

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206352Orig1s000**

**021567Orig1s035**

**CHEMISTRY REVIEW(S)**



# CHEMISTRY REVIEW TEMPLATE



## Chemistry Assessment Section

### FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 206352/000  
 Org. Code: 530  
 Priority: 3Y  
 Stamp Date: 02-DEC-2013  
 PDUFA Date: 02-JUN-2014  
 Action Goal:  
 District Goal: 03-APR-2014

Sponsor: BRISTOL MYERS SQUIBB  
 5 RESEARCH PKY 2DW 223  
 WALLINGFORD, CT 06492  
 Brand Name: REYATAZ (ATAZANAVIR)  
 Estab. Name:  
 Generic Name: ATAZANAVIR SULFATE  
 Product Number; Dosage Form; Ingredient; Strengths  
 001; POWDER; ATAZANAVIR; 50MG

FDA Contacts:	Y. SUN	Prod Qual Reviewer		3017961388
	A. CUFF	Product Quality PM	(HF-01)	3017964061
	S. BEAM	Regulatory Project Mgr	(HFD-730)	3017960080
	S. MILLER	Team Leader		3017961418

Overall Recommendation:	ACCEPTABLE	on 08-APR-2014	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 23-DEC-2013	by EES_PROD		
	PENDING	on 23-DEC-2013	by EES_PROD		

Establishment: CFN: (b) (4) FEI: (b) (4)  
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER  
 FINISHED DOSAGE RELEASE TESTER  
 FINISHED DOSAGE STABILITY TESTER

Profile: POWDERS (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE



# CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

## FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

**Establishment:** **CFN:** **FEI:** 3004531790  
 BRISTOL MYERS SQUIBB - CRUISERATH  
 CRUISERATH ROAD, MULHAUDDART  
 DUBLIN PIKE, , IRELAND

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
 DRUG SUBSTANCE RELEASE TESTER

**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 23-DEC-2013

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

---

**Establishment:** **CFN:** (b) (4) **FEI:** (b) (4)  
 (b) (4)

**DMF No:** **AADA:**

**Responsibilities:** FINISHED DOSAGE MANUFACTURER

**Profile:** POWDERS (b) (4) **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 08-APR-2014

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

---

**Establishment:** **CFN:** 9610172 **FEI:** 3002806583  
 SWORDS LABORATORIES LTD DIV OF BRISTOL MYERS SQUIBB  
 WATERY LANE  
 SWORDS, DUBLIN, , IRELAND

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
 (b) (4)

**Profile:** (b) (4) **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 01-APR-2014

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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/s/

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KIMHAK N NOY  
06/11/2014

**Memorandum**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**Date: May 30, 2014**

**From: Yichun Sun, Ph.D.**  
**Review Chemist, ONDQA**  
**Division of New Drug Quality Assessment II**  
**ONDQA**

**Through: Stephen Miller, Ph.D.**  
**CMC Lead, Branch V**  
**Division of New Drug Quality Assessment II**  
**ONDQA**

**Rapti Madurawe, Ph.D.**  
**Chief, Branch V**  
**Division of New Drug Quality Assessment II**  
**ONDQA**

**To: CMC Review #1 of NDA 206352**

**Subject: Final Approval Recommendation for NDA 206352 and S-035 of NDA 21567**

At the time when the CMC review #1 was written, resolution of issues on **Labels and Labeling**, which also contains the prescription information for the NDA 21567 (S-035 of NDA 21567) was pending. Additionally, the final PMC agreement to develop a new dissolution method was still pending.

**Evaluation of Label/Labeling**

On May 15, 2014, BMs provided the final PMC amendment to develop a new dissolution method. On May 16, 2014, the NDA applicant (BMS) provided the mock up container labels. The applicant also agreed to all the CMC changes made to the package insert, which also include the prescription information for the NDA 21567. All the labels/labeling issues for the NDA and the supplement (S-035) of NDA 21567 are now **satisfactorily resolved**. The dosage form of the drug product in NDA 206352 is "Oral Powder". The (b) (4) name, (b) (4), was removed from (b) (4) in the drug title for both NDAs 206352 and 21567, as recommended in the FDA advice letter dated May 6, 2014. BMS proposes to submit the (b) (4) for the capsule formulation to NDA 21-567 as a CBE-0 after approval of supplement S-035. Additionally, in the email dated May 16, 2014, BMS proposes to execute the following actions to communicate the changes related to the drug title within approximately 2

weeks of using the revised packaging and labeling associated with both the capsule and the availability of the new Reyataz oral powder formulation:

- A written communication to inform all providers that [REDACTED] <sup>(b) (4)</sup> is now going to be called “atazanavir” as an administrative change but not a change to the actual product itself for both capsules and the new “oral powder” formulation. The letter will request each HCP to inform patients who are currently receiving Reyataz capsules about the name change.
- A written communication to inform all Pharmacies and wholesalers stocking Reyataz of the administrative name change for both capsules and new oral powder formulations. The letter will request pharmacists to inform patients of the name change for the first refill of any current prescriptions.
- A field communications to inform both sales and Medical Science Liaisons (MSLs) regarding the administrative name change with direction that sales force will proactively inform HCPs of the name change while MSLs will be prepared to reactively answer any questions received regarding the HCP communications or the name change itself.

The CMC sections of the final package insert, and mock up container labels are attached (**Attachment - 1**).

