynche**

Background:

This teleconference was scheduled at the request of DAVDP to discuss the chemistry issues regarding NDA 20-945 Norvir (ritonavir capsules) soft gelatin 100 mg.

Action Items:

1. Agreement was reached on a Phase 4 commitment to [redacted]

3. The Division agrees to use Abbott's proposed drug product acceptance criteria [redacted] provided that the statistical analysis on total related impurities will meet a "Not More Than [redacted] w/w)" limit at a projected [redacted] time point. Abbott agreed to submit the requested statistical analyses.

4. Agreement was reached on a Phase 4 commitment to [redacted]

5. [redacted]

6. The expiration dating period at approval will be [redacted] Abbott currently plans to [redacted]

Concurrence:
HFD-530/Miller /S/
HFD-530/Lo-
HFD-530/Lynche 7/6/99

cc:
Original NDA 20-945
Division File
HFD-530/Lynche
HFD-530/Struble
HFD-530/Lo

TELECON MINUTES

Save as V:\DAVDP\Lynches\NDA 20-945

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 16, 1999

To: Becky Welsh, Sr. Regulatory Administrator

Address: Abbott Laboratories

From: Kim Struble, Pharm.D., Regulatory Review Officer

Through: Jeff Murray, M.D., M.P.H., Medical Team Leader

NDA: 20-945

Subject: Norvir SEC Labeling comments

Based on our review we have the following recommendations in the Clinical Pharmacology: Pharmacokinetics Section.

Clinical Pharmacology: Pharmacokinetics

After a single 600 mg dose under non-fasting conditions, in two separate studies, the soft gelatin capsule (n=57) and oral solution (n=18) formulations yielded mean +/- SD areas under the plasma concentration time curve (AUCs) of 121.7 +/- 53.8 and 129.0 +/- 39.3 ug • h/mL, respectively. Relative to fasting conditions, the extent of absorption of ritonavir from the soft gelatin capsule formulation was 13% higher when administered with a meal (615 Kcal; 14.5% fat, 9 % protein, and 76% carbohydrate).

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.

Sylvia Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

cc:
Original NDA 20-945
Division File
HFD-530/CSO/Lynche
HFD-530/RRO/Struble
HFD-530/MO/Murray

Facsimile

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 15, 1999

To: Becky Welsh, Sr. Regulatory Administrator

Address: Abbott Laboratories

From: Kim Struble, Pharm.D., Regulatory Review Officer

Through: Jeff Murray, M.D., M.P.H., Medical Team Leader

NDA: 20-945

Subject: Norvir SEC Labeling comments

Please refer to your revised package insert dated May 28, 1999. Based on our review we have the following recommendations. We will be available to discuss any of these recommendations during a teleconference.

Clinical Pharmacology: Pharmacokinetics.

Please delete the following statement:

[ ]

WARNINGS:

Please amend the sildenafil subsection as follows. These recommendations are consistent with the recently revised Viagra package insert.

"Particular caution should be used when prescribing sildenafil in patients receiving NORVIR. Co-administration of NORVIR with sildenafil is expected to substantially increase sildenafil concentrations (11 fold increase in AUC) and may result in an increase in sildenafil-associated adverse events, hypotension, syncope, visual changes, and prolonged erection ——— (see PRECAUTIONS: Drug Interactions, Table 4 Established Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies and the complete prescribing information for sildenafil).

PRECAUTIONS:

Under the Established Drug Interactions: Clarithromycin section please include the following statement:

"No dose adjustment for patients with normal renal function is necessary."

Please amend the following headings in Table 4 as follows:

"Predicted Drug Interactions: Use with Caution,
Dose Decrease of Coadministered Drug May Be Needed (see WARNINGS)"

"Predicted Drug Interactions: Use with Caution,
Dose Increase of Coadministered Drug May Be Needed (see WARNINGS)"

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.

Sylvia Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

cc:
Original NDA 20-945
Division File
HFD-530/CSO/Lynche
HFD-530/RRO/Struble
HFD-530/MO/Murray

Facsimile

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 2, 1999

To: Becky Welsh, Sr. Regulatory Administrator

From: Ko-Yu Lo, Ph.D., Chemistry Reviewer KL 6/2/99

Through: Stephen Miller, Ph.D., Chemistry Team Leader /S/ 6/2/99

NDA: 20-945

Subject: Norvir SEC Chemistry requests

The following chemistry results are for NDA 20-945 Ritonavir soft gelatin capsules, 100 mg (modified soft gelatin formulation).

With regard to ritonavir drug substance:

1. Based on production experience and data submitted to NDA 20-659/NC dated March 12, 1999, please address the following:

   Is there a relation between route of synthesis, manufacturing site, and level of Form II in ritonavir bulk drug? The levels of From II in lots produced by the —— process at the Italy site varied from —— to —— For example, lots produced in November 1998 were found to have —— (# 47124TL) —— (#47126TL) —— (#47128TL), and —— (#47130TL) of Form II respectively. Please clarify whether these lots were produced by an identical procedure?

