

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-417

CHEMISTRY REVIEW(S)

Memorandum

Date: January 14, 2010

To: **NDA 22-417** [NORVIR (ritonavir), Tablets, 100 mg]

From: Dorota Matecka, Ph.D., Chemistry Reviewer, Branch IV, DPMA II, ONDQA

Through: Steve Miller, Ph.D., Acting Branch Chief, Branch IV, DPMA II, ONDQA

Re: **CMC Recommendation for NDA 22-417**

The overall recommendation regarding the CGMP status of the facilities involved in the manufacture of the drug substance and drug product via this NDA was changed by the Office of Compliance from "WITHHOLD" to "ACCEPTABLE" on December 18, 2009 (see attached). The action taken on the first review cycle was Complete Response because of the withhold recommendation for the drug product manufacturing site, Abbott, Germany.

Therefore, from the chemistry, manufacturing and controls standpoint, the NDA is now recommended for approval.

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 22417/000	Sponsor:	ABBOTT LABS
Org. Code:	530		200 ABBOTT PARK RD
Priority:	3S		ABBOTT PARK, IL 60064
Stamp Date:	19-DEC-2008	Brand Name:	RITONAVIR
PDUFA Date:	11-FEB-2010	Estab. Name:	
Action Goal:		Generic Name:	RITONAVIR
District Goal:	13-DEC-2009	Product Number; Dosage Form; Ingredient; Strengths	001; TABLET, FILM COATED; RITONAVIR; 100MG

FDA Contacts:	J. DAVID	Project Manager	301-796-4247
	D. MATECKA	Review Chemist	301-796-1415
	S. MILLER	Team Leader	301-796-1418

Overall Recommendation:	ACCEPTABLE	on 18-DEC-2009	by A. INYARD	()	
	ACCEPTABLE	on 11-DEC-2009	by E. JOHNSON	(HFD-320)	301-796-3334
	WITHHOLD	on 14-OCT-2009	by E. JOHNSON	(HFD-320)	301-796-3334

Establishment:	CFN: 9610142	FEI: 3002807401	
	ABBOTT GMBH & CO. KG KNOLLSTRASSE LUDWIGSHAFEN, GERMANY		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	(b) (4)	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-DEC-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	CFN: 1411365	FEI: 1411365	
	ABBOTT LABORATORIES 14TH & SHERIDAN RD NORTH CHICAGO, IL 60064		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-DEC-2009		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: (b) (4)
Profile: (b) (4) OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-DEC-2009
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: (b) (4)
Profile: (b) (4) OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-DEC-2009
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22417	ORIG-1	ABBOTT LABORATORIES	RITONAVIR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DOROTA M MATECKA
01/14/2010

STEPHEN P MILLER
01/14/2010

NDA 22-417

NORVIR[®] (ritonavir) Tablets, 100 mg

Abbott Laboratories

Dorota Matecka, Sharmista Chatterjee and Bogdan Kurtyka

ONDQA

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CHEMISTRY REVIEW



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Chemistry Review Data Sheet

1. NDA 22-417
2. REVIEW #: 1
3. REVIEW DATE: 15-Oct-2009
4. REVIEWERS: Dorota Matecka, Sharmista Chatterjee, Bogdan Kurtyka
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	18-Dec-2008
BC	29-Jan-2009
BC	05-Feb-2009
BC	13-Feb-2009
BC	31-Mar-2009
IR	19-May-2009
BC	03-Jun-2009
IR	17-Jul-2009
BC	17-Jul-2009
BC	05-Aug-2009
IR	08-Sep-2009
BC	22-Sep-2009
IR	08-Oct-2009
BC	13-Oct-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	18-Dec-2008
BC	29-Jan-2009
BC	05-Feb-2009
BC	13-Feb-2009
BC	31-Mar-2009

Chemistry Review Data Sheet

BC	03-Jun-2009
BC	17-Jul-2009
BC	22-Sep-2009
BC	13-Oct-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Abbott Laboratories
Address:	200 Abbott Park Road, PA76, AP30-1E Abbott Park, IL 60064-6157
Representative:	Mary Konkowski Manager, Global Pharmaceutical Regulatory Affairs
Telephone:	(847) 938-3063

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NORVIR®
- b) Non-Proprietary Name (USAN): ritonavir tablets
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Film-coated tablet

