CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202155Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 202570, ELIQUIS (Apixaban) Tablets, 2.5 and 5.0 mg
Date: 22-JUN-2012

The NDA for ELIQUIS (Apixaban) film coated tablets (Bristol Myers Squibb) was submitted via a 501(b)(1) NDA application (standard review clock). All consults to this review have been completed.

The drug substance is adequately characterized and controlled; including Ames positive starting materials, impurities, and one intermediate.

The drug product immediate release, film coated tablets (2.5 mg [yellow debossed with "893'] and 5.0 mg [pink debossed with "894"]) are packaged for commercial distribution in HDPE bottles of 60 or 180 count as well as a 14 count blister package (5.0 mg) for physician samples.

An expiry period of 36 months for the commercial packages when stored at USP controlled room temperature is approved. For the finished tablets in the bulk container, and expiry of 12 months at ICH intermediate condition is also approved.

This NDA is recommended for approval from a Chemistry, Manufacturing and Controls standpoint.

Respecfully submitted,

Richard (Rik) Lostritto, Acting Deputy Office Director, ONDQA

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/s/

RICHARD T LOSTRITTO
06/22/2012

MEMORANDUM

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

DATE: May 18, 2012

TO: File

THROUGH: Ramesh K. Sood, Ph.D., Branch Chief, ONDQA

FROM: Charles F. Jewell Jr, Ph.D., Sr. Regulatory Review Chemist, ONDQA

SUBJECT: Final Chemistry, Manufacturing and Controls (CMC) Approval Recommendation for NDA 202-155 (Apixaban)

On 28 February 2012 the CMC review for the NDA 202-155 (Apixaban) was filed indicating the adequacy of the application from the CMC perspective, pending a decision from the Office of Compliance on GMP inspection results of the establishments involved in the manufacturing process of apixaban drug substance and drug product.

This memo is to confirm the overall acceptable rating based on the GMP inspection results of all the pertinent sites, see the detailed report below.

This confirms that NDA 202-155 (Apixaban) is approved from the CMC perspective.

Final Establishment Evaluation Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 202155/000	**Action Goal:**	
Stamp Date:	28-SEP-2011	**District Goal:**	28-JAN-2012
Regulatory:	28-MAR-2012		
Applicant:	BRISTOL MYERS SQUIBB	**Brand Name:**	ELIQUIS
	4000	**Estab. Name:**	
	PRINCETON, NJ 085434000	**Generic Name:**	APIXABAN
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	110	001; TABLET; APIXABAN; 2.5GM 002; TABLET; APIXABAN; 5MG	

Application Comment: THIS IS A QUALITY BY DESIGN APPLICATION. CONTACT ONDQA FOR PARTICIPATION ON INSPECTIONS. (on 03-OCT-2011 by D. HENRY () 3017964227)

A FORMAL RISK ASSESSMENT WAS CONDUCTED AND [redacted] (b) (4)

FDA Contacts:	D. HENRY	Project Manager	3017964227
	C. JEWELL	Review Chemist	3017964232
	K. SRINIVASACHAR	Team Leader	3017961760

Overall Recommendation:	ACCEPTABLE	on 27-MAR-2012	by D. SMITH	(HFD-323)	3017969643
	PENDING	on 04-OCT-2011	by EES_PROD		
	PENDING	on 04-OCT-2011	by EES_PROD		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9610221 **FEI:** 3002806546

BRISTOL MYERS SQUIBB

CONTRADA FONTANA DEL CERASO
ANAGNI, , ITALY

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment:

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

TABLETS, PROMPT RELEASE NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	04-OCT-2011				HENRYD
SUBMITTED TO DO	06-OCT-2011	Product Specific			SMITHDE
QBD SITE - PLS SEE APPLICATION COMMENTS REGARDING RTR					
ASSIGNED INSPECTION TO IB	06-OCT-2011	GMP Inspection			PHILPYE
INSPECTION SCHEDULED	16-FEB-2012		08-MAR-2012		IRIVERA
DO RECOMMENDATION	27-MAR-2012			ACCEPTABLE	BRYKMANR
FACILITY ACCEPTABLE RECOMMENDATION IS ONLY PROVIDED FOR THE REFERENCED APPLICATIONS. FACILITY OVERALL ACCEPTABILITY IS PENDING RECEIPT OF EIR AND ACCOMPANYING DOCUMENTATION.				INSPECTION	
OC RECOMMENDATION	27-MAR-2012			ACCEPTABLE	SMITHDE
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	04-OCT-2011				HENRYD
SUBMITTED TO DO	06-OCT-2011	GMP Inspection			SMITHDE
LAST EI COVERING TCM PROFILE WAS 2003, THIS EER IS FOR PACKAGING WHICH IS NOT QBD RELATED - PS CRITERIA IS FOR RELEASE TESTING AS SUBMITTED IN EER FOR CTL PROFILE AS GS/GMP INSPECTION					
ASSIGNED INSPECTION TO IB	06-OCT-2011	GMP Inspection			PHILPYE
INSPECTION SCHEDULED	16-FEB-2012		08-MAR-2012		IRIVERA
DO RECOMMENDATION	27-MAR-2012			ACCEPTABLE	BRYKMANR
FACILITY ACCEPTABLE RECOMMENDATION IS ONLY PROVIDED FOR THE REFERENCED APPLICATIONS. FACILITY OVERALL ACCEPTABILITY IS PENDING RECEIPT OF EIR AND ACCOMPANYING DOCUMENTATION.				INSPECTION	
OC RECOMMENDATION	27-MAR-2012			ACCEPTABLE	SMITHDE
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 2623458 **FEI:** 2623458

BRISTOL MYERS SQUIBB MANUFACTURING COMPANY

RD #3 KM 77.5
HUMACAO, PR 00791

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment:

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	04-OCT-2011				HENRYD
SUBMITTED TO DO	06-OCT-2011	Product Specific			SMITHDE
QBD APPLICATION - PLS SEE APPLICATION COMMENTS					
ASSIGNED INSPECTION TO IB	12-DEC-2011	Product Specific			RHERNAND
INSPECTION SCHEDULED	12-DEC-2011		30-JAN-2012		RHERNAND
DO RECOMMENDATION	13-FEB-2012			ACCEPTABLE	RHERNAND
ACCEPTABLE RECOMMENDATION BASED ON INSPECTIONAL RESULTS. ESTABLISHMENT INSPECTION CONDUCTED FROM JANUARY 23, 2012 TO FEBRUARY 2, 2012 AND CLASSIFIED NAI.				INSPECTION	
OC RECOMMENDATION	13-FEB-2012			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 1825662 **FEI:** 1825662

BRISTOL-MYERS SQUIBB COMPANY, INC.