**Recommendation:**

All pending issues on Label/Labeling are now satisfactorily resolved for NDAs 206352 and S-035 of NDA 21567, and therefore, from the ONDQA’s perspective, this NDA and S-035 of NDA 21567 are recommended for **APPROVAL**. An expiration dating period of **24 months** is granted for the drug product of NDA 206352. See CMC Review #1 (May 9, 2014) for information about the Post-Marketing Commitment for development of a new dissolution method, and for additional background.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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YICHUN SUN  
05/30/2014

STEPHEN MILLER  
05/30/2014

I concur, this NDA is recommended for approval from the product quality perspective.

RAPTI D MADURawe  
06/02/2014

# **NDA 206352**

**REYATAZ<sup>®</sup> (Atazanavir) Oral Powder**

**Bristol-Myers Squibb Company**

**Yichun Sun, Ph.D.**

**Branch IV**

**Division of New Drug Quality Assessment II**

**Office of New Drug Quality Assessment**

**CMC REVIEW OF NDA 206352**

**For the Division of Antiviral Products (HFD-530)**

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# Chemistry Review Data Sheet

1. NDA: 206352
2. REVIEW #: 1
3. REVIEW DATE: 9-May-2014
4. REVIEWER: Yichun Sun, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 56897	03-September-1998
IND 56, 897 (S-0839)	25-May-2012
IND 56, 897 (S-0848)	10-September-2012
IND 56, 897 (S-0855)	19-October-2012
IND 56, 897 (S-0863)	22-January-2013
IND 56, 897 (S-0867)	18-March-2013
IND 56, 897 (S-0848) (Biowaiver)	10-September-2012
IND 56, 897 (S-0867) (Biowaiver)	18-March-2013
NDA 21567 (Initial Submission)	20-December-2002
NDA 21567 (S-0033)	15-August-2008
NDA 21567 (S-0046)	08-May-2009
NDA 21567 (S-0052)	19-August-2009
NDA 21567 (S-0068)	16-June-2010
NDA 21567 (S-0095)	20-May-2011
NDA 21567 (S-0120)	11-May-2012
NDA 21567 (S-0123)	09-August-2012
NDA 21567 (S-0133)	14-August-2013
NDA 21567 (S-0135)	28-August-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	02-December-2013
Amendment	19-February-2014
Amendment	12-March-2014
Amendment	15-April-2014

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Bristol-Myers Squibb Company  
Address: 5 Research Parkway  
Wallingford CT 06492  
Representative: Lisa Percival  
Telephone: 860-508-9480

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Reyataz  
b) Non-Proprietary Name (USAN): Atazanavir Sulfate  
c) Code Name/# (ONDQA only): BMS-232632/ATZ  
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
  - Submission Priority: Priority Review

## 9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: HIV-1 protease inhibitor

11. DOSAGE FORM: Oral Powder

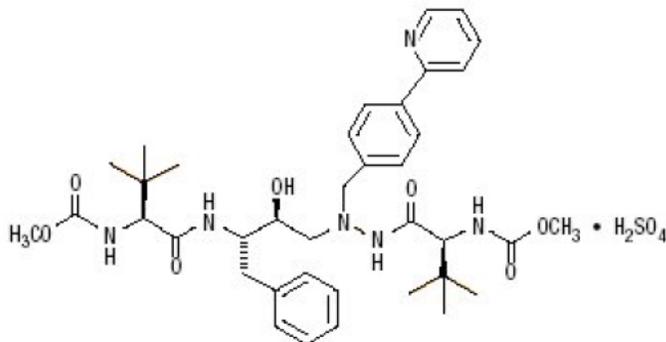
12. STRENGTH/POTENCY: 50 mg/packet

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

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

(3S,8S,9S,12S)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1)



### Structural Formula of Atazanavir Sulfate

Empirical formula:  $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$

Molecular weight: 802.9

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate	NA	NA
	IV			1	Adequate	NA	NA

<sup>1</sup> 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")

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

#### B. Other Documents: NA

## 18. STATUS:

## ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Acceptable	8-April-2014	R. Safaai-Jazi
Pharm/Tox	N/A	----	----
Biopharm	Acceptable with a request of PMC	8-May-2014	O. Eradiri
LNC	N/A	----	----
Methods Validation	N/A	----	----
DMEPA	N/A	----	----
EA	Claim for Categorical Exclusion is granted. See p.144	9-May-2014	Y. Sun
Microbiology	Acceptable	19-December-2013	B. R. Riley

# The Chemistry Review for NDA 206352

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Biopharmaceutics reviewer (Dr. Eradiri) recommends approval with a PMC request (see Dr. Eradiri's review dated May 8, 2014).

The Product Quality Microbiology reviewer (Dr. Riley) recommends approval from a Product Quality Microbiology perspective (see Dr. Riley's review dated Dec 23, 2013).

The Office of compliance has made a final "Acceptable" recommendation on the facilities involved.

Labeling negotiations are not complete at this time.

Therefore, from the ONDQA perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125(b)(6), until all labeling issues have been resolved.

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

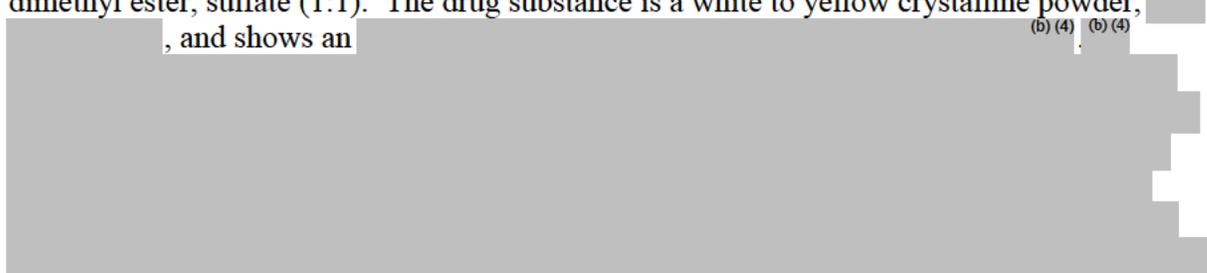
The applicant commits to develop a new dissolution method for the drug product. Details of the commitment will be provided in the addendum to this review.