   We would like to discuss your plans for on-going screening of Form II in bulk ritonavir.

2. Please provide batch analysis on representative lots of bulk ritonavir manufactured by ———— at the North Chicago and Italy sites. We would like to reassess the drug substance specifications based on these batch analyses.

3. Please provide a study update on ritonavir polymorphism, if available. We would like to know your future plans for this project.

With regard to ritonavir soft gelatin capsules, 100 mg (modified soft gelatin formulation):

4. Please provide data to support the [redacted] and in the capsules through the shelf life of the soft gelatin capsules.

5. Please address/clarify/verify the following:

a) Based on experience with [redacted] lots # 44-992-AR-R1, 45-712-AF, 45-716-AF, and 45-717-AF, you indicate that manufacture of [redacted] (NDA amendment Vol. 02, p. 091 and p.102). Please (i) provide a reason for allowing a [redacted] Manufacturing Directions, Amendment Vol. 02, p.072), and (ii) clarify whether the [redacted]

b) For [redacted] the following in-process tests will only be conducted at the completion of the [redacted]

c) [redacted]

d) [redacted]

e) [redacted]

6. Please provide batch analysis on primary stability lots, supportive stability lots, and pertinent sublots for an evaluation of the drug product specifications. We would like to discuss the limits of the DP specifications with you based on the available data from ritonavir drug substance (Item #2 above), ritonavir modified soft gelatin formulation, and ritonavir original T-1B formulation. We recommend that (i) the ~~ specification include a release as well as a shelf life specification, and (ii) the ~~ specification be determined by both microscopic examination and visual inspection.

7. Post approval stability protocols (Table 1-4) were found acceptable. We recommend that the ~~ specification be determined by both microscopic examination and visual inspection. Post approval stability commitments were found acceptable. In order to have the most complete picture of the resistance of ritonavir soft gelatin capsules to crystallization upon storage, we additionally recommend that a ~~

8. (a) An interim expiration dating period for the modified soft gelatin formulation will be granted based on the stability data submitted to the FDA prior to NDA approval. That is, a ~~ expiry based on the ~~ stability data submitted on 4/30/99, or a ~~ expiry if the ~~ physical stability update will be provided on 6/14/99.

   (b) We recommend that the expiration dating period be reassessed at a time when at least ~~ stability data on 3 post approval stability lots are available. The reassessment will be based on the data from the NDA stability lots, the post approval stability lots, and the ~~

9. Please provide information (i.e., product names, lot number, quantity, and analytical results) on method validation samples.

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/

Sylvia Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

cc:
Original NDA 20-945
Division File
HFD-530/CSO/Lynche
HFD-530/RRO/Struble
HFD-530/CR/Lo

Facsimile

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

/S/

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: May 28, 1999

To: Becky Welsh, Sr. Regulatory Administrator

/S/ 5/28/99

Address: Abbott Laboratories

From: Jeffrey Murray, M.D., M.P.H., Medical Team Leader
Kim Struble, Pharm.D., Regulatory Review Officer 5/28/99

NDA: 20-945

S

Subject: Norvir SEC Labeling comments

Listed below are the draft clinical and biopharm comments for the Drug Interaction sections of the package insert. Our changes are depicted as double-underlines. Comments regarding the SEC formulation in the Pharmacokinetic and How Supplied section will be provided following receipt of your proposed changes. Please also submit a combined patient package insert for both the oral and capsule formulations as separate NDA labeling supplements. We will be available to discuss any of these items with you during a teleconference.

1. Please amend the CONTRAINDICATIONS section as follows:

NORVIR ~~[redacted]~~ listed in Table 3 (see PRECAUTIONS: Table 4: Contraindications) because....

2. Please amend the WARNINGS: Drug Interactions section as follows:

The magnitude of the interactions between ritonavir and the drugs listed in Table 4: Predicted Drug Interactions ~~[redacted]~~ cannot be predicted with any certainty. When co-administering ritonavir with any agent listed in Table 4: Predicted Drug Interactions section, special attention is warranted

3. Please delete the text under PRECAUTIONS. ~~[redacted]~~ section.

4. Please include the following text and table under PRECAUTIONS: Drug Interactions

3 Draft Labeling Page(s) Withheld

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.