4601 HIGHWAY 62 E
MOUNT VERNON, IN 476209682

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment:

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	04-OCT-2011				HENRYD
SUBMITTED TO DO	06-OCT-2011	Product Specific			SMITHDE
QBD SITE - PLS SEE APPLICATION COMMENTS					
ASSIGNED INSPECTION TO IB	06-OCT-2011	Product Specific			PDOMINGO
(b) (4) INSPECTION PAT DISTRICT GOAL 1/28/2012					
ASSIGNED INSPECTION TO IB	06-OCT-2011	Product Specific			PDOMINGO
DO RECOMMENDATION	02-FEB-2012			ACCEPTABLE	DOMBROWSKIR
PS PREAPPROVAL EI OF FIRM (DATED 1/17-24/12 FOR APPL 202155) CLASSIFIED VAI; SITE APPROVAL RECOMMENDED				INSPECTION	
OC RECOMMENDATION	02-FEB-2012			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE (b) (4)

Establishment Comment: (b) (4) (on 03-OCT-2011 by (b) (4))

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	04-OCT-2011				(b) (4)
OC RECOMMENDATION	06-OCT-2011			ACCEPTABLE	(b) (4)
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE (b) (4)

Establishment Comment: (b) (4) (on 03-OCT-2011 by (b) (4))

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	04-OCT-2011				(b) (4)
SUBMITTED TO DO	06-OCT-2011	10-Day Letter			(b) (4)
PERFORMS (b) (4) - ONDQA HAS NOT INDICACTED THIS AS A QBD SITE					
UNDER REVIEW	06-OCT-2011				PHILPYE
DO RECOMMENDATION	13-DEC-2011			ACCEPTABLE	STOCKM
				BASED ON FILE REVIEW	
OC RECOMMENDATION	14-DEC-2011			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: (b) (4) ESTABLISHED FOR THE DRUG SUBSTANCE PROCESS (on 03-OCT-2011 by D. HENRY () 3017964227)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	04-OCT-2011				HENRYD
SUBMITTED TO DO	06-OCT-2011	Product Specific			SMITHDE
QBD SITE - (b) (4) ESTABLISHED - PLS SEE APPLICATION COMMENTS					
UNDER REVIEW	06-OCT-2011				PHILPYE
DO RECOMMENDATION	31-OCT-2011			ACCEPTABLE	STOCKM
				BASED ON FILE REVIEW	
OC RECOMMENDATION	31-OCT-2011			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

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/s/

CHARLES F JEWELL
05/18/2012

RAMESH K SOOD
05/18/2012

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

METHODS VALIDATION REPORT SUMMARY

TO: Charles Jewell and William Adams, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: charles.jewell@fda.hhs.gov; William.adams@fda.hhs.gov
Phone: (301)-796-4232 and (301)-796-1321
Fax: (301)-796-9747

FROM: FDA
Division of Pharmaceutical Analysis
James Allgire, Team Leader
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3813

Through: Benjamin J. Westenberger, Deputy Director
Phone: (314) 539-3869

SUBJECT: Methods Validation Report Summary

Application Number: NDA 202155

Name of Product: Eliquis (apixaban) Tablets, 2.5 mg and 5 mg

Applicant: Bristol-Myers Squibb Company

Applicant's Contact Person: Porter P. Layne, group Director, GRS

Address: P.O. Box 4000, Princeton, NJ 08543-4000

Telephone: 609-252-4722 Fax: 609-252-6000

Date Methods Validation Consult Request Form Received by DPA: 12/08/11

Date Methods Validation Package Received by DPA: 12/08/11

Date Samples Received by DPA: 12/23/11

Date Analytical Completed by DPA: 03/12/12

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments:

Cover memo and summary of results are attached.

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-3815

Date: March 12, 2012

To: Charles Jewell, Review Chemist (HFD-800)
William Adams, Review Chemist (HFD-800)

Through: B. J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis, (HFD-920)

From: Michael Trehy, Chemist (HFD-920)

Subject: Method Validation for NDA 202155
Eliquis® Apixaban 2.5 mg tablets

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

- 95011145 Apixaban Tablets – Identification, Potency and Content Uniformity (HPLC) and method
- 95011189 Apixaban Tablets – Potency, Impurities/Degradants, Identification (HPLC)

The Division of Pharmaceutical Analysis (DPA) has the following comment pertaining to this method.

A typographical error on page 9 of method 95011145 was found.

(b) (4)

Method: 95011145 Apixaban Tablets – Identification, Potency and Content Uniformity (HPLC)

Identity: relative retention time of sample to standard [redacted]

Potency: [redacted] % limit [redacted] %

Content uniformity % label claim:

[redacted]

%

acceptance value [redacted]

Method: 95011189 Apixaban Tablets – Potency, Impurities/Degradants, Identification (HPLC)

Identity: relative retention time of sample to standard [redacted]

Potency: [redacted] limit [redacted] %

% Impurities: prep-1 prep-2 avg(2) Limit

[redacted]

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/s/

JAMES F ALLGIRE
03/13/2012

BENJAMIN J WESTENBERGER
03/15/2012

NDA 202,155

Eliquis®
(Apixaban Tablets, 2.5mg & 5.0mg)

Bristol-Myers Squibb

Charles Jewell (Drug Substance)
William M. Adams (Drug Product)
Yong Wang ((b) (4) methods)
Office of New Drug Quality Assessment

For the Division of Cardiorenal Products

Table of Contents

CMC Review Data Sheet

1. NDA 202,155

2. REVIEW #2

3. REVIEW DATE: 27 Feb 2012

4. **REVIEWER:** Charles Jewell, Ph.D. (drug substance)
William M. Adams (drug product)
Yong Wang, Ph.D. ((b) (4) methods)

5. PREVIOUS DOCUMENTS:

N-002 Amendment (CMC RU)	03 Nov 2010
N-004 Amendment (updated CMC RU)	30 Sep 2011
IR01 Letter (CMC)	17 Nov 2011
IQP Memo	07 Nov 2011
PQM Memo to OC (API)	08 Nov 2011
N-017 Amendment (response to IR 01 Letter)	09 Dec 2011
PQM Memo to OC (DP)	07/Dec 2011
IR 02 Letter (Biopharm)	16 Dec 2011
N-023 Amendent (response to IR 02 Letter)	23 Dec 2011
IR 03 Letter (CMC/Biopharm)	03 Feb 2012
CMC Review 01	15 Feb 2012

6. SUBMISSION(S) BEING REVIEWED:

Telcon regarding IR 03 Letter	(08 Feb 2012)
N-042 Amendment (response to IR 03 Letter)	14 Feb 2012
N-047 Amendment (follow-up CMC information)	27 Feb 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Bristol-Myers Squibb
Address:	P.O. Box 4000 Princeton, NJ 08543-4000
Representative:	Porter P. Layne, MBA, Group Director, GRS
Telephone:	(609) 252-4722

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Eliquis
b) Non-Proprietary Name (USAN):	Apixiban
c) **Code Name/# (ONDQA only):**	---

CMC Review Data Sheet

d) Chem. Type/Submission Priority (ONDQA only):

- **Chem. Type:** 1
- **Submission Priority:** S

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

10. PHARMACOL. CATEGORY: Anticoagulant

11. DOSAGE FORM: Film-Coated Tablet

12. STRENGTH/POTENCY: 2.5mg and 5.0mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

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

_____SPOTS product – Form Completed

__√__Not a SPOTS product

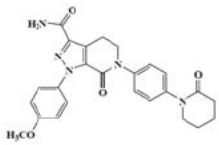
1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide

Molecular Formula $C_{25}H_{25}N_5O_4$

Molecular Weight 459.5 amu

Molecular Structure



17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF#	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments[3]
(b) (4)	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

CMC 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)
[3] Include reference to location in most recent CMC Review

B. Other Supporting Documents: None

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE	STATUS/ REVIEWER	COMMENTS
EES				Pending
Pharm/Tox		15 Feb 2012	J.P.Lai	Approvable
Non-Clinical		21 Feb 2012	P.Harlow	Approvable
Biometrics		15 Feb 2012	M.Jackson	Approvable
Biopharm	dissolution	24 Feb 2012	S.Suarez	Approvable
ODS/DMEPA	trade name	06 Dec 2011	M.Walker	Granted
Methods Validation	MV consult to St. Louis			Pending
EA	categorical exclusion			granted in CMC Review 01

The CMC Review for NDA 202,155

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC perspective, the application is found to be adequate, pending a decision from the Office of Compiance on GMP inspection results. A memorandum with final recommendation will be entered in DARRTS after a final overall recommendation is made by the Office of Compliance regarding the cGMP status of all manufacturing facilities.