### II. Summary of Chemistry Assessments

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

##### Drug Substance

The drug substance, Atazanavir sulfate (ATV), is an azapeptide inhibitor of HIV-1 protease known chemically as (3S,8S,9S,12S)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1). The drug substance is a white to yellow crystalline powder, (b) (4), and shows an (b) (4), (b) (4)



(b) (4)  
 More detailed information on the physical and chemical characteristics of the drug substance is provided in NDA #21-567 (Reyataz<sup>®</sup> Capsules), which was approved on June 20, 2003.

#### Drug Product

The drug product, REYATAZ (atazanavir sulfate) Powder, is proposed to be used in combination with other antiretroviral agents for the treatment of HIV-1 infection. The drug product is available for oral administration and comes in a packet containing 50 mg of atazanavir as atazanavir sulfate per 1.5 g of powder. The powder is off-white to pale yellow and contains the following inactive ingredients: aspartame, sucrose, and orange-vanilla flavor.

(b) (4)  
 The identity, strength, purity and quality (b) (4) of the drug product are adequately controlled by the drug product specification. The proposed expiration dating period of **24 months** is supported by the long-term and accelerated stability data provided. The drug product qualifies for categorical exclusion from the preparation of an environmental assessment according to 21 CFR 25.31(b).

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

REYATAZ is a protease inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The recommended daily dosage of REYATAZ Powder is based on body weight and shown in the following Table.

#### **Dosage for Pediatric Patients (10 kg to less than 25 kg) for REYATAZ Powder with Ritonavir<sup>a</sup>**

Body weight	REYATAZ dose	Ritonavir <sup>b</sup> dose
10 kg to less than 15 kg	200 mg (4 packets)	80 mg
15 kg to less than 25 kg	250 mg (5 packets)	80 mg

<sup>a</sup>: The REYATAZ and Ritonavir dose should be taken together once daily with food.

<sup>b</sup>: Ritonavir solution.

REYATAZ Powder should be taken with the smallest amount of food or beverage possible (such as applesauce, yogurt, milk, liquid infant formula, or water). The mixture of REYATAZ Powder and food or beverage should be administered to the child within 1 hour of mixing, making sure the child eats or drinks the full amount. If water is used, the REYATAZ/water mixture must be taken with food. REYATAZ powder must be taken with ritonavir.

**C. Basis for Not-Approval Recommendation**

21CFR 314.125(b)(6)

- Label and labeling issues have not been resolved. An advice letter has been sent to the applicant recommending that the (b) (4) be removed from the established name of the drug substance. Additionally, the dosage form name, (b) (4), is recommended to be changed to "Oral Powder". "Oral Powder" is recommended by ONDQA based on the final determination made in the ONDQA Precedence Meeting held on May 7, 2014.

**III. Administrative****A. Reviewer's Signature**

/s/ Y. Sun, Ph.D.

**B. Endorsement Block**Yichun Sun, Ph.D.  
Reviewer\_\_\_\_\_  
DateStephen Miller, Ph.D.  
CMC lead\_\_\_\_\_  
DateRapti Madurawe, Ph.D.  
Branch Chief\_\_\_\_\_  
DateAlthea Cuff, M.S.  
Project Manager\_\_\_\_\_  
Date**C. CC Block**

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/s/  
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YICHUN SUN  
05/09/2014

STEPHEN MILLER  
05/09/2014

RAPTI D MADURawe  
05/09/2014

**MEMORANDUM**

**Date:** May 1, 2014

**NDA#:** 206,352/SD#4

**Drug:** Reyataz (Atazanavir) Dry Powder

**Sponsor:** Bristol-Myers Squibb (BMS)

**To:** Yichun Sun, Ph.D.  
Chemist  
CDER/OPS/ONQA/DNDQAI/BRIV

**Cc:** Kuei-Meng Wu, Ph.D.  
Pharmacologist  
CDER/OND/OAP/DAVP

Stephen Miller, Ph.D.  
Chemist  
CDER/OPS/ONDQA/DNDQAI

**From:** Mark W. Powley, Ph.D.  
Pharmacologist  
CDER/OND/OAP/DAVP

**Concurrence:** Hanan Ghantous, Ph.D., DABT  
Supervisory Pharmacologist  
CDER/OND/OAP/DAVP

**Subject:** Risk Assessment for Impurities in Atazanavir Dry Powder

**Background**

This review focuses on the safety of [redacted] (b) (4). These chemicals were detected as leachables from the bulk powder packaging used with atazanavir dry powder for oral use in pediatric patients. Based on bulk sample stability testing at 9 months, levels of these 2 impurities were below [redacted] (b) (4)%. Table 1 summarizes the maximum potential daily exposures to [redacted] (b) (4) in the final pouch dose form.