Sylvia Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

cc:
Original NDA 20-945
Division File
HFD-530/CSO/Lynche
HFD-530/RRO/Struble
HFD-530/MO/Murray

Facsimile

Appl_key: N020945

DRUG_NAM NORVIR(RITONAV SPONSOR: ABBOTT LABS

User: lynches Date: 4/20/99 1:37:01 PM Contacted: Jean-Louis Robert

Stephen Miller had a telephone discussion with Jean-Louis Robert (CPMP/EMEA) about the status of Norvir and Fortovase Soft Gel Caps in Europe and US.

Regarding Ritobavir Sift Gelatin Caps

Jean-Louis: was surprised to learn that Abbott expects

Stephen Miller: One registration batch in resubmitted NDA had approx — Form II in DS .

Jean-Louis: that batch probably not in European application.
maybe as Abbott to justify max level of Form II as a "variation" (supplement)

MCA will provide an inspector for the — manuf site

Should FDA and MCA inspectors be there at same time?

Appl_key: N020945

DRUG_NAM NORVIR(RITONAV **SPONSOR:** ABBOTT LABS

User: lynches **Date:** 6/16/99 10:31:53 AM **Contacted:** Becky Welch

FDA participants: Ko-yu Lo, Sylvia Lynche

Abbott participants: Becky Welch, Eugene Sun, John Morris, Laman AlRazzak, Efraim Shek, Soumajeet Ghosh, John Wolfinger

This teleconference was scheduled at the request of DAVDP to discuss the chemistry issues regarding the June 9, 1999 facsimile for Norvir (ritonavir capsules) soft gelatin 100 mg.

Action Items:

Drug 2 form substance has very limited data. After receive the annual report will decide on the outcome.

Will review data on the Impurity (related substance)

Abbott will check to see if there is a carton label as oppose to a bottle label.

Appl_key: N020945

DRUG_NAM NORVIR(RITONAV **SPONSOR:** ABBOTT LABS

User: lynches **Date:** /24/99 10:52:42 AM **Contacted:**

On February 24, 1999 Stephen Miller and myself had a telecon with Ms. Becky Welch and Dr. Eugene Sun to discuss the following recommendations for the resubmission of Ritonavir SEC.

The Division feels that rebsubmission in February 1999 is appropriate, given the medical desirability of reintroducing a capsule dosage form, and data which at present indicates that physical stability may be acceptable at — after release.

The following have been identified as major review issues, which could have a significant impact on our review of this application:

1. Uncertain status of the pivotal bioequivalence study (M98-966).
2. Data to support the proposed — expiration dating period. We will base our evaluation of stability on the — supplemental data / — in combination with the full — study report.
3. Timing of review cycle. Because of the medical need issues, the Division proposes to complete the review of this NDA one month (estimate July 1999) after the submission of the — stability update (estimate June 1999). This would correspond to an approximate 4.5 month review cycle for the resubmission.
4. Extension of expiration dating period. According to our present knowledge, there is some possibility of —

—)ecause of this situation, extension of expiry beyond — require more than the usual real time data from the stability lots.
5. post-approval stability commitments. The Division may recommend modifying the current proposals, which are for — This will be negotiated with the Applicant during review.

Abbott reponses:

Dr. Eugene Sun asked if they would advised of any deficiencies in the pivotal bioequivalences study prior to our anticipated July action. Dr. Stephen Miller replied yes, based on eariler discussions with Dr. Kellie Reynolds (Biopharma Team Leader).

Ms Becky Welch pointed out that expiry beyond — s very important for — Abbott and the Division will work out the best approach (extent of data and filing mechanism) during review of the NDA.

Appl_key: N020945

DRUG_NAM NORVIR(RITONAV SPONSOR: ABBOTT LABS

User: carmouzeg Date: 2/22/99 9:55:44 AM Contacted: Becky Welsh

Record of Teleconference

NDA:□□20-945

Date:□□February 22, 1999

Drug:□□Norvir (ritonavir)

Sponsor:□Abbott Laboratories

BETWEEN: Representatives of Abbott Laboratories
Becky Welch, Regulatory Affairs

AND:□Representatives of DAVDP
Grace Carmouze, Project Manager (for Sylvia Lynche)
Steve Miller, Ph.D, Chemistry Team Leader

SUBJECT: □Discussion of CMC issues regarding ritonavir capsules

Background:
This teleconference was scheduled to discuss CMC issues regarding the manufacturing of ritonavir capsules.

Discussion:□

- It was acknowledged that a 30-page fax from the sponsor was received on 2/19/99.
- It was requested that the sponsor send additional [redacted] data.
- The sponsor agreed to send these data by COB 2/22/99.
- It was agreed that feedback would be available 2/24/99 regarding the acceptability of an end of February filing.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Record of Teleconference

NDA: 20-945

Date: November 13, 1998

Drug: Norvir SEC

Sponsor: Abbott Laboratories

BETWEEN: **Representatives of Abbott Laboratories**
Becky Welch, Sr. Administrator, Regulatory Affairs

AND: **Representatives of DAVDP**
Steve Miller, Ph.D., Chemistry Team Leader
Heidi Jolson, M.D., M.P.H., Director
Debra Birnkrant, M.D., Deputy Director
Kim Struble, R.Ph., Regulatory Review Officer
Debra Gump, R.Ph., Regulatory Management Officer

SUBJECT: **Follow-up from November 12, 1998 teleconference**

Background:

This teleconference was held to clarify the result of the teleconference dated November 12, 1998 in reference to the timeline for NDA 20-945.