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx OTC

Chemistry Review Data Sheet

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

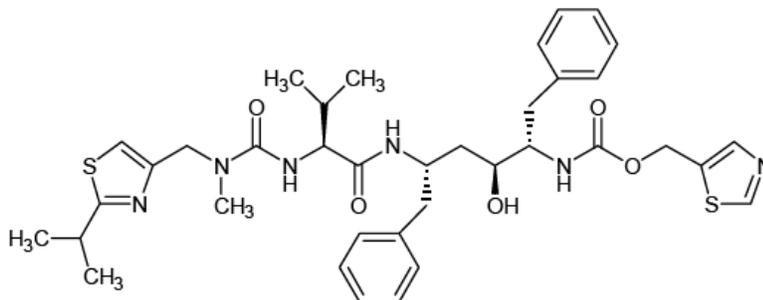
_____ SPOTS product – Form Completed

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*, 8R*, 10R*, 11R*)]-

CAS Registry number: 155213-67-5
 Molecular formula: C₃₇H₄₈N₆O₅S₂
 Molecular weight: 720.95
 Structural formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	4	N/A		
	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	4			

Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-659	Norvir Oral Solution
NDA	20-945	Norvir SGC
NDA	21-906	Kaletra (lopinavir/ritonavir) Tablets, 200 mg/50 mg

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	WITHHOLD	14-Oct-2009	
Pharm/Tox	Acceptable	30-Mar-2009	
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	Acceptable	04-Sep-2009	
EA	N/A (request for a categorical exclusion)		
Microbiology	N/A		

The Chemistry Review for NDA 22-417

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, an overall "WITHHOLD" site recommendation from the Office of Compliance has been made on October 14, 2009. Therefore, from the CMC perspective, this NDA is not recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

The review of this NDA has been conducted by a team of three reviewers. Sharmista Chatterjee reviewed the Pharmaceutical Development, Manufacture, and Comparability Protocol sections of the NDA (P2.3, P3, and R2, respectively). Bogdan Kurtyka conducted the review of all NIR methods proposed for the testing of ritonavir extrudate and finished product. Dorota Matecka reviewed the remaining subsections of the drug product section (P).

A. Description of the Drug Product(s) and Drug Substance(s)

The proposed drug product, Norvir® (ritonavir) Tablet, contains 100 mg of ritonavir drug substance, a strong CYP3A inhibitor.

Per pre-NDA agreements, all CMC information for the ritonavir drug substance, has been cross referenced to the approved NDA 20-659 for Norvir (ritonavir) Oral Solution. Ritonavir is a BCS class IV compound (low solubility and low permeability). Two crystalline forms (I and II) of ritonavir have been isolated. (b) (4)

The proposed drug product, ritonavir tablets, 100 mg, is an (b) (4), a white film-coated oval tablet debossed with the corporate Abbott "A" logo and the Abbo-Code NK. This tablet is a new dosage form of ritonavir that was developed in order to obtain a solid solution formulation using the hot-melt extrusion technology, a process similar to the manufacturing process of Kaletra (lopinavir/ritonavir, 200 mg/50 mg) Tablets (approved via NDA 21-906). (b) (4)

(b) (4)
(u) (4)

Executive Summary Section

(b) (4)

(b) (4) The currently proposed ritonavir tablet formulation includes one additional excipient, calcium hydrogen phosphate as (b) (4), as compared to the lopinavir/ritonavir tablet formulation. All inactive ingredients of this proposed formulation (including the film coating) are commonly used pharmaceutical excipients that are utilized at levels previously approved for other dosage forms, except for copovidone, which would be higher for the proposed formulation than for Kaletra Tablets at the recommended therapeutic dose. This issue was consulted with the pharm/tox reviewer of this application who found the proposed level of copovidone acceptable (please refer to review by Dr. Pritam Verma, dated 30-Mar-2009).

Ritonavir tablets are manufactured (b) (4)

(b) (4)

(b) (4)

Executive Summary Section

(b) (4) Design space is defined in terms of linear ranges of these CPP. It is noted that the applicant has not per se defined a list of Critical Quality Attributes (CQA) in the NDA, though the term CQA has been used throughout the NDA. It can be inferred from the information provided that the CQA are: finished drug product chemical and physical stability, assay, content uniformity and dissolution.