Table 1. Leachable exposures<sup>a</sup> in atazanavir dry powder

	Clinical Doses	
	200 mg (10 to <15 kg)	250 mg (15 to < 25 kg)
[redacted] (b) (4)	≤ [redacted] (b) (4) mg/kg/day	≤ [redacted] (b) (4) mg/kg/day
[redacted] (b) (4)	≤ [redacted] (b) (4) mg/kg/day	≤ [redacted] (b) (4) mg/kg/day

<sup>a</sup> based on [redacted] (b) (4) in proposed clinical doses of atazanavir

## Safety Evaluation

Both (b) (4) have been reported to be negative in the standard bacterial reverse mutation assay (b) (4) as well as chromosomal aberration assays in human lymphocytes (b) (4). General toxicology data for (b) (4) comes from dietary studies in (b) (4). The primary concern noted for both chemicals was (b) (4) following 81 weeks of administration. Although the incidence was not dose-dependent, this effect was observed in males and females at all doses tested. Based on the (b) (4) lesion, the LOAEL for (b) (4) were (b) (4), respectively. The effect was not detected in 13-week range-finding studies. An increased incidence of (b) (4) was also noted in the 81-week studies; however, the effect lacked dose-dependence and was limited to males. Therefore, the studies were considered insufficient to definitively characterize the carcinogenic potential of (b) (4). Note that it is not possible to rule out volatility of test article as a confounding factor in the dietary studies (b) (4).

The 81-week dietary studies served as the basis of formal risk assessments performed by the Agency for Toxic Substances and Disease Registry (b) (4) and the US Environmental Protection Agency (b) (4). The ATSDR derived chronic minimal risk levels (MRL; estimate of human exposure likely to be without appreciable risk of adverse non-cancer effects) of (b) (4) mg/kg/day for (b) (4) and (b) (4) mg/kg/day for (b) (4). The EPA calculated a non-cancer/oral reference dose (RfD; estimate of human exposure likely to without appreciable risk, including sensitive subgroups, of deleterious non-cancer effects during a lifetime) of (b) (4) mg/kg/day for (b) (4). It is noteworthy that the EPA assessment described (b) (4) as a more severe disease infants and children vs. adults. (b) (4)

Using the risk assessment principles described for residual solvents in ICH Q3C(R5), permissible daily exposures (PDE) for (b) (4) were determined to be (b) (4) mg/kg/day and (b) (4) mg/kg/day, respectively. Calculations are shown in the Appendix.

## Conclusions

The primary concern with (b) (4) is (b) (4) toxicity, a potentially significant concern for certain subgroups of the intended atazanavir oral powder treatment population (e.g., children  $\leq$  5 years of age). Maximum levels of both leachables appear acceptable per the ATSDR risk assessment. In contrast, levels of (b) (4) exceed the limits determined by the FDA and/or EPA risk assessments by (b) (4) fold. Based on the totality of information, (b) (4) do not pose a substantial risk at the levels described.

## References

(b) (4)



## Appendix

Permissible Daily Exposure = LOAEL/ (F1 x F2 x F3 x F4 x F5)

Based on occurrence of (b) (4) in the 81-week dietary studies in mice:

F1 = 12 (extrapolation from mice to humans)

F2 = 10 (account for variability between individuals)

F3 = 1 (study  $\geq$  1 year in mice)

F4 = 10 (severe toxicity)

F5 = 10 (LOAEL used instead of NOAEL)

$$\begin{aligned} \text{(b) (4)} \\ \text{PDE} &= \text{(b) (4)} \text{ mg/kg/day} / (12 \times 10 \times 1 \times 10 \times 10) \\ &= \text{(b) (4)} \text{ mg/kg/day} \end{aligned}$$

$$\begin{aligned} \text{(b) (4)} \\ \text{PDE} &= \text{(b) (4)} \text{ mg/kg/day} / (12 \times 10 \times 1 \times 10 \times 10) \\ &= \text{(b) (4)} \text{ mg/kg/day} \end{aligned}$$

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/s/  
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MARK W POWLEY  
05/01/2014

HANAN N GHANTOUS  
05/02/2014

# Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

## I. Review Cover Sheet

- 1. DMPQ Reviewer: **Krishna Ghosh**
- 2. NDA/BLA Number: **NDA 206352**  
Submission Date: **12/2 /2013**  
21<sup>st</sup> C. Review Goal Date: **May 9, 2014**  
PDUFA Goal Date: **6/2/2014**

### 3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Reyataz
Established or Non-Proprietary Name (USAN) and strength:	Atazanavir Sulphate/ 50 mg (b) (4)
Dosage Form:	Powder for Oral use /Pediatric ( proposed)

### 4. SUBMISSION PROPERTIES:

Review Priority :	Priority Review
Applicant Name:	Bristol Myers Squibb CO
Responsible Organization (OND Division):	DAVP

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

## II. Application Detail

1. INDICATION: Treatment of HIV infection.
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 50 mg
4. Rx/OTC DISPENSED: Rx      OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		X		
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug				
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		x		
10.	Other (e.g., expedited for an unlisted reason)	X			Priority review granted . PDUFA June 2, 2014

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
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### III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

<b>A. COMPLETENESS OF FACILITY INFORMATION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
12.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
13.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
14.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #? 2. Do comments in EES indicate a request to participate on inspection(s)? 3. Is this first application by the applicant?	X		

\*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQ. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
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<b>B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
16.	Have any Comparability Protocols been requested?		X	

<b>IMA CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
17.	Does this application fit one of the EES Product Specific Categories?		X	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		
19.	<b>From a CGMP/facilities perspective, is the application fileable?</b>  If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

## IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):			

Manufacturing Highlights				
<b>1. Drug Substance</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	The manufacturing process is simple with no complex issues at this time.
<b>2. Drug Product</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	The manufacturing process is simple with no complex issues identified at this time.