Discussion:

- Ms. Welch stated that the sponsor understood that the upcoming action that the Division would be taking on NDA 20-945 would be a "Not Approvable".

- Ms. Welch stated that they would have the ethanol data early in December 1998.

Concurrence:
HFD-530/Chem TL /S.Miller/ /S/ 1/19/98

cc:
IND
Division File
HFD-530/RRO/K.Struble
HFD-880/Biopharm ATL/K.Reynolds
HFD-530/Chem TL /S.Miller
HFD-530/Chem/K.Lo
HFD-530/RMO/D.Gump

Record of Teleconference

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Record of Teleconference

NDA: 20-945

Date: November 12, 1998

Drug: Norvir SEC

Sponsor: Abbott Laboratories

BETWEEN: **Representatives of Abbott Laboratories**
Becky Welch
Eugene Sun
Ann Hsu
Richard Bertz
John Bauer
Roland Catherall
Laman Alrazzak

AND: **Representatives of DAVDP**
Kellie Reynolds, Pharm.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Steve Miller, Ph.D., Chemistry Team Leader
Ko-yu Lo, Ph.D., Chemistry Reviewer
Heidi Jolson, M.D., M.P.H., Director
Debra Birnkrant, M.D., Deputy Director
Kim Struble, R.Ph., Regulatory Review Officer
Sylvia Lynche, Pharm.D., Regulatory Management Officer
Debra Gump, R.Ph., Regulatory Management Officer

SUBJECT: Discussion regarding upcoming action for NDA 20-945

Background:

This teleconference was requested to discuss the timeline for NDA 20-945. In light of the Norvir shortage in July 1998, the pending NDA for the Norvir SEC formulation was effected by this event.

Discussion:

1. Abbott proposes in the November 11, 1998 facsimile submission to amend the NDA with a commitment to provide [redacted] real time stability data on the modified SEC plus simulation data in support of an [redacted] shelf life for this product. The [redacted] data set would be available on January 30, 1999, and, under this scenario, [redacted] data could

not be provided prior to the proposed action date of February 24, 1999. Following a careful review of the proposed timeline and the information summary, DAVDP views that data to be amended in the next two months are insufficient/inadequate to demonstrate the product stability (i.e) over the proposed expiration dating period. DAVDP feels that extending the review clock by three months with the proposed amendments is not likely to resolve the outstanding stability issue, and that resubmission when more stability data are available would be preferred.

2. DAVDP informed the sponsor that an action letter for the NDA would be issued by the PDUFA date of November 24, 1998. This decision is based on scientific as well as regulatory consideration.

3. DAVDP stated that the CMC package for the resubmission should contain a minimum of real time stability data on the registration batches at the time of resubmission, with a stability update planned during the review cycle. The shelf life of the product will be determined based on the real time stability data as well as supporting data (if the results from experiments in Item 5a are favorable). Both DAVDP and Abbott agreed to further discuss the contents of the CMC package in subsequent teleconferences.

4. Abbott expressed their understanding of FDA's position for issuing an action letter and would be committed to generate adequate data in response to the FDA letter, but requested to have the option of being allowed to deviate from their commitment in the event of new developments. DAVDP agreed to revisit if situation justified.

5. DAVDP's comments for the 10/13/98 amendment and 11/11/98 fax are as follows:

   a) , in modified SEC -- Data from the original SEC has demonstrated a DAVDP views data on the modified SEC that could be amended by 1/99 as limited and insufficient to determine the for this formulation. If Abbott intends to extrapolate the observed from the original SEC as a supporting data to justify the shelf life of the modified SEC, more data points on the modified SEC should be collected to establish a simila between the two formulations. Potential supporting data to address the shelf life issue include: ; for the two SEC formulations, no crystal formation under the conditions examined in the simulation studies, and a favorable results from the bioavailability study that will assess the impact of crystalline Form II on the BA of the ritonavir SEC. DAVDP and Abbott plan to discuss the details in subsequent teleconferences.

   b) - The on-going stability protocol DAVDP requested that Abbott amend their protocol for The results of the study would provide answers to the questions: (i) in the modified SEC? Abbott agreed to revise their stability protocol.