The manufacturing section (section P.3.3) includes a detailed description of the manufacturing process, with target values of all the NCPP and ranges shown in bold for all the CPP. Per agency's recommendation this section was revised to include details about (b) (4) concurrent with provided development data. Since the (b) (4)

The specification tests for the finished drug product, ritonavir tablets, 100 mg, include identification, assay, degradation products, water content, uniformity of dosage units, dissolution and description. In addition, microbial limit testing will be performed as a Periodic Quality Indicator Test using reduced testing (skip lot) for TAMC, TYMC, and E. coli. on at least two batches per year. During the review, a number of deficiencies relating to the drug product specification (tests, analytical procedures and acceptance criteria) were identified and several comments requesting additional information and/or revisions were forwarded to the applicant. (b) (4)

In addition, the originally proposed Uniformity of Dosage Units testing for the drug product included Weight Variation as an alternate test (per USP<905>). In response to the Agency's comment, this proposed test was revised to include testing by Content Uniformity only since the proposed ritonavir tablets contain 100 mg ritonavir (b) (4) by weight), which is below the 25 mg/25% threshold in USP <905>. The proposed acceptance criteria for degradation products of ritonavir are similar to the ones previously approved for Kaletra Tablets. The qualification at the shelf-life limit for each of the specified degradation products was based on human exposure of the impurities in other Norvir and Kaletra commercial products. The ritonavir (b) (4) (b) (4) is the only degradant that has a higher daily exposure from the ritonavir tablet than from the currently approved Norvir SGC or Norvir Oral Solution. The issue of a daily (b) (4) exposure and the proposed limit have been consulted with the pharm/tox reviewer of this application who found the proposed acceptance criterion for (b) (4) acceptable (refer to review by Dr. Pritam Verma, dated 30-Mar-2009).

Stability information provided in the initial NDA submission and updated via the amendment dated 31-Mar-2009 include stability data for three batches of tablets (one pilot-scale and two

Executive Summary Section

production-scale batches) stored at 25°C/60% RH and 30°C/75% RH. The 12-month acceptable stability data for 30-count/60 mL bottles and 6-month acceptable stability data for 60-count/100 mL bottles have been provided via the 31-Mar-2009 amendment. The 6-month results of accelerated testing at 40°C/75% RH have also been provided for those batches. Additionally, results of open dish studies and stability data at 50°C/amb for ritonavir tablets, 100 mg, were submitted. Supportive stability information includes stability results for Kaletra Tablets. This overall stability information supports the expiration dating of 18 months for the drug product.

The proposed labeling and container labels, after including the DMEPA recommendations, have been found acceptable.

(b) (4)

**B. Description of How the Drug Product is Intended to be Used**

The approved dose of ritonavir for the treatment of HIV infection is 600 mg BID. Additionally ritonavir is used at reduced doses (100 mg once daily to 200 mg twice daily) in combination with other approved protease inhibitors.

Norvir (ritonavir) Tablets, 100 mg, are packaged in 30-count bottles for the U.S. market and 60-count bottles for PEPFAR. The 30-count container/closure system includes 60 mL (2 oz) HDPE bottles with (b) (4) child resistant caps; and the 60-count container/closure (b) (4) include 100 mL round and 3 oz square HDPE bottles with (b) (4) child resistant caps.

The storage conditions statement are recommended for this drug product: “Store NORVIR film-coated tablets at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°- 86°F) [see USP controlled room temperature]. Dispense in original container or USP equivalent tight container (60 mL or less). For patient use: exposure of this product to high humidity outside the original or USP equivalent tight container (60 mL or less) for longer than 2 weeks is not recommended.” This statement is similar to the one approved for Kaletra Tablets. The expiration dating for the product is 18 months.

C. Basis for Approvability or Not-Approval Recommendation

The initial NDA submission and amendments provide adequate chemistry, manufacturing and controls information for the proposed drug product, Norvir (ritonavir) Tablets, 100 mg.

Executive Summary Section

However, due to the deficiencies identified at one of drug product manufacturing facility, Abbott GmbH, Germany, an overall “WITHHOLD” recommendation was made on October 14, 2009 by the Office of Compliance for the facilities submitted in this NDA. Therefore, this application is not recommended for approval from the CMC point of view.