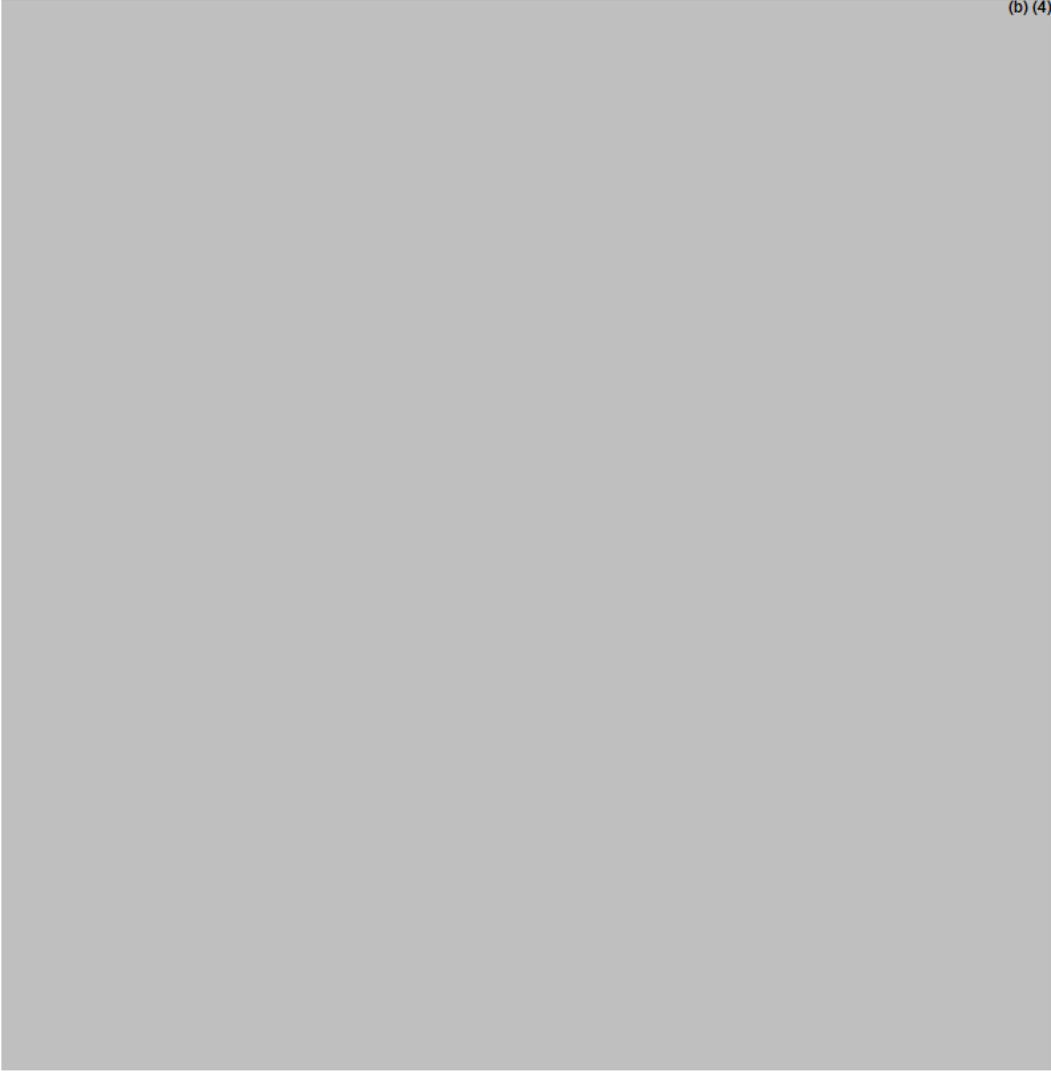
OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
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**3. Facility-Related Risks or Complexities (e.g., number of foreign sites, large number of sites involved, etc.)**

**Additional information on Manufacturing issues or Complexities**

None

(b) (4)



OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
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**Manufacturing Facilities Chart** (generated from 602A DARRTS report and OMPQ macro):

Note: See Coki Chart

For each EER, indicate PAI recommendation on the Manufacturing Facilities Chart above (e.g., PS, GMP, 10 Day, AC based on file review). This is the recommendation that will be entered into EES.

Establishment Name	FEI Num	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Most Recent Milestone	Most Recent EER Compliance Status	Comments
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4) - VAI	Inspection Scheduled	Pending	New Dosage Form for the establishment
				(b) (4) - NAI	Under review	Pending	Currently under case review
				(b) (4) - NAI	OC Recommendation	Ac	
				(b) (4) - NAI	OC Recommendation	Ac	

## V. Overall Conclusions and Recommendations

<b>Is the application filable? (yes/no)</b> yes
<b>At this time, is a KTM warranted for any PAI? No</b>
<b>Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? No</b>
Comments for 74 Day Letter
1. N/A
2.
3.

## REVIEW AND APPROVAL (DARRTS)

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

KRISHNA GHOSH  
03/12/2014

MAHESH R RAMANADHAM  
03/12/2014

ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications

## IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **206-352**

2. DATES AND GOALS:

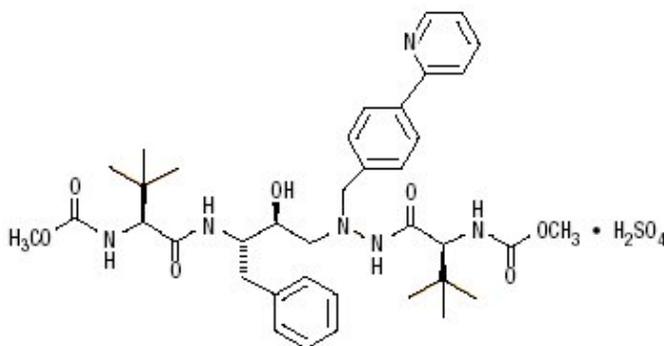
Letter Date:	Submission Received Date : Dec 2, 2013
Reviews Due in DARRTS: May 9, 2014	PDUFA Goal Date: June 2, 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Reyataz
Established or Non-Proprietary Name (USAN):	Atazanavir sulfate
Dosage Form:	Pediatric Powder for Oral Use (proposed)
Route of Administration	Oral
Strength/Potency	50 mg packet
Rx/OTC Dispensed:	Rx