   c) and Analysis (Experiment 4 and 5) -- DAVDP requests Abbott to extend the beyond the proposed period. Abbott indicates that examination of or a longer storage period is not a problem, however, may have some technical problems.

d) Stability of SEC containing Form II [redacted] and [redacted] levels (Experiment 6 for worse case scenario) – Abbott identifies that the [redacted] evels used in the two [redacted] lots were [redacted] and [redacted] Stability of the capsules will be monitored according to the protocol (p. 14, 10/13/98 submission).

e) [redacted] – Abbott clarifies that the placebo formulation #1-20 (Table 1, pp. 7-8, 10/13/98 submission) was prepared [redacted]

6. Regarding the bioavailability study, Abbott indicated that test formulation [redacted] dissolved plus [redacted] orm II) is based on data obtained from Experiment 2 (see 5e). See Dr. Reynolds's comment on study rationale and design.

7. Abbott clarified the objective of the bioavailability study that will be conducted to determine whether the presence of crystalline ritonavir contributes, positively or negatively, to the bioavailability of solubilized ritonavir. The purpose of this study is to determine whether (1) the crystals achieve some degree of solution in vivo and contribute to bioavailability, or (2) the crystals generate further precipitation in vivo, resulting in greater loss of bioavailability. This is not a bioequivalence study that will assess whether ritonavir capsules containing the "worst case scenario" amount of crystals are bioequivalent to capsules containing no crystals. DAVDP indicated that, although a bioequivalence study evaluating the effect of crystals was expected, the proposed study should provide useful information.

Concurrence:
HFD-880/Biopharm ATL/K.Reynolds/ 11/13/98
HFD-530/Chem TL /S.Miller// 11/18/98

cc:
IND
Division File
HFD-530/RRO/K.Struble
HFD-880/Biopharm ATL/K.Reynolds
HFD-530/Chem TL /S.Miller
HFD-530/Chem/K.Lo
HFD-530/RMO/D.Gump

Record of Teleconference

Address:v:\davdp\green\gump\gump\20945\telecons\981112.doc

Contact History For: N020945

Description: NORVIR(RETONAVIR)SEC **Sponsor:** ABBOTT LABS

Date Stamp	User	Contact	Reason
9/18/98 8:54:58 AM	gumpd	Becky Welch	Sponsor Initiated

Record of Industry Meeting

Meeting Date: □□September 18, 1998

NDA Number: □□20-945

Drug:□□□Norvir SEC□

Indication:□□Treatment of HIV Infection

Sponsors:□□□Abbott Laboratories

Type of Meeting: □CMC Meeting

FDA Attendees:
Stephen Miller, Ph.D., Chemistry Team Leader
Chi Wan Chen, Ph.D. Director, DNDC-III, Office of New Drug Chemistry
Ko-yu Lo, Ph.D., Chemistry Reviewer
Heidi Jolson, M.D., M.P.H., Director
Debra Birnkrant, M.D., Deputy Director
Walla Dempsey, Ph.D., Associate Director
Kim Struble, R.Ph., Regulatory Review Officer
Jeff Murray, M.D., M.P.H., Team Leader
Kellie Reynolds, Ph.D., Clinical Pharmacology and Biopharmaceutics Acting Team Leader
Arzu Selen, Ph.D., Clinical Pharmacology and Biopharmaceutics Deputy Director
Debra Gump, R.Ph., Regulatory Management Officer

External Constituents:

Abbott Laboratories:
Marcia Thomas, Vice President, QA/RA
Roland Catherall, PPD Regulatory Affairs
John Leonard, M.D., PPD Pharmaceutical Development
Eugene Sun, M.D., PPD Antiviral Venture Head
John Bauer, M.D., PPD, Analytical
Laman Al-Razzak, Ph.D., Sr. Project Manager PARD
John Wolfinger, Vice President QA-PPD
Becky Welch, Regulatory Affairs, Sr. Admin

Background:

The sponsor requested this meeting on August 28, 1998, as a result of the recent identification of a new polymorph (form II) of ritonavir. The formation of this new polymorph will have significant implications for the current NDA application of the ritonavir soft elastic capsule (SEC) formulation. The SEC formulation which is contained in NDA 20-945 is based on the [redacted] It has been found that form II is significantly less soluble that form I, requiring the sponsor to modify the original SEC formulation. The sponsor has determined that the solubility of form II in the SEC [redacted] is [redacted] Therefore the sponsor proposes that the existing SEC formulation can be modified slightly, without the addition of new excipients, to accommodate both form I and form II of ritonavir at a [redacted] capsule strength. 100 mg. The modifications that the sponsor proposes are as follows: 1) [redacted] and 2) [redacted] to ensure that ritonavir solubility is maintained throughout the manufacturing process and during subsequent storage conditions.