III. Administrative

A. Reviewer’s Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22417	ORIG-1	ABBOTT LABORATORIES	RITONAVIR

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/s/

DOROTA M MATECKA
10/15/2009

SHARMISTA CHATTERJEE
10/15/2009

NORMAN R SCHMUFF
10/15/2009

Initial Quality Assessment
Branch IV
Pre-Marketing Assessment Division II

OND Division: Division of Anti-Viral Products
NDA: 22-417
Applicant: Abbott
Stamp Date: Dec 19, 2008
Proposed Trademark: Norvir
Established Name: Ritonavir
Dosage Form: Tablets
Route of Administration: Oral
Strength: 100 mg
Indication: Therapy for HIV Infection
Reviewer: Dorota Matecka
PAL: Stephen Miller

	YES	NO
Acceptable for filing:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Summary and Critical Issues

Summary

This NDA is in the eCTD format and was available in the EDR on the stamp date of Dec 19, 2008. It is a new dosage form of ritonavir using hot-melt extrusion to prepare a solid solution formulation that aims to achieve the room temperature stability (chemical and solid-state form) and high bioavailability of the Kaletra (lopinavir and ritonavir) Tablets, which uses a similar manufacturing process. This will be reviewed on a standard (10 month) timeline.

This tablet will be used primarily as a PK booster for other antiretroviral drugs (ARVs), based on ritonavir's potent inhibition of the cytochrome CYP 3A4. Typical daily doses for boosting of other ARVs are 100-200 mg per day. Ritonavir can also be used as an antiretroviral agent (HIV protease inhibitor) when dosed at 600 mg BID. Contrary to recommendations from DAVP, the proposed package insert focuses almost exclusively on the rarely-used 600 mg BID therapeutic dose. This may be a clinical review issue. Abbott provides further discussion on the indications in an amendment to the ritonavir IND (Dec 22, 2008 IND 43,718 / SDN-641).

Bioequivalence studies are included in this submission. Somewhat higher values of PK parameters relative to earlier formulations were discussed in PreNDA meetings.

IND Development

The discussion and agreements reached during the PreNDA meeting (Sept 23, 2008) are available from DARRTS, and a copy is located at:

ondcS1 on cdsnas\DPA2\Branch 4\DAVP Applications\43 718 Ritonavir including Norvir Tab NDA\Final FDA Mtg Minutes Sept 23 2008 from DARRTS.pdf

Some documentation on earlier IND development is located at:

ondcS1 on cdsnas\DPA2\Branch 4\DAVP Applications\43 718 Ritonavir including Norvir Tab NDA\43 718 Ritonavir.doc

Other Applications that are Relevance to this Review

NDA 21-906 Kaletra (lopinavir and ritonavir) Tablets, 200 mg / 50 mg; approved Oct 2005; similar hot-melt extrusion technology. A copy of the CMC NDA review is located at: ondcS1 on cdsnas\DPA2\Branch 4\DAVP Applications\51 715 Kaletra\NDA Reviews of Kaletra Tablets\21906 CMC review from DFS.doc

NDA 20-945 Norvir (ritonavir) Soft Gelatin Capsules, 100 mg. Approved June 1999; semi-solid fill contains ritonavir solution in co-solvents.

NDA 20-659 Norvir (ritonavir) Oral Solution, 80 mg/mL. Approved March 1996; solution in co-solvents; palatability issues.

NDA 20-680 Norvir (ritonavir) Hard Gelatin Capsules, 100 mg. Approved March 1996; Discontinued in 1999 due to lowered bioavailability caused by crystallization of newly discovered Form II polymorph (b) (4)

Drug Substances

Per agreement at the Sept 23, 2008 PreNDA meeting, Abbott will cross-reference the Norvir Oral Solution NDA (20-659) for all drug substance information, and also provide a summary of significant changes since approval of the Norvir Soft Gelatin Capsule in 1999. Accordingly, the following table is provided in Module 3:

Table 1. History of Manufacturing and Control Changes for Ritonavir Drug Substance

NDA	Supplement	Date Submitted	Date Approved	Filing Type	Description
20-659	S-024	03/02/00	09/01/00	CBE-0	(b) (4)
20-945	S-011	05/30/02	09/03/02	PA	
20-659	S-029	08/28/02	02/28/03	CBE-30	
20-659	S-031	07/22/03	01/22/04	CBE-0	
20-659	S-037	12/27/06	06/28/07	CBE-30	
20-659	S-041	11/28/07	05/29/08	CBE-30	

NDA 20-659, Norvir Liquid
 NDA 20-945, Norvir SGC

(b) (4)

Drug Product

The product is white film-coated oval tablet debossed with the corporate Abbott "A" logo and the Abbo-Code NK.