4. INDICATION: Treatment of HIV infection.

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



6. NAME OF APPLICANT (as indicated on Form 356h):

Bristol-Myers Squibb Co.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

**7. SUBMISSION PROPERTIES:**

Review Priority:	Priority
Submission Classification (Chemical Classification Code):	Type 5 (new formulation, or new applicant for approved dosage form)
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DAVP

**8. CONSULTS:**

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology		X	
Methods Validation		X	
Environmental Assessment		X	
CDRH		X	
Other		X	

ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications

## Overall Filing Conclusions and Recommendations

### CMC:

<b>Is the Product Quality Section of the application fileable from a CMC perspective?</b>
<input checked="" type="radio"/> Yes <input type="radio"/> No
CMC Filing Issues:
1.

<b>Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?</b>
<input checked="" type="radio"/> Yes <input type="radio"/> No
CMC Comments for 74-Day Letter:
<ol style="list-style-type: none"><li>1. Confirm that the expiration dating period begins when the atazanavir sulfate is combined with excipients.</li><li>2. Update the NDA to include the current drug substance specification, and a discussion of any physiochemical properties that may impact the performance of the drug product.</li><li>3. Based on the outcomes from the June 29, 2012 meeting, we expected this NDA to include 36 months of supporting stability data for the <sup>(b) (4)</sup> aspartame formulation of the powder. Please amend the NDA to include that information, or reference its location if this information is already included in the NDA.</li><li>4. Submit to the NDA the document, "Risk Assessment for <sup>(b) (4)</sup> in Atazanavir Dry Powder for Oral Use in Pediatrics," DCN 930073815, or reference its location if this information is already included.</li><li>5. A request for input should go to Drs. Rik Lostritto and Yana Mille for confirmation that the established name should use the term "Powder" (rather than <sup>(b) (4)</sup>), and for advice on revising how the name should appear on the container labels. We should also ask for their input on our recommendation to ask BMS to voluntarily replace <sup>(b) (4)</sup> with "atazanavir".</li></ol>

### Biopharmaceutics:

<b>Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?</b>
<input checked="" type="radio"/> Yes <input type="radio"/> No
Biopharmaceutics Filing Issues:
1.

<b>Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?</b>
<input type="radio"/> Yes <input checked="" type="radio"/> No
Biopharmaceutics Comments for 74-Day Letter:

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

**Microbiology:**

<b>Is the Product Quality Section of the application fileable from a Microbiology perspective?</b>	
<b>Yes</b>	<b>No</b>
<b>Microbiology Filing Issues:</b>	
This NDA is fileable per Dr. Bryan Riley's Microbiology Filing Review in DARRTS (Dec 23, 2013). That review also recommends NDA approval, so no further review of this NDA from the Product Quality Microbiology perspective is anticipated.	

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

**Summary of Initial Quality Assessment**

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended?	Yes	No
Suggested expertise for team:		
Yichun Sun (DS and DP)		
Okpo Eradiri (Biopharm)		
Angelica Dorantes (Biopharm Secondary Review)		
Rapti Madurawe (Secondary Review)		
Althea Cuff (ONDQA PM)		
Sammie Beam (DAVP PM)		

**Summary of Critical Issues and Complexities**

**CMC Assessment**

**Overview**

This powder formulation (50 mg/ (b) (4)) adds more flexibility for pediatric dosing. The existing approved products are capsules of 150, 200 and 300 mg strength.

**Drug Substance**

Entirely referenced to NDA 21-567, except that information on the DS manufacturers is provided.

From Dr. Daniel Boring's 2003 review of NDA 21-567:

- Atazanavir sulfate is a crystalline material with low water solubility a neutral pH. It is most soluble in acidic media and least soluble in basic media. Studies indicate that the drug substance may exist in several morphic forms, solvates and hydrates. (b) (4)
- Atazanavir sulfate is slightly soluble (4-5 mg/mL, free base) in water at neutral pH. However, under the Biopharmaceutics Classification System (BCS) atazanavir is classified as highly soluble (highest dose, 400 mg is soluble in less than 250-mL of water). Since it is a weak organic base, it is most soluble at acidic pH, reaching a peak of 5.2 mg/mL at pH 1.9. It is practically insoluble at alkaline pH. Atazanavir sulfate is soluble in propylene glycol and freely soluble in methanol and 95% ethanol. The pH of a saturated aqueous solution is 1.9

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

Based upon this information, it would likely take approximately 10 mL of water to dissolve the atazanavir sulfate in a single (b) (4), or 40 mL of water for the lower dose of 200 mg.

**Drug Product**

(b) (4)

During IND development the aspartame was (b) (4) at the request of the EU Pediatric Committee. Additional sucrose was added to (b) (4)

The LOA from (b) (4) for their Orange-Vanilla flavoring mixture references the July 22, 1999 and the Sept 30, 1998 amendments to DMF (b) (4) for this material, (b) (4)

(b) (4) were chosen (b) (4) to reduce risk of miscount during dosing and adulteration.