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

None at this time.

II. Summary of CMC Assessments

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

Drug Substance

Apixaban drug substance is a non-hygroscopic crystalline powder (melting point range of (b) (4) °C). (b) (4) has been identified during the polymorph screening. This form is consistently produced by the commercial process. Apixaban has demonstrated adequate stability to support a (b) (4) retest period and it is not sensitive to heat, light or moisture (when stored in (b) (4) or other appropriate container). It is manufactured at the applicant's facility in Swords, Dublin, Ireland. The manufacturing site has an acceptable rating by the office of compliance.

Apixaban is a non-ionizable compound, so its solubility is not affected by changes in pH. The average solubility of apixaban in aqueous media (from pH (b) (4)) at 37°C ± 3% is (b) (4) mg/mL. At the doses proposed in the application (2.5 and 5.0 mg) the dose to solubility ratio is (b) (4) of aqueous buffer over the above pH range. Using the Biopharmaceutical Classification System (BCS), apixaban is classified as a BCS Class III drug (high solubility/low permeability).

The commercial manufacturing process utilizes (b) (4) An appropriate control strategy and (b) (4)

(b) (4)

The drug substance is (b) (4)

.

(b) (4)

The drug substance is adequately characterized by elemental analysis, ultraviolet and visible absorption spectral analysis, infrared spectral analysis, nuclear magnetic resonance spectral analysis, mass spectral analysis and single crystal x-ray analysis. The molecule has no chiral centers.

The disposition of all identified impurities is well understood and demonstrated controlled in the commercial manufacturing process. This includes impurities related t (b) (4)

Batch analysis data includes 33 batches of drug substance produced by (b) (4) different processes (24 of these by the commercial process and 8 at commercial scale). The batch analysis data confirms consistent quality by the commercial process.

Analytical methods are adequately described and validated. The HPLC method for assay and impurities was (b) (4)

Adequate stability studies and forced degradation studies have been performed by the applicant. The data supports a retest period of (b) (4) when stored as recommended. The drug substance shows little if any degradation under long term and accelerated storage conditions, and is not sensitive to light. Degradation does occur somewhat under stressed conditions; treatment with base, acid or peroxide for 14 days lead to hydrolysis related product albeit in limited amounts. On stability the drug substance was monitored for appearance, color, assay, impurities/degradants, (b) (4) and X-ray diffraction (no polymorphic changes have been detected in stability studies).

The applicant originally sought relief from (b) (4) in the drug substance release specification, but at the Agency's request, they have included these in the release specification. Also the applicant did not want to report changes in operational parameters that were not critical quality attributes and handle them under their own quality management system, but at the Agency's request, they have agreed to report all changes in operational

parameters outside the approved ranges as outlined in 21 CFR 314.70 even though they will be monitored by their own quality management system.

Drug Product

Eliquis® (apixaban tablets), 2.5 mg and 5.0 mg, is presented as an immediate release, film coated tablet to be distributed as a 60 or 180-count HDPE bottle with a [(b) (4)] a 10-count clear [(b) (4)] blister package; and a 14-count clear blister package (5.0 mg physician sample). The application also describes and qualifies [(b) (4)], but labels and labeling are not provided.

The 2.5 mg tablet is yellow, round, biconvex and debossed "893" (bisect) "2 ½". The 5.0 mg tablet is pink, oval, biconvex and debossed "894" (bisect) "5". Formulation ingredients consist of active, [(b) (4)] (lactose and microcrystalline cellulose), [(b) (4)] (croscarmellose sodium), [(b) (4)] (sodium lauryl sulfate), [(b) (4)] (magnesium stearate) and [(b) (4)] film coating. The coating is shown to be [(b) (4)] A [(b) (4)] No excipient is novel or of human origin. [(b) (4)]/TSE issues are adequately addressed for the lactose (sourced from [(b) (4)]). Core and coating excipients are USP/NF/EP grade. Adequate specifications have been established for the excipients and film coating materials. Copies of certificates of analysis for the excipient lots used in the NDA registration batches are provided.

GMP inspections are pending for the proposed tablet manufacturing sites in the U.S. and Puerto Rico, and for the proposed contract packaging site in Italy.

Commercial batch size is stated to be [(b) (4)] units for 2.50 tablets or [(b) (4)] units for 5.0 mg tablets). Tablets are manufactured from [(b) (4)]

Specifications for release and stability include testing for appearance, identity (Raman, IR, HPLC), assay (HPLC), related substances (HPLC), dosage uniformity (HPLC), disintegration (USP), dissolution (HPLC) and microbial limits (USP). Related susbstances include specified,

unspecified and total impurities. Microbial limits testing is to be performed on [redacted] batch. Descriptions of the analytical method are complete and provided in sufficient detail. Method validations, performed at the product development site, are complete and sufficient to support the intended use for each method. [redacted] The proposed criteria are justified by ICH guidances, batch analysis data and stability study results, and appropriate developmental studies. A proposal to use [redacted]. Product release testing will include assay and content uniformity by HPLC and dissolution testing. A procedure and criterion for dissolution have been accepted. Reference standards used for the assay and related substances testing are those used for drug substance testing.

Batch analysis data for each tablet strength is submitted for multiple clinical, developmental, and stability batches manufactured and packaged at the developmental site using the clinical film-coating. Data were also provided for process validation, stability and commercial batches manufactured and packaged at both proposed commercial sites using the commercial film-coating. All tablets manufactured since the phase 3 clinical studies used the same core formulations and manufacturing process. Batch sizes varied from [redacted] units. The analytical test results show consistency across manufacturing sites, tablet strengths, batch sizes, and tablet coating.

The packaging presentations are multi-dose and unit dose container closure systems. Components for the multi-dose system are a [redacted] white opaque HDPE bottle with [redacted] A [redacted] white opaque HDPE bottle with [redacted] is described as a [redacted]. Components for the unit dose system are [redacted]. Acceptance specifications are adequate for each listed component. Type III DMFs for each component are cited and letters of authorization are provided for each listed DMF.

Stability studies are performed by a contract laboratory on 3 tablet batches mamufactured at the product developmental site using the commercial formulation and process made with 3 drug substance batches obtained by commercial process at the commercial site. Studies are performed on each tablet strength in the commercial packaging configurations; a [redacted] (not proposed for approval); and a simulated bulk shipping/storage container. Storage was at refrigeration, room temperature, ICH intermediate, ICH accelerated, open dish, 50°C, ICH photostability and freeze-thaw cycling (in a HDPE bottle) conditions. Bulk containers are stored at ICH intermediate condition only. Testing is for appearance, assay, impurities, disintegration, dissolution, [redacted] and microbial limits. Microbial limits testing is performed only on commercial packages stored at refrigeration, room temperature and ICH intermediate conditions. Study data shows no chemical degradation, no change in drug release at 30-minutes, and no microbial growth over time across tablet strength, batches, storage conditions, or packaging systems/configurations. The data is provided as tabulations and graphic presentations. The data shows no significant moisture uptake in the blister packages at stress conditions; no microbial growth in any package at room temperature; no degradation in any package at any condition; and no sensitivity to light in the HDPE bottles.