Discussion Items:

·□Dr. Miller asked the sponsor to [redacted]

Contact History For: N020945

Description: NORVIR(RETONAVIR)SEC **Sponsor:** ABBOTT LABS

Date Stamp	User	Contact	Reason

·□Dr. Miller recommended that the sponsor start to generate data now to identify the critical parameters that govern the crystallization of Form II from the dosage form. He asked them to try to identify the relative importance of . He asked the sponsor to provide the specification for n release and stability.

·□Dr. Miller stated that it would be very important to have data to assess the likelihood of crystallization under conditions that meaningfully simulate the SEC content after of storage. This data will be critical for review of the modified SEC application, since the levels of the capsule fill are anticipated to

·□Dr. Miller stated that he would like the sponsor to perform a bio study to assess and establish some amount of crystals in the capsules. Several different ways of preparing the capsules were discussed. It was agreed that the sponsor would submit this study for review. It was clarified that the sponsor will submit one bio study in November 1998 and one bio study in December 1998.

·□The sponsor was asked to provide toxicology data that was provided to the EMEA regarding the

·□Dr. Murray inquired about the possibility of the formation of crystals in the gut. The sponsor stated that crystal formation was very unlikely in the gut.

·□Dr. Miller asked the sponsor to identify the critical parameters for

·□Dr. Miller stated that

Meeting Minutes Prepared By:□□□□□□□□

Meeting Chair:□□□□□□□□□□

Attachments:
Concurrence:
HFD-830/Dir/C.W.Chen/ 10/29/98
HFD-530/Chem TL/S.Miller/ 11/17/98
HFD-530/Chem/K.Lo/ 11/13/98
HFD-530/MTL/J.Murray/ 10/27/98

cc: □
Original NDA
Division File
HFD-530/MTL/J.Murray
HFD-530/RRO/K.Struble
HFD-530/Dir/C.W.Chen
HFD-530/Chem TL/S.Miller
HFD-530/Chem/K.Lo
HFD-880/Biopharm ATL/K.Reynolds
HFD-530/RMO/D.Gump

Meeting Minutes

NDA 20-945/August 28, 1998 Correspondence

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: September 4, 1998

TO: Becky Welch, Regulatory Affairs

FROM: Ko-yu Lo, Ph.D., Chemistry Reviewer

THROUGH: Stephen Miller, Ph.D., Chemistry Team Leader

NDA: 20-945

SUBJECT: Chemistry Information Request

Please provide prior to our meeting the following:

1. Please describe your proposed CMC data package that would support the modified SEC formulation.

2. Please provide (or predict) the [redacted] in the [redacted], and the level of [redacted] the capsule contents of the modified SEC formulation at the [redacted] at the time of release, and on storage at 5°C.

3. Please determine the [redacted] in the anticipated capsule contents of the modified SEC formulation at the time of release. If this shows [redacted] at 5°C, what data are available to demonstrate that crystallization does not occur on storage at that temperature?

4. Please explain the relatively [redacted] observed for the prevalidation batches (E900505, E900507) using [redacted] as compared to approximately [redacted] levels observed for the rest of the stability batches. What are the [redacted], for the validation batches manufactured at the end of July?

5. Please summarize the stability data on the earlier SEC formulation that show the [redacted] in the capsule fill that are encountered during storage at 5°C. Although the [redacted] content of the fill was not a standing specification for these

studies, the importance of [redacted] makes it essential that some data at longer time points be available to guide our discussions.

The following comments and requests pertain to data that may be necessary for reaching a decision about approvability of a modified SEC dosage form.

1. How does adding [redacted] effect the manufacturing parameters for SEC manufacture?

2. If room temperature storage is planned for the time the capsules are held by the patients, some type of [redacted] study may be valuable to document the changes in [redacted] that may be anticipated to occur.

We are providing the following 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.

Debra A. Gump, R.Ph.
Regulatory Management Officer
Division of Antiviral Drug Products

cc:
Original IND
Division File
HFD-530/MO TL/J.Murray
HFD-530/RRO/K.Struble
HFD-530/Chem TL/S.Miller
HFD-530/Chem/K.Lo
HFD-530/RMO/D Gump

Klimp
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 11, 1998

TO: Jeanne Fox, Regulatory Affairs

FROM: Janice Jenkins, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader

8/11/98

THROUGH: Sam Maldonado, M.D., M.P.H., Acting Team Leader

8/11/98

NDA: 20-945

SUBJECT: Labeling Changes to Pharmacokinetics Section and Information Request

Labeling Change:

1. **Change**

[———]

To

"After a single 600 mg dose under non-fasting conditions, ———

[———]

2. For the last sentence in the first paragraph ("Relative to fasting conditions, the extent of absorption of ritonavir from soft gelatin....."), please report the change in extent of absorption as the mean and standard deviation of the individual differences.