The manufacturing process involves (b) (4)

(b) (4)

For the related product, Kaletra Tablets, Abbott has submitted a supplement for (b) (4)

The registration batches consist of:

- 07-014263/4 pilot scale (b) (4) manufactured in May 2007
- 07-014310 production scale (b) (4) manufactured in Aug 2007
- 07-014311 production scale (b) (4) manufactured in Aug 2007

The commercial scale is (b) (4)

EES

Already entered (Jan 8, 2008 by D. Matecka)

Pharmaceutical Development, Quality Control Strategy including DP Specifications

Approx 100 pages are included in P2, and describe how the process was developed:

- Formulation development studies

- DOE studies were used to establish the process parameters for the (b) (4) step and the (b) (4) step.
- (b) (4)
- Set-points and ranges are proposed for critical parameters
- Ranges or 1-sided limits are generally proposed for non-critical parameters

The manufacturing process description in P.3.3 generally has ranges shown for the critical and non-critical process parameters, with critical ones identified as such in bold text. Some process parameters (b) (4) are not part of the process description.

(b) (4)

(b) (4)

There is no test to verify (b) (4) The justification for this (in 3.P.5.6.9) mentions the in-process test for clarity of the (b) (4) (b) (4) (b) (4)

that was used during development going to be included in the on-going and future stability studies? Would it be worth adding a note to future reviewers about this test, which could be used when future changes to the DP manufacturing process or the container-closure might impact the stability towards (b) (4)

(b) (4)

Assay may be determined by Near IR Spectroscopy (NIR) of table cores as an in-process test. Is more information provided than the extremely brief summary in Section 3.2.P.5.2? Would it be valuable to obtain input from a Chemist with NIR expertise?

The DP specification table is included in the Appendix to this IQA.

Packaging Configuration

- HDPE bottle (60 mL) of 30 tablets with child-resistant cap and induction seal (US marketing)

- HDPE bottle (100 mL) of 60 tablets with child-resistant cap and induction seal (non-US, e.g., PEPFAR)
- HDPE bottle (3 oz) of 60 tablets with child-resistant cap and induction seal (non-US, e.g., PEPFAR)

Stability

The original NDA submission contains 6 mo of primary stability data which is consistent with the plans made during the PreNDA meeting and in a March 2008 amendment (SDN-631). For some reason the stability studies on the registration lots were not started until Dec 7, 2007 (approximately 3 months and 6 months after manufacture).

(b) (4)

Open-dish studies on (b) (4) occurred when samples with approximately (b) (4) were held at 40 deg C for 3 months, but not when held at 30 deg C for 6 mo. In these experiments the Tg was approximately 27 deg C.

For chemical stability, the (b) (4) appears to be the one degradant which can give higher exposures (mg/day at maximum dose) compared to the previously-approved ritonavir drug products. The new animal tox data provided in the Justification of Specifications section (Table 4) should be evaluated by the Pharm/Tox reviewer to verify that the proposed acceptance criteria for (b) (4) is qualified. How is the acceptance criterion of (b) (4) justified given that the level in the registration batches was approx (b) (4) with little change on stability?

At the PreNDA meeting (Sept 23, 2008), we discussed plans for a 30-count bottle for US distribution, and a 60-count bottle that would be used for distribution outside the US (e.g., for the PEPFAR program). Agreements were reached for submission of 6-mo data on the 30-count bottle and 1-mo data on the 60-count bottle, with the data set including long-term data at 30°C/75%RH, which is the long-term condition that is recommended for PEPFAR applications.

The tablets in the 60-count stability samples are from the pilot scale batch which was manufactured in May 2007. Since the 60-count studies were initiated in Aug 2008, what is used for the “initial values?”