Although the studies do not address bulk storage followed by commercial package storage, this is not expected to be an issue since tablets show no degradation in any of the packages studied. Concur that the data supports an initial expiry period of 36 months for the commercial packages when stored at USP controlled room temperature, and stability for finished tablets in the bulk container stored up to 12 months at ICH intermediate condition.

(b) (4)

Submitted are draft labels for 60- and 180-count bottles without bottle cartons, 10-count blister cards with 10-card cartons, and 14-count blisters without carton (5.0 mg physician sample), and a draft package insert with medication guide. The CMC information on the draft labels and labeling is acceptable.

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

The recommended dose is 5.0 mg taken twice daily with or without food.

C. Basis for Approvability or Not-Approval Recommendation

GMP inspections of the manufacturing and packaging sites are not yet completed.

III. Administrative

A. Reviewer's Signature: (See appended electronic signature page)

Charles Jewell, ONDQA

William M. Adams, ONDQA

Yong Wang, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

C. CC Block: entered electronically in DFS

D. Henry/PMQ/ONDQA
K. Srinivasachar/CMC Lead/ONDQA

Executive Summary Section

A. Blaus/Regulatory PM/DCRP

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/s/

CHARLES F JEWELL
02/27/2012

YONG WANG
02/27/2012

WILLIAM M ADAMS
02/28/2012

RAMESH K SOOD
02/28/2012

NDA 202,155

Eliquis®
(Apixaban Tablets, 2.5mg & 5.0mg)

Bristol-Myers Squibb

Charles Jewel (Drug Substance)
William M. Adams (Drug Product)
Yong Wang ((b) (4) methods)
Office of New Drug Quality Assessment

For the Division of Cardiovascular and Renal Products

Table of Contents

APPEARS THIS WAY IN THE ORIGINAL

CMC REVIEW DATA SHEET

1. NDA 202155

2. REVIEW #1

3. REVIEW DATE: 15 Feb 2012

4. **REVIEWER:** Charles Jewell, Ph.D. (drug substance)
William M. Adams (drug product)
Yong Wang, Ph.D. ((b) (4) methods)

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

N-002 Amendment (CMC RU)	03 Nov 2010
N-004 Amendment (updated CMC RU)	30 Sep 2011
IR01 Letter (CMC)	17 Nov 2011
IQP Memo	07 Nov 2011
PQM Memo to OC (API)	08 Nov 2011
N-017 Amendment (response to IR 01 Letter)	09 Dec 2011
PQM Memo to OC (DP)	07/Dec 2011
IR 02 Letter (Biopharm)	16 Dec 2011
N-023 Amendment (response to IR 02 Letter)	23 Dec 2011
IR 03 Letter (CMC/Biopharm)	03 Feb 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Bristol-Myers Squibb
Address:	P.O. Box 4000 Princeton, NJ 08543-4000
Representative:	Porter P. Layne, MBA, Group Director, GRS
Telephone:	(609) 252-4722

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Eliquis
b) Non-Proprietary Name (USAN): Apixiban
c) **Code Name/# (ONDQA only):** ---
d) Chem. Type/Submission Priority (ONDQA only):

- **Chem. Type:** 1
- **Submission Priority:** P

CMC Review Data Sheet

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

10. PHARMACOL. CATEGORY: Anticoagulant

11. DOSAGE FORM: Film-Coated Tablet

12. STRENGTH/POTENCY: 2.5mg and 5.0mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

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

_____SPOTS product – Form Completed

__√__Not a SPOTS product

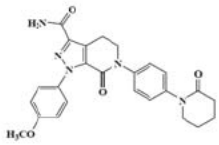
1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide

Molecular Formula $C_{25}H_{25}N_5O_4$

Molecular Weight 459.5 amu

Molecular Structure



17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF#	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments[3]
(b) (4)	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[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)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents: None

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				
EES				Pending
Pharm/Tox				
Biopharm				Pending
ODS/DMEPA				
Methods Validation				
EA				
Microbiology				

The CMC Review for NDA 202,155

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is currently NOT ADEQUATE for approval due to unresolved issues regarding drug substance specifications and the drug product manufacturing and control information.

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

None at this time.

II. Summary of CMC Assessments

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

Drug Substance

Apixaban drug substance is a non-hygroscopic crystalline powder (melting point range of (b) (4) has been identified during the polymorph screening. This form is consistently produced by the commercial process. Apixaban has demonstrated adequate stability to support a (b) (4) retest period and it is not sensitive to heat, light or moisture (when stored in (b) (4) or other appropriate container). It is manufactured at the applicant's facility in Swords, Dublin, Ireland. The manufacturing site has an acceptable rating by the office of compliance.

Apixaban is a non-ionizable compound, so its solubility is not affected by changes in pH. The average solubility of apixaban in aqueous media (from pH 1.2 to pH 6.8) at 37°C ± 3% is 0.040 mg/mL. At the doses proposed in the application (2.5 and 5.0 mg) the dose to solubility ratio is (b) (4) mL of aqueous buffer over the above pH range. Using the Biopharmaceutical Classification System (BCS), apixaban is classified as a BCS Class III drug (high solubility/low permeability).

The commercial manufacturing process utilizes (b) (4)

[redacted] (b) (4)

The drug substance is adequately characterized by elemental analysis, ultraviolet and visible absorption spectral analysis, infrared spectral analysis, nuclear magnetic resonance spectral analysis, mass spectral analysis and single crystal x-ray analysis. The molecule has no chiral centers.

The disposition of all identified impurities is well understood and demonstrated controlled in the commercial manufacturing process. This includes impurities related to [redacted] (b) (4)

Batch analysis data includes 33 batches of drug substance produced by [redacted] (b) (4) different processes (24 of these by the commercial process and 8 at commercial scale). The batch analysis data confirms consistent quality by the commercial process.

Analytical methods are adequately described and validated. The HPLC method for assay and impurities was [redacted] (b) (4)

Adequate stability studies and forced degradation studies have been performed by the applicant. The data supports a retest period of [redacted] (b) (4) when stored as recommended. The drug substance shows little if any degradation under long term and accelerated storage conditions, and is not sensitive to light. Degradation does occur somewhat under stressed conditions; treatment with base, acid or peroxide for 14 days lead to hydrolysis related product albeit in limited amounts. On stability the drug substance was monitored for appearance, color, assay, impurities/degradants, [redacted] (b) (4) and X-ray diffraction (no polymorphic changes have been detected in stability studies).

At this point, a complete response is recommended from the drug substance perspective until the drug substance final comments are given adequate response from the sponsor. The applicant is being asked by the Agency via a final information request to commit to including appropriate tests for [redacted] (b) (4) for all batches of drug substance. The applicant is also being asked to report all changes to the manufacturing process regardless of whether or not they occur in critical process parameters or non-critical process parameters. The applicant has

been requesting regulatory relief on these three issues but the Agency does not support the adequacy of their justifications.