Information Request:

1. Please provide a copy of the formulation for [redacted] (batch # 23-546-AR-R1/7321N), similar to table 1 page 32 of Volume 1 "List of Ingredients - Standard Amount and Ranges of Each Ingredient in Ritonavir [redacted] ng Soft Elastic Capsules".

We are providing the following 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/

Debra A. Gump, R.Ph.
Regulatory Management Officer
Division of Antiviral Drug Products

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: July 9, 1998

TO: Rebecca A. Welch
Sr. Regulatory Affairs Administrator

ADDRESS: Abbott Laboratories
100 Abbott Part Road
Abbott Park, IL 60064

FROM: Debra A. Gump, Regulatory Management Officer, HFD-530.

THROUGH: Ko-Yu Lo, Ph.D., Chemistry Reviewer, HFD-530
Stephene P. Miller, Ph.D., Chemistry Team Leader, HFD-530

NDA: 20-945 Ritonavir Capsules, Soft Gelatin

SUBJECT: CMC Recommendations/Comments/Requests

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1. Oleic acid manufactured at [redacted] was [redacted] (Vol. 6, p. 158). Please identify the source of raw materials and the site of production for oleic acid (i.e. [redacted], that will be used to manufacture the production batches of Ritonavir SEC. If the [redacted] sourced oleic acid is to be used, please (a) amend this formation to the NDA and [redacted] DMF # [redacted] with a [redacted] statement, and (b) indicate whether the DP specification on [redacted] will remain as the proposed NMT [redacted] We would like to discuss the specifications for Ritonavir SEC with you when this issue is clarified.

2. There is a typo in Document S43D.03990 and S43D.03994 Formula/Process Specification for Ritonavir SEC (Vol. 2, p. 018 and p. 023 respectively). Please change the amount of BHT from [redacted] to [redacted] and amend the revised document to the NDA.

3. [redacted]

4. Please provide typical chromatogram of Ritonavir SEC analyzed by Method [redacted] (Vol. 2, p.102).

5. Based on the [redacted] stability data of product stored at 5° C, we recommend an expiry period of [redacted] for Ritonavir SEC when stored at 5° C (2° - 8° C). Based on the [redacted] of 25° C/60% RH stability data for product stored for [redacted] at 5° C, the proposed label statement of [redacted] was found acceptable.

6. Post approval stability protocol and move protocol were found acceptable. However, there is a typo in these documents (Vol. 6, p. 257). Please change [redacted] to [redacted] and amend the revised protocols to the NDA.

7. The proposed proprietary name and established name NORVIR[R] [redacted] is not acceptable due to our current CDER preference to avoid suffixes, and the lack of a "soft gelatin capsule" dosage form category in the current USP. You may wish to consider other options, and revise the labeling accordingly. One possible option is NORVIR[R] (ritonavir capsules) soft gelatin. In such case, the heading of the package insert and the container labels will be the following:

   Package Insert

   NORVIR[R]

   [redacted]

   Container Labels

   [redacted]

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/

Debra A. Gump.
Regulatory Management Officer,
Division of Antiviral Drug Products

Concurrence:
HFD-530/Chem/KYLo
HFD-530/Chem/SMiller
HFD-530/CSO/DGump

cc:
Original NDA 20-945
HFD-530/Chem/KYLo
HFD-530/Chem/SMiller
HFD-530/CSO/DGump
HFD-830/CChen

HIV 020 Gump

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: July 1, 1998

TO: Becky Welch, Regulatory Affairs

FROM: Janice Jenkins, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader 7-1-98

THROUGH: Jeff Murray, M.D., M.P.H., Acting Team Leader 7-1-98

NDA: 20-945

SUBJECT: Questions regarding the ——— in the proposed dissolution method.

Please provide the following information regarding the proposed dissolution method for ritonavir soft elastic capsules:

1. Which ——— were evaluated?
2. What ——— concentrations were used?
3. What criteria were used to establish the most appropriate ——— for use in the dissolution medium for this product (submit relevant data in support of the choice).

We are providing the following 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.

Debra A. Gump, R.Ph.
Regulatory Management Officer
Division of Antiviral Drug Products

cc:
Original NDA
Division File
HFD-530/ATL/S.Maldonado
HFD-530/RRO/K.Struble
HFD-530/Biopharm TL/J.Jenkins
HFD-530/RMO/D.Gump

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Record of Teleconference

NDA: **20-945**

Date: **July 9, 1998**

Drug: **Norvir SEC**

Sponsor: **Abbott Laboratories**

BETWEEN: **Representatives of Abbott Laboratories**
Becky Welch, Regulatory Affairs

AND: **Representatives of DAVDP**
Debra Gump, R.Ph., Regulatory Management Officer
Ko-yu Lo, Ph.D., Chemistry Reviewer

SUBJECT: Discussion of ——— used in the SEC formulation

Background:
This teleconference was scheduled to discuss the use of the ——— in the SEC formulation. The ——— used in the US is not an acceptable ——— for use in Europe by the EMEA. Due to this recent information the sponsor proposes to delete the use of the ——— in both the US and in Europe.