Two impurities (b) (4) were identified as leachables from the (b) (4), and the hold time for the in-process (b) (4)

Pharm/Tox discussion would be valuable to confirm low risk at these levels. This document is mentioned in the QOS Intro: "Risk Assessment for (b) (4) in Atazanavir Dry Powder for Oral Use in Pediatrics," DCN 930073815.

Are there two Identity methods in the DP specification, or is the IR by Attenuated Total Reflectance an alternative to HPLC? If the latter, should they add second routine ID method, perhaps UV Diode Array on the HPLC?

**Labeling**

Highlights section of the PI: REYATAZ® (atazanavir (b) (4) (b) (4))

Other sections of PI typically use: (b) (4) or REYATAZ (b) (4).

Container labels:

REYATAZ®  
(atazanavir (b) (4))  
(b) (4)  
50 mg

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

**Prescribing Information:**

REYATAZ powder must be mixed with food or beverage and taken with ritonavir.

**Table 2: Dosage for Pediatric Patients (10 kg to less than 25 kg) for REYATAZ (b) (4) with Ritonavir<sup>a</sup>**

Body weight	REYATAZ dose	ritonavir <sup>b</sup> dose
10 kg to less than 15 kg	200 mg (4 packets)	80 mg
15 kg to less than 25 kg	250 mg (5 packets)	80 mg

<sup>a</sup> The REYATAZ and ritonavir dose should be taken together once daily with food.

<sup>b</sup> Ritonavir solution.

**Instructions for Mixing REYATAZ (b) (4)**

REYATAZ (b) (4) should be taken with the smallest amount of food or beverage possible (such as applesauce, yogurt, milk, liquid infant formula, or water). If water is used, the REYATAZ/water mixture must be taken with food. Caregivers must be instructed to place the food in a small container, or if mixing with a beverage place the beverage in a drinking cup or baby bottle. Caregivers must be instructed to settle the packet contents by tapping the packet, and to use a clean pair of scissors to cut open the packet on the dotted line. They should mix the contents of the packet with the food or beverage. This must be done for each packet required for the prescribed dose. The mixture should be administered to the child within 1 hour of mixing, making sure the child eats or drinks the full amount. The mixture may be left at room temperature during the 1 hour. Additional food may be given to the child after they have consumed the REYATAZ/food or REYATAZ/beverage mixture. REYATAZ powder must be taken with ritonavir.

**Section 11 – Description**

REYATAZ (b) (4) is available for oral administration and comes in a packet containing 50 mg of atazanavir as atazanavir sulfate per 1.5 g of powder. The powder is off-white to pale yellow and contains the following inactive ingredients: aspartame, sucrose, and orange-vanilla flavor.

**Section 16 – How Supplied**

## ONDQA Initial Quality Assessment (IQA) and Filing Review For Pre-Marking Applications

REYATAZ (b)(4) Powder is an orange-vanilla flavored powder, packed in child-resistant packets containing 50 mg of atazanavir as atazanavir sulfate in 1.5 g of powder. REYATAZ (b)(4) Powder for oral use is supplied in cartons (NDC 0003-3638-10) of 30 packets each. [See *Dosage and Administration* (2.2).]

REYATAZ (b)(4) Powder should be stored at or below 30°C (86°F). Once the REYATAZ (b)(4) Powder is mixed with food or beverage, it may be kept at room temperature 20°C to 30°C (68°F-86°F) for up to 1 hour. REYATAZ (b)(4) Powder should be stored in the original packet and should not be opened until ready to use.

### Biopharmaceutics Assessment

#### Biopharmaceutics Critical Issues or Complexities

**Background:** The sulphate salt of Atazanavir, an azapeptide protease inhibitor of HIV-1, is already approved in a capsule formulation for the treatment of HIV-1 infections (NDA 21-567) in combination with other antiretrovirals. In this NDA, the Applicant is seeking approval for the powder formulation, for oral use by the pediatric patient population. The powder is to be mixed with food prior to ingestion. Per agreement with FDA, the Applicant also identifies this submission as Supplement S-035 to the approved NDA, # 21-567.

**Submission:** Two Phase 3b pediatric studies in infants and children, aged between 3 months and 11 years, to demonstrate safety and efficacy of proposed doses of atazanavir in combination with ritonavir form the clinical basis for this NDA. The to-be-marketed powder formulation differs from the formulation used in the clinical trials in aspartame content; a biowaiver for a bridging bioequivalence study has therefore been requested in the NDA.

**Review:** The NDA contains sufficient biopharmaceutics data/information for review. The Biopharmaceutics review will focus on the evaluation and acceptability of the following:

- Adequacy of the dissolution method;
- Adequacy of the proposed dissolution acceptance criterion;
- Adequacy of the data supporting the biowaiver request.

**Recommendation:** This NDA is fileable from the Biopharmaceutics perspective.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

**FILING REVIEW CHECKLIST**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

<b>A. GENERAL</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		Summarized in QOS-Intro  Primary stability data submitted exceeds minimum recommended at Nov 2012 meeting.