Drug Product

Eliquis® (apixaban tablets), 2.5 mg and 5.0 mg, is presented as an immediate release, film coated tablet to be distributed as a 60 or 180-count HDPE bottle with (b) (4) ; a 10-count clear (b) (4) blister package; and a 14-count clear blister package (5.0 mg physician sample). The application also describes and qualifies (b) (4) , but labels and labeling are not provided.

The 2.5 mg tablet is yellow, round, biconvex and debossed "893" (bisect) "2 ½". The 5.0 mg tablet is pink, oval, biconvex and debossed "894" (bisect) "5". Formulation ingredients consist of active, (b) (4) (lactose and microcrystalline cellulose), (b) (4) (croscarmellose sodium), (b) (4) (sodium lauryl sulfate), (b) (4) (magnesium stearate) and (b) (4) film coating. The coating is shown to be (b) (4) (b) (4) No excipient is novel or of human origin. (b) (4) TSE issues are adequately addressed for the lactose (sourced from (b) (4)). Core and coating excipients are USP/NF/EP grade. Adequate specifications have been established for the excipients and film coating materials. Copies of certificates of analysis for the excipient lots used in the NDA registration batches are provided.

GMP inspections are pending for the proposed tablet manufacturing sites in the U.S. and Puerto Rico, and for the proposed contract packaging site in Italy.

Commercial batch size is stated to be (b) (4) units for 2.50 tablets or (b) (4) (b) (4) units for 5.0 mg tablets). Tablets are manufactured from

[redacted]

Specifications for release and stability include testing for appearance, identity (Raman, IR, HPLC), assay (HPLC), related substances (HPLC), dosage uniformity (HPLC), disintegration (USP), dissolution (HPLC) and microbial limits (USP). Microbial limits testing is to be performed on [redacted]. Descriptions of the analytical method are complete and provided in sufficient detail, however revised system suitability criteria have been requested. Method validations, performed at the product development site, are complete and sufficient to support the intended use for each method. [redacted] The proposed criteria are justified by ICH guidances, batch analysis data and stability study results. The proposed criteria include limits for specified, unspecified and total impurities. Revision of the impurity criteria has been requested. A proposal to use [redacted]. Reference standards are those used for drug substance testing.

Batch analysis data for each tablet strength is submitted for multiple clinical, developmental, and stability batches with the clinical coating made at the developmental site; and for process validation, stability and commercial batches with the commercial coating made at the proposed commercial sites. All tablets from phase 3 clinical on used the same core formulations and manufacturing process. Clinical batches varied in size from [redacted] units. The NDA registration batches are manufactured and packaged at the product development site. The analytical test results show consistency across manufacturing sites, tablet strengths, batch sizes, and tablet coating.

The packaging presentations are multi-dose and unit dose container closure systems. Components for the multi-dose system are described as [redacted] white opaque HDPE bottle with [redacted] is omitted from the [redacted]. Components for the unit dose system are [redacted]. Acceptance specifications are adequate for each listed component. Type III DMFs for each component are cited and letters of authorization are provided for each listed DMF.

Stability studies are performed by a contract laboratory on 3 tablet batches manufactured at the product developmental site using the commercial formulation and process made with 3 drug substance batches obtained by commercial process at the commercial site. Studies are performed on each tablet strength in the commercial packaging configuration; a [redacted] (not proposed for approval); and a simulated bulk shipping/storage container. Storage conditions are refrigeration, room temperature, ICH

intermediate, ICH accelerated, open dish, 50°C, ICH photostability and freeze-thaw (in a HDPE bottle) conditions. Bulk containers are stored at ICH intermediate condition only. Testing is for appearance, assay, impurities, disintegration, dissolution, (b) (4) and microbial limits. Microbial limits testing is performed only on commercial packages stored at refrigeration, room temperature and ICH intermediate conditions. Study data shows no chemical degradation, change in drug release at 30-minutes, or microbial growth over time across tablet strength, batches, storage conditions, or packaging systems/configurations. The data is presented as tabulations and graphic presentations. Concur with the applicant that the data supports an initial expiry period of 36 months for the commercial packages when stored at USP controlled room temperature and for bulk containers stored for up to 12 months at ICH intermediate conditions. The data shows no significant moisture uptake in the blister packages at stress conditions; no microbial growth in any package at room temperature; no degradation in any package at any condition; and no sensitivity to light in the HDPE bottles. Although the studies do not address bulk storage followed by commercial package storage, this is not expected to be an issue since tablets show no degradation in the packages studied.

Submitted are draft labels for 60- and 180-count bottles without bottle cartons, 10-count blister cards with 10-card cartons, and 14-count blisters without carton (5.0 mg physician sample), and a draft package insert with medication guide. The CMC information on the draft labels and labeling is acceptable.

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

The recommended dose is 5.0 mg taken twice daily with or without food.

C. Basis for Approvability or Not-Approval Recommendation

There are unresolved issues regarding drug substance specification, and drug product manufacturing and controls. An IR letter detailing these issues was issued 03 Feb 2012.

III. Administrative

A. Reviewer's Signature: (See appended electronic signature page)

Charles Jewell, ONDQA

William M. Adams, ONDQA

Yong Wang, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

C. CC Block: entered electronically in DFS

D. Henry/PMQ/ONDQA
K. Srinivasachar/CMC Lead/ONDQA
A. Blaus/Regulatory PM/DCRP

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/s/

CHARLES F JEWELL
02/15/2012

YONG WANG
02/15/2012

WILLIAM M ADAMS
02/15/2012

RAMESH K SOOD
02/15/2012

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

METHODS VALIDATION CONSULT REQUEST FORM

TO: **FDA**
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Charles Jewell and William Adams, CMC Reviewer
Kasturi Srinivasachar, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: charles.jewell@fda.hhs.gov; william.adams@fda.hhs.gov
Phone: (301)-796 4232 and (301)-796 1321
Fax.: (301)-796 9747

Through: Ramesh Sood
Phone: (301)-796 1466
and
Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 202155

Name of Product: Eliquis (apixaban) Tablets, 2.5 mg and 5 mg

Applicant: Bristol- Myers Squibb Company

Applicant's Contact Person: Porter P. Layne, Group Director, GRS

Address: P.O. Box 4000, Princeton, NJ 08543-4000

Telephone: 609-252 4722 Fax: 609-252 6000

Date NDA Received by CDER: **9/28/2011**

Date of Amendment(s) containing the MVP: **9/28/2011**

DATE of Request: **December 1, 2011**

Requested Completion Date: **1/20/2012**

PDUFA User Fee Goal Date: **3/28/2012**

Submission Classification/Chemical Class: NME

Special Handling Required: No

DEA Class: N/A

Format of Methods Validation Package (MVP)

☐ Paper ☒ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

ATTACHMENT(S): *Methods Validation Request Sheet*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	**METHODS VALIDATION REQUEST**	NDA # 202155

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION
Apixaban Reference Standard	0.05 g/unit; 9 units/kit	Lot No. 5L00876
Apixaban Impurity Cocktail	(b) (4) g/unit; 3 units/kit	Lot No. 66412-044
Apixaban FCT, 2.5 mg	(b) (4) tablets/unit; 3 units/kit	Lot No.0C65474
Apixaban FCT, 5 mg	(b) (4) tablets/unit; 3 units/kit	Lot No. 0J63085
		See Section 3.2.R.2 for additional details

⇒ ITEM 2: **Contents of Attached Methods Validation Package**	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	3.2.P.1
Specifications/Methods for New Drug Substance(s)	3.2.S.4.1
Specifications/Methods for Finished Dosage Form(s)	3.2.P.5.1
Supporting Data for Accuracy, Specificity, etc.	See Item. 3
Applicant's Test Results on NDS and Dosage Forms	3.2.S.4.4 3.2.P.5.4 (Dosage Form)
Other: MVP	3.2.R.