Discussion:

- It was agreed that the sponsor would delete the ——— from the SEC formulation. The sponsor will also provide a revised description of the capsule in the label.

- Dr. Lo asked the sponsor provide CMC information on the ——— lot in support of the proposed ———.

- It was clarified that the source of oleic acid will be changed to a ——— source for the production batches of the SEC. ——— statement will be submitted.

- As a result of manufacturing site change for oleic acid, the current HPLC method ——— for determination of ——— in the SEC was found not suitable. The sponsor stated that they would be submitting a revised method for review.

- Dr. Lo stated that the proposed name NORVIR [redacted] was not acceptable due to our current CDER preference to avoid [redacted] and the lack of a "[redacted] dosage form category in the current USP.

Concurrence:
HFD-530/Chem/K.Lo/ 11/23/98

cc:
Original IND
Division File

Record of Teleconference

Address:v:\davdp\green\gump\gump\20945\telecons\980709.doc

Contact History For: N020945

Description: NORVIR(RETONAVIR)SEC **Sponsor:** ABBOTT LABS

Date Stamp	User	Contact	Reason
5/28/98 8:42:27 AM	gumpd	Becky Welch	Sponsor Initiated

Record of Teleconference

NDA:□□20-945

Date:□□May 28, 1998

Drug:□□Norvir SEC

Sponsor:□Abbott Laboratories

BETWEEN:□Representatives of Abbott Laboratories
Becky Welch, Regulatory Affairs

AND:□□Representatives of DAVDP
Debra Gump, R.Ph., Regulatory Management Officer
□□□□Ko-yu Lo, Ph.D., Chemistry Reviewer

□□SUBJECT: □Discussion of CMC issues regarding Norvir SEC
□of the

Background:
This teleconference was scheduled to discuss CMC issues regarding the manufacturing of Norvir SEC.

Discussion:□

· It was clarified that the drug substance would be the —— material and would only be used for the SEC formulation.

· The sponsor stated that the Florida District has recommended approval for the —— manufacturing process for the SEC.

cc:
Original NDA
Division File

Record of Teleconference

Address:v:\davdp\green\gump\gump\20945\telecons\980528.doc

6/10/98 8:35:15 AM gumpd Becky Welch FDA Initiated

Ms. Gump telephoned Ms. Welch to request a disk for the Norvir SEC label. Ms. Welch stated that she would send one ASAP.

6/23/98 9:44:56 AM gumpd Becky Welch FDA Initiated

Ms. Gump contacted Ms. Welch to inquire about the study report for the bioequivalence study (M96-617)lists Lot #23-546-AR-R1 as that for the — ng SEC. According to the dissolution data presented in Table IV of Volume 4 p. 174, this lot number corresponds to dosage strength —— , which is not the subject of this NDA. The table identifies Lot #23-544-AR-R1 as the —— strength used in the study. She asked the sponosr to clarify the Lot # used for the — mg capsules used in the bioequivalence study.

Contact History For: N020945

Description: NORVIR(RETONAVIR)SEC **Sponsor:** ABBOTT LABS

Date Stamp	User	Contact	Reason
11/21/97 12:41:01 PM	gumpd	Becky Welch	FDA Initiated

Ms. Gump called Ms. Welch to inquire about the NDA. Ms. Welch stated that the NDA will be sent Friday, November 21, 1997. It will be 10 volumes. Ms. Gump asked to have 3 desk copies of Volume 1. Ms. Welch stated that would not be a problem.

11/26/97 12:46:54 PM	gumpd	Becky Welch	FDA Initiated

Ms. Gump called and left a message on Ms. Welch's voicemail, that even though the NDA did not incur a User Fee, the User Fee sheet still needed to be completed and submitted to the NDA.

3/25/98 10:31:14 AM	gumpd		No Action

DAVDP Attendees: Barbara Davit, Ko-Yu Lo, Steve Miller, Steve Gitterman, Kim Struble, Walla Dempsey, Deb Gump

Chemistry:
1. Dr. Lo stated that there were no manufacturing problems with this NDA, although she did have some questions for the sponsor.
2. The inspection was scheduled for this week.
3. The sponsor plans to update the stability data at ———
4. Dissolution: the use of ——— method looks reasonable
5. Dr. Lo to look at DMF

Biopharm:
No comments at this time.

Clinical:
No comments at this time.

5/15/98 8:40:40 AM	gumpd	Becky Welch	FDA Initiated