<b>B. FACILITIES*</b>				
<b>* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			NA

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		356h

**C. ENVIRONMENTAL ASSESMENT**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		25.31(b): increase but not to exceed 1 ppb

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?		X	All DS information is cross-referenced to NDA 21-567
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	All DS information is cross-referenced to NDA 21-567
14.	Does the section contain information regarding the characterization of the DS?		X	All DS information is cross-referenced to NDA 21-567
15.	Does the section contain controls for the DS?		X	All DS information is cross-referenced to NDA 21-567
16.	Has stability data and analysis been provided for the drug substance?		X	All DS information is cross-referenced to NDA 21-567
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	All DS information is cross-referenced to NDA 21-567
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	All DS information is cross-referenced to NDA 21-567

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		A narrative description and flow chart is included.  Executed batch records for DP manufacture and packaging are included in 3.2.R.
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		See Point 19, above.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		50 mg strength in (b) (4)
24.	Does the section contain controls of the final drug product?	X		Attached below
25.	Has stability data and analysis been provided to support the requested expiration date?	X		12 mo of long-term (5°C and 30°C/75%RH) and accelerated data are provided on 3 production batches.  36 mo of supportive data were expected to be included.  (b) (4)  (b) (4)  Will also place 3 production batches from each DP manufacturing site on long-term and accel.  Proposed 24 mo expiry.
26.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	
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F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
28.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	IV		(b) (4)	Aug 14, 2013	
	III			May 7, 2013	

I. LABELING				
	Parameter	Yes	No	Comment
31.	Has the draft package insert been provided?			
32.	Have the immediate container and carton labels been provided?			Attached below

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
33.	Does the application contain dissolution data?	X		Proposed dissolution method for routine QC release testing: USP 2, (b) (4) rpm, (b) (4) mL of (b) (4) (b) (4). Sections 1.12.5 and 3.2.P.2.2.3.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

<b>J. BIOPHARMACEUTICS</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
34.	Is the dissolution test part of the DP specifications?		X	Rationale for excluding dissolution is that > (b) (4) % release occurs within (b) (4) min. This rationale will be assessed during NDA review.
35.	Does the application contain the dissolution method development report?	X		Elements of dissolution method development are incorporated in the biowaiver request (1.12.5, page 72).
36.	Is there a validation package for the analytical method and dissolution methodology?	X		Section 3.2.P.5.3.
37.	Does the application include a biowaiver request?	X		Section 1.12.5. A biowaiver request for a BE study bridging TBM product and the clinical batch.
38.	Are there adequate data supporting the waiver?	X		Section 1.12.5.
39.	Does the application include an IVIVC model?		X	
40.	Is information such as BCS classification mentioned, and supportive data provided?	X		Applicant ascribes BCS Class 2 to the compound in biowaiver request document.
41.	Is information on mixing the product with foods or liquids included?	X		In-use stability data are included.
42.	Is there any <i>in vivo</i> BA or BE information in the submission?	X		PK data were generated in 2 Phase 3b studies: #'s AI424020 and AI424397.
<b>FILING CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
43.	<b>ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	X		
44.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			N/A
45.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			N/A
46.	Are there any potential review issues identified?	X		See CMC review comments on page 3

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marketing Applications**

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**Appendix 1. Composition of Drug Product**

**Table 3.2.P.1-2: Composition of ATV POU (b)(4) 50 mg, as the Free Base**

Component	Quality Standard	Function	Quantity per (b)(4)	
			%w/w	(mg)
Atazanavir Sulfate <sup>a</sup>	In-house <sup>b</sup>	Active Ingredient	(b)(4)	(b)(4)
Aspartame	NF, Ph.Eur.	(b)(4)		(b)(4)
Sucrose	NF, Ph.Eur.			
Orange Vanilla Flavor	Non-compendial			
<b>Total (b)(4) Fill Weight</b>			<b>100.00</b>	<b>1500.00<sup>e</sup></b>

<sup>a</sup> Atazanavir sulfate is 1:1 ratio of atazanavir, the active moiety, and hydrogen sulfate. The amount of atazanavir is theoretically equivalent to (b)(4)

<sup>b</sup> The drug substance specification for atazanavir sulfate is presented in the NDA #21-567 for Reyataz<sup>®</sup> Capsules.

<sup>c</sup> The quantity is based on the theoretical assay “as is” of (b)(4) mg of atazanavir sulfate is equivalent to 50 mg of atazanavir.

<sup>d</sup> Sucrose is the (b)(4)

<sup>e</sup> The (b)(4) is filled with a (b)(4) overfill to accommodate the delivery loss due to unrecoverable powder from the sachet. Hence, the target fill weight for the (b)(4) is (b)(4) mg to ensure that 100% of the dose is delivered for atazanavir sulfate POU.

NF = National Formulary

Ph.Eur. = European Pharmacopoeia

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**Appendix 2. DP Specification**

<u>TEST</u>	<u>METHOD</u>
<b>1. Description</b>	
Off-white to pale yellow powder, free from visible evidence of contamination.	
<b>2. Identification</b>	
HPLC	95011022(S) HPLC
The retention time of the major peak in the sample chromatogram must correspond to that in the standard chromatogram.	
IR:ATR	5315A(G), 250596(S) -
Must be comparable to a standard spectrum run under the same conditions.	
Informational note Alternate method to Identification by HPLC.	
<b>3. Potency</b>	
	95011022(S) HPLC
[REDACTED] (b) (4)	
<b>4. Impurities/Degradants</b>	
Individual Unspecified	95013317(S) -
[REDACTED] (b) (4)	
Total	95013317(S) -
[REDACTED] (b) (4)	
<b>5. Uniformity of Dosage Units</b>	
Content Uniformity	356X(G), 95011022(S) USP/EP/JP/ChP
Must comply with the harmonized requirements.	
<b>6. Microbial Limits</b>	
Total Aerobic Microbial Count	250595(S), 5450A(G) -
[REDACTED] (b) (4)	
Total Yeasts and Molds Count	250595(S), 5450A(G) -
[REDACTED] (b) (4)	
Escherichia Coli	250595(S), 5450A(G) -
[REDACTED] (b) (4)	

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**Appendix 3 Container Labels**

(b) (4)



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/s/  
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