⇒ ITEM 3: **REQUESTED DETERMINATIONS**
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.

Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
95011145	Apixaban Tablets -- Identification, Potency and Content Uniformity (HPLC)	3.2.P.5.2 and 3.2.R.2.3	**0**	Method Validation Report in 3.2.R.2.4 and 3.2.P.5.3
95011189	Apixaban Tablets -- Potency, Impurities/Degradants, Identification (HPLC)	3.2.P.5.2. and 3.2.R.2.3	**0**	This is the primary method for Impurities/Degradants and an alternative method for Potency and Identification Method Validation Report in 3.2.P.5.3 and 3.2.R.2.4

Additional Comments:

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method

6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

KASTURI SRINIVASACHAR
12/01/2011

RAMESH K SOOD
12/07/2011

JEANNIE C DAVID
12/08/2011
ONDQA Methods Validation Project Manager

DATE: November 30, 2011

TO: Extended Apixaban (NDA 202-155) Review Team

FROM: William (Mike) Adams (william.adams@fda.hhs.gov; 301-796-1321

THROUGH: Ramesh Sood, Ph.D., Branch Chief

SUBJECT: **CMC (Chemistry, Manufacturing & Controls) Product Quality Manufacturing Memo for Drug Product for the upcoming Pre-Approval Inspection.**

The proposed drug product is an oral film-coated tablet in two strengths, 2.5mg and 5.0mg, which are packaged in HDPE bottles and clear (b) (4) blister packs. Tablets are stated to be manufactured and controlled at the BMS sites at Humacao, P.R. and Mount Vernon, IL. Packaging is stated to be performed at the BMS sites at Mount Vernon, IL for blisters and bottles, and at Agnani, Italy for blisters. The packaging system for transfer of bulk tablets between sites has not been described in detail and the controls for release and acceptance at each site are being requested.

The application includes (b) (4) for tablet formulation and in-process material attributes. Both are addressed in the product development discussion which is under review.

(b) (4)

(b) (4)

The NDA provides only a very terse narrative description and a schematic without process details. The drug product is manufactured by (b) (4) (attachment 1). A detailed description of the manufacturing process with process parameters and in-process controls, and the sampling scheme for in-process testing is being requested.

The tablet manufacturing process; specifications for batch release and real time release testing (RTRT) procedures; and analytical methods for in-process and product release testing were developed and validated at the BMS (New Brunswick, NJ) site. The product release specifications (attachment 2) are described in detail and the method validation studies are essentially complete. The analytical methods are either compendial or RP-HPLC with C18 columns. There is a method validation for what is likely to be the BMS (New Brunswick, NJ) site. There is no analytical method transfer study information for the controls sites at Humacao, P.R. and Mount Vernon, IL.

Reviewer's Identified Risks

Based on our preliminary review of the sponsor's submission, we identified the following items as potential risks to drug product quality:

(b) (4)

(b) (5)

Contact Information

- Drug Substance: Charles Jewel ((charles.jewell@fda.hhs.gov; 301-796-4232)
- Drug Product: William (Mike) Adams (william.adams@fda.hhs.gov; 301-796-1321
- Biopharmaceutics: Saundra Suarez (saundra.suarez@fda.hhs.gov; 301-796-2158)
- (b) (4) Methods and Testing: Yong Wang (yong.wang@fda.hhs.gov; 301-796-1139)
- Project Manager, Quality: Don Henry (don.henry@fda.hhs.gov; 301-796-4227)
- CMC Lead: Kasturi Srinivasachar (kasturi.srinivasachar@fda.hhs.gov; 301-796-1760)
- Branch Chief: Ramesh Sood (ramesh.sood@fda.hhs.gov; 301-796-1466)

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/s/

WILLIAM M ADAMS
12/05/2011

RAMESH K SOOD
12/07/2011

DATE: November 07, 2011

TO: Extended Apixaban (NDA 202-155) Review Team

FROM: Charles Jewell, Ph.D. 301-796-4232, charles.jewell@fda.hhs.gov, Reviewer of Drug Substance Section

THROUGH: Ramesh Sood, Ph.D., Branch Chief

SUBJECT: **CMC (Chemistry, Manufacturing & Controls) Product Quality Manufacturing Memo for Drug Substance for the upcoming Pre-Approval Inspection.**

Swords Laboratories, Watery Lane, Swords, County Dublin, Ireland has been proposed as the main manufacturing site for Apixaban drug substance for use in NDA 202155. This site is a facility of Bristol-Myers Squibb, the applicant for the subject NDA. This site has direct responsibility for the following:

- Quality control testing and release of (b) (4)
- Manufacture, quality control testing and release of (b) (4)
- Manufacture, quality control testing and release of apixaban

(b) (4), provided to this site by two external vendors who have contracts with the applicant to provide this material. (b) (4) has been designed as an important step in ensuring the quality of apixaban drug substance.

(b) (4)

Synopsis of the Manufacturing Process

(b) (4)

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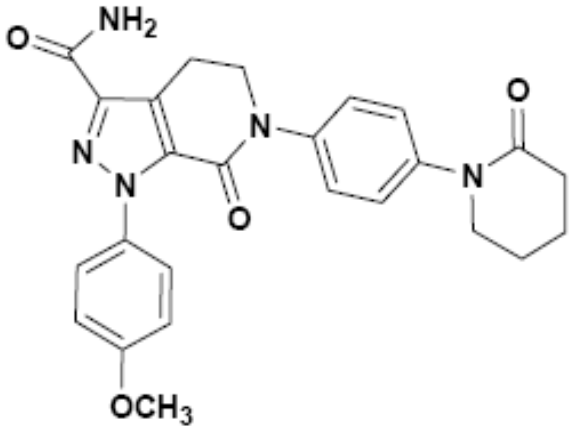
Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	202155
Applicant:	Bristol Myers Squibb and Pfizer
Letter Date:	3 Nov 2010
Stamp Date:	3 Nov 2010
PDUFA Date:	TBD
Tradename:	None proposed at this time
Established Name:	Apixaban
Dosage Form:	Tablets, 2.5 mg and 5 mg
Route of Administration:	Oral
Indication:	Prevention of stroke or systemic embolism associated with atrial fibrillation
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes



Summary

This is a rolling submission of reviewable units in e-CTD format for the NME apixaban. The first reviewable unit (Pharmacology/Toxicology) was submitted on September 29, 2010 and the second reviewable unit, consisting of Quality and Clinical Pharmacology/Biopharmaceutics Modules was submitted on November 3, 2010. The quality information for this NDA is now complete and includes the QOS (Module 2) and Module 3. The final reviewable unit (Clinical) is planned for the week of February, 28, 2011 and the review clock for this NDA will start when this is in house. (b) (4) [redacted]. This NDA meets the criteria for a QbD submission and incorporates QbD principles in the development of both drug substance and drug product manufacturing processes.