In addition to the primary stability data on the registration batches, supportive stability data is provided on Kaletra Tablets and on an earlier batch of Norvir Tablets with a (b) (4) film-coating (06-007311 manufactured May 2006).

The proposed expiry period is 18 months. The proposed storage conditions are:

- Controlled Room Temperature for climatic Zones I/II
- Not more than 30°C for climatic Zones III/IV (this is the same as the red variant of Kaletra tablets which is intended for the PEPFAR program)

There is a statement that tablets that patients should limit exposure of tablets to high humidity outside the bottle (or equivalent USP tight container) to 2 weeks. A similar statement was crafted for the Kaletra tablets, based on open dish stress studies.

Labeling

Color mock-ups of the container labels (bottle labels) are provided in Module 1. For each count (30 and 60 tablets) there are two bottle labels which appear identical – what is the purpose?

The 60 count bottle labels do not contain NDC numbers, which is probably appropriate given that they will not be marketed within US. Interestingly, these non-US labels include a yellow bar and the US labels have a red bar. Isn't this the opposite color scheme from the Kaletra Tablets, where the non-US tablets have a red film-coat, and the US tablets have a yellow film-coat? A copy of the supplement review for the PEPFAR color variant of the Kaletra Tablet is located at: ondcS1 on cdsnas\DPA2\Branch 4\DAVP Applications\51 715 Kaletra\NDA Reviews of Kaletra Tablets\21906 S-001 CMC review from DFS.doc

The 60 count bottles include the proprietary name, Norvir, in addition to the established name. This is different from the Kaletra example, where the bottles for the PEPFAR program had only the established name. We have recommended that PEPFAR products generally not have a proprietary name on the container labels. However, for drugs where the proprietary name is already associated with an approved US product, it may be acceptable to include the proprietary name on the PEPFAR or non-US container label.

There are no carton labels – do we want to suggest that carton labels be submitted to give that option if it is desired by some recipient nations in the PEPFAR program?

The Package insert is provided in the PLR format.

Early action needed:

1. Pharm/Tox evaluation of new qualification data for [REDACTED] (b) (4) exposure.
2. Determine if input from a Chemist with NIR expertise would be valuable for the Assay procedure in the DP specification.

Comments for 74-Day Letter

- 1) None identified

D. Comments/Recommendation:

Based on the information assessed for this IQA, this NDA is judged to be complete for filing. Issues which may merit discussion are highlighted with a question mark in this IQA.

Stephen P. Miller, Ph.D.
Pharmaceutical Assessment Lead

See DFS
Date

Norman Schmuff, Ph.D.
Branch Chief

See DFS
Date

Appendix – DP Components; DP Specification

Table 1. Composition of Ritonavir, Film-Coated Tablets, 100 mg

Component	Quality Standard	Function	Amount/Unit
	(b) (4)		
Ritonavir	USP	Active	100.0 mg
Copovidone, Compendial (b) (4)	NF	[Redacted]	(b) (4)
Sorbitan Monolaurate Compendial	NF		
Colloidal Silicon Dioxide, Compendial	NF		
	(b) (4)		
Sodium Stearyl Fumarate, Compendial	NF		
Colloidal Silicon Dioxide, Compendial	NF		
Anhydrous Dibasic Calcium Phosphate, Compendial	USP		
Uncoated Tablet Weight	N/A		
(b) (4)	(b) (4)		
	USP		
Total Tablet Weight	N/A		

(b) (4)



(AJ) 2 pages of CMC has been withheld in full immediately following this page as B4 CCI/TS

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-417 Applicant: Abbott

Stamp Date: Dec 19, 2008

Drug Name: Norvir Tablets NDA/BLA Type: 3

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		In Section 1.1.2
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?		X	All sites have been entered into EES
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		By reference to NDA 20-659
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases and at the pre-NDA meetings been included?	X		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		In Section 1.4.1
10	Is information on the investigational formulations included?	X		
11	Is information on the methods validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?			NA

IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. **None identified**

Stephen P. Miller, Ph.D.

Jan 27, 2008

Reviewing Chemist

Date

Norman Schmuft, Ph.D.

See DFS

Team Leader/Supervisor

Date

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Stephen Paul Miller
1/27/2009 01:32:57 PM
CHEMIST
IQA for orig NDA

Norman Schmuff
1/29/2009 06:05:36 PM
CHEMIST