Apixaban is an anticoagulant that acts as a selective, reversible inhibitor of the coagulation factor Xa. Clinical development of this drug was carried out under IND 68,598. (b) (4) [redacted] Four CMC specific meetings have been held with the sponsor on May 11 and June 15, 2006, Sep. 19, 2007 and Sep. 11, 2009. The meetings in 2006 were concerned with the designation of starting materials for the synthesis of apixaban, control of genotoxic impurities and dissolution methodology. The EOP2 meeting in 2007 focused on the control strategy for potentially genotoxic impurities in the drug substance including (b) (4) [redacted], drug product dissolution methodology and the use of in-vitro dissolution profile comparisons to establish the bioequivalency of tablets used in the clinical trials to those intended for marketing which are of different shape and color. The sponsor stated that QbD concepts would be employed in the development of drug substance and drug product manufacturing processes and provided an overview of their strategy. (b) (4) [redacted].

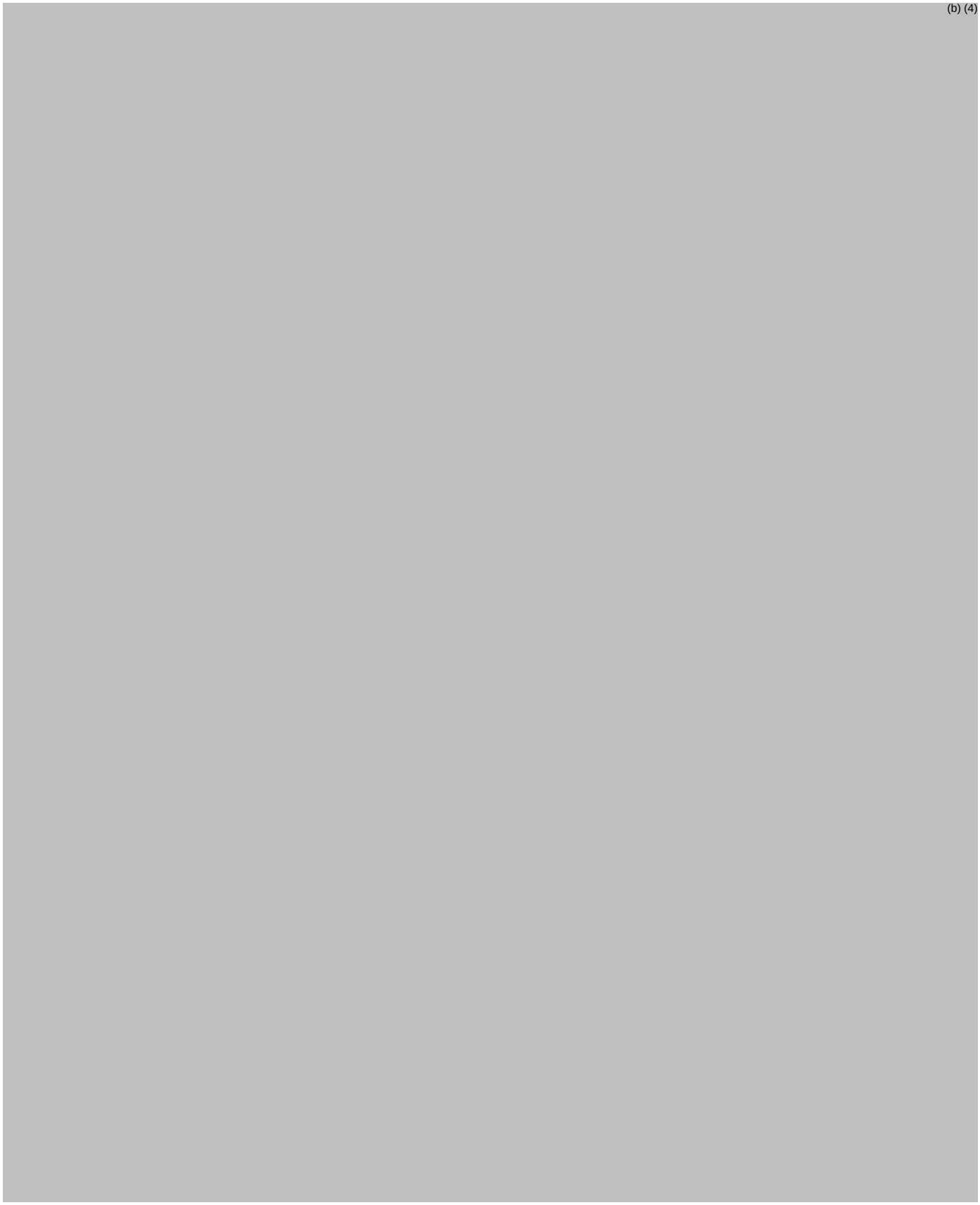
The Type C CMC meeting in 2009 was held primarily to discuss BMS' QbD strategy for the manufacturing and control of apixaban drug product. A major item for discussion was the sponsor's proposal to implement (b) (4) [redacted]. The agency agreed, in principle, with these approaches but did not concur with the proposed sampling strategy for content uniformity. The sponsor was recommended to provide additional justification in a complete NDA data package for review. (b) (4) [redacted].

Furthermore, this proposal would be [redacted] (b) (4)

Drug Substance

Apixaban is a non-hygroscopic crystalline powder with [redacted] (b) (4) Batch data for a number of batches, ranging from early small scale toxicology batches to recent commercial scale batches made by the current [redacted] (b) (4) have been submitted. In addition, test data from apixaban batches representative of the commercial scale and process for attributes not included in the specification e.g [redacted] (b) (4) content have also been provided. Stability studies have been carried out on the drug substance packaged in two configurations of [redacted] (b) (4) Data from 3 primary, pilot scale batches manufactured by a process representative of the commercial process [redacted] (b) (4) stored under long term and accelerated conditions are available and it is stated that no changes were observed in any of the test parameters at any storage condition. A retest period of [redacted] (b) (4) is proposed based on data at 25˚C/60% RH and 30˚C/65% RH through 36 months.

QbD Aspects: The development of the apixaban drug substance manufacturing process utilizes QbD concepts. [redacted] (b) (4)


(b) (4)

Drug Product

Apixaban film-coated tablets are immediate release dosage forms available in 2 strengths, 2.5 and 5 mg. Standard compendial excipients are used in the tablet cores. The film-coating, which is [redacted], is used to [redacted]. The coating [redacted] a combination of ingredients which meet compendial requirements. A commo [redacted] Both Phase 3 and the proposed commercial tablets are film-coated and differ only in the shape and film-coat color/composition. Specifications proposed for release of apixaban tablets include the following test attributes: description, identification, assay, content uniformity, disintegration and microbial limits. Batch analysis data have been submitted for clinical, registration/stability and commercial scale batches representative of the commercial formulation manufactured at both BMS facilities in New Brunswick, NJ and Humacao, Puerto Rico. The proposed commercial batch sizes will vary within the range [redacted] tablets for 2.5 mg strength and [redacted] tablets for the 5 mg strength. The container closure system for apixaban 2.5 mg tablets is a [redacted] HDPE bottle with a [redacted]. An additional package presentation, [redacted] blisters, is also proposed. The 5 mg strength will be packaged in [redacted] HDPE bottles as well as in blisters. Stability data have been provided for 3 pilot scale batches of each strength. A [redacted] has been applied to tablet counts in [redacted] HDPE bottles. For the 2.5 mg strength, 24 months of long term data at 25˚C/60% RH and 6 months at 40˚C/75% RH are available in addition to stress and photostability data. The test parameters include appearance, assay, impurities, disintegration, dissolution, [redacted], tablet hardness and microbial limits. For the 5 mg strength, 30 months of long term data at 25˚C/60%RH have been provided in addition to data at accelerated and stress conditions. The applicant states that apixaban tablets are stable under all conditions tested and proposes a shelf-life of 36 months for both strengths. No statistical analysis has been performed in support of the proposed shelf-life. [redacted]

QbD Aspects: A comprehensive pharmaceutical development section has been submitted in Section 3.2.P.2. Quality risk assessments and design of experiments (DoE) were performed to understand the input raw materials required for a robust formulation and the impact of variability associated with the input raw materials and manufacturing process parameters on the critical quality attributes of the drug product. The data obtained were used to establish [redacted] and to define the control strategy for the commercial manufacture of apixaban tablets. Starting from the Quality Target Product Profile, the applicant has identified the following CQAs that can impact the safety and efficacy of apixaban tablets: identity, assay, impurities/degradants, content uniformity, dissolution and disintegration. Since the initial [redacted]

(b) (4)

Critical Review Issues

Drug substance

- Are the proposed specifications, particularly the impurity acceptance criteria, for (b) (4) materials acceptable? (b) (4)
- Is the control strategy for potential genotoxic impurities acceptable? Has the applicant convincingly demonstrated that there is no need to routinely test drug substance batches for these impurities?
- Have the proposed (b) (4) been adequately verified to allow the conclusion tha (b) (4) will have no impact on drug substance quality?
- Regarding drug substance specifications:
  - (b) (4)
  -
  -
  -

- Is the justification (i.e. low levels determined for 14 batches) for the omission of [redacted] testing satisfactory?

Drug Product

- Have satisfactory excipient compatibility studies been performed?
- A [redacted] has been proposed for apixaban tablets which should be evaluated in depth to confirm that [redacted] within the stated ranges will have no effect on product performance.
- Is the [redacted] described in sufficient detail taking into account the recommendations provided in the pre-NDA meeting? Is there confidence that using this [redacted] ?
- Are the acceptable ranges proposed fo [redacted] adequately justified?
- At the pre-NDA meeting, the Applicant had stated they would propose [redacted] What problems have they encountered and what, if any, suggestions can be provided to facilitate implementation of this control strategy?
- Regarding specifications for apixaban film coated tablets
  - BMS proposes to perform [redacted] . This should be evaluated by ONDQA Biopharmaceutics. At the pre-NDA meeting, BMS was told that this was not acceptable since the [redacted] . The applicant was advised to develop a better method and supply additional information before a decision could be made to [redacted] Has BMS complied with these requests?
  - BMS proposes to [redacted] At the pre-NDA meeting they were advised that although this could be acceptable, a "high burden of scientific proof" would be required. Has BMS provided sufficient data and assessment of risk to justify omission of this testing?
  - Is skip lot testing acceptable for the microbial limits test?
  - Are the [redacted] methods shown to be equivalent for the identification of apixaban?
- The primary stability studies reported include the test attributes [redacted] dissolution and tablet hardness, however, these parameters are not part of the protocols for the 3 production batches and annual batches. Is this acceptable?
- The stability data were generated for apixaban 2.5 mg tablets packaged in HDPE bottles without a [redacted] whereas for the 5 mg strength HDPE bottles with a [redacted] were used. It is claimed that the stability of these two strengths is equivalent and so, the data for the 5 mg tablets support the addition of a [redacted] to the HDPE bottles for the 2.5 mg strength. Is this claim tenable?

Comments and Recommendations

The CMC section is complete and the application is fileable; however, labeling is not available at this time. A categorical exclusion from EA has been requested. Manufacturing, testing and packaging facilities will be entered into EES when the official clock starts for this submission. (b) (4) The reviewers should be familiar with QbD submissions since both drug substance and drug product sections contain significant elements of QbD. For the manufacture of apixaban tablets, an (b) (4) . Since there is an extensive discussion of these methods, including model development and maintenance in 3.2.P.2, it is advisable to consult a reviewer with expertise in this area. (b) (4) a Division-Level Regulatory Briefing is recommended.

Kasturi Srinivasachar	Jan. 6, 2011
Pharmaceutical Assessment Lead	Date
Ramesh Sood, Ph.D.	Jan. 6, 2011
Branch Chief	Date

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/s/

KASTURI SRINIVASACHAR
01/06/2011

RAMESH K SOOD
01/07/2011

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

/s/

CHARLES F JEWELL
11/08/2011

RAMESH K SOOD
11/08/2011

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number: 202155	**Supplement Number and Type: Orig-1**	**Established/Proper Name: Apixaban**
Applicant: Bristol Myers Squibb	**Letter Date: 9/28/2011**	**Stamp Date: 9/28/2011**

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:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		for drug substance section.
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		for drug substance section.
3.	Are all the pages in the CMC section legible?	X		for drug substance section.
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		for drug substance section.

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
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? **This question is not applicable for synthesized API.**			NA

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

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

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	Y		Description is an incomplete synopsis which fails to include details of the manufacturing operations.
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?		N	Critical steps are identified, but not described in any detail
21.	Is there a batch production record and a proposed master batch record?		N	(b) (4) is an incomplete diagram of the manufacturing process
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		N	Investigational batches are listed, but data is provided
23.	Have any biowaivers been requested?	Y		(b) (4)
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	Y		Description is complete
25.	Does the section contain controls of the final drug product?	Y		Specification is complete, but needs to be refined
26.	Has stability data and analysis been provided to support the requested expiration date?	Y		Data addresses strengths, packaging configurations and manufacturing sites.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	Y		Studies in NDA section 3.2.P.2 are not sufficient to support the proposed (b) (4)

28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	Y		(b) (4) [redacted]

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	Y		Validation studies are incomplete and there is no data from the site of use

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			N/A

H. BIOPHARMACEUTICS			
Parameter	**Yes**	**No**	**Comment**
Does the section contain information/data supporting the dissolution method and acceptance criterion, including method development procedures and method validation reports?	Y		Additional information is needed to support the proposed dissolution acceptance criterion
Has dissolution been identified as a critical quality attribute?	Y		
Does the section contain information on the impact of manufacturing variables on dissolution?	Y		Information is incomplete.
Does the section contain biopharmaceutics information (dissolution, bioavailability/bioequivalence) use to guide (b) (4) [redacted] under the QbD approach?		N	(b) (4) [redacted]. Additional information is needed to support this proposal.

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

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

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)		(b) (4)		Jan. 5, 2010	
				Sep. 9, 2010	
	III			Aug. 10, 2009	
	III			Aug. 10, 2009	
	III			Jan. 12, 2010	
	III			Aug. 19, 2009	
	II			Jun. 8, 2010	

J. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		

33.	Have the immediate container and carton labels been provided?	X		

K. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Describe filing issues here or on additional sheets
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		IR questions will be prepared before the 74-day letter is due.

{See appended electronic signature page}

Charles F. Jewell Jr. — October 21, 2011
William M. Adams — October 25, 2011
Sandra Suarez — October 26, 2011
Yong Wang — October 28, 2011

{See appended electronic signature page}

Name of
Branch Chief — Date
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

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

/s/

CHARLES F JEWELL
10/28/2011

WILLIAM M ADAMS
11/04/2011

SANDRA SUAREZ
11/06/2011

YONG WANG
11/07/2011

RAMESH K SOOD
11/07/2011