CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206316Orig1Orig2s000

CHEMISTRY REVIEW(S)

CMC Memo to File

To:	NDA 206316
Date	15 December 2014
Sponsor:	Daiichi-Sankyo
Drug:	Edoxaban Tablets, 15 mg, 30 mg and 60 mg
Subject	OC recommendation
Reviewer	Dr. Akm Khairuzzaman

Pursuant the overall "acceptable" recommendation given on 14-Nov-2014 for the manufacturing facilities by the Office of Compliance, the CMC recommendation is no changed to "**Recommended for Approval**" from CMC perspective.

HFD-/Division File
HFD-120

Akm Khairuzzaman, Ph.D.
Chemistry Reviewer

Olen Stephens, Ph.D.
Acting Branch Chief, ONDQA

Attachment

(b) (4)

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

/s/

AKM KHAIRUZZAMAN
12/15/2014
Recommended for Approval from CMC point of view

OLEN M STEPHENS
12/15/2014

Savaysa (edoxaban) tablets

NDA 206316

Summary Basis for Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: Daichii Sankyo.
US Agent: Doreen V. Morgan
399 Thornall Street, 10th Floor
Edison
NJ 08837

Indication: To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (DCRP)

Treatment of deep vein thrombosis and pulmonary embolism (DHP)

(b) (4)

Presentation: The product will be available in 15 mg, 30 mg, and 60 mg strength, immediate release, film coated tablets. The tablets are orange, round-shaped, debossed with "DSC L15" (15 mg tablets), pink, round shaped, debossed with "DSC L30" (30 mg), and yellow, round shaped, debossed with "DSC L60" (60 mg tablets). The tablets are packaged in HDPE bottles with 7, 30, 90 and 500 counts. The tablets are also available in (b) (4) aluminum foil blister unit dose packages of 7 and 10 counts.

EER Status: Overall recommendation is pending as of 2-Oct-2014.

Consults: ONDQA Biopharmaceutics - Acceptable with PMC (Sandra Suarez, 9-Sep-2014).

Microbiology - Acceptable (Steven Donald, 3-Apr-2014)

Methods Validation - Acceptable (Jason Rodriguez, 5-Sep-14)

EA – Categorical exclusion granted.

Post-Approval Agreements: The biopharmaceutics reviewer recommends Post-Marketing Commitment from the company to develop an improved discriminating and canonical method and set the final dissolution acceptance criteria for the product using the new method.

Drug Substance:

The drug substance, edoxaban tosylate, a new molecular entity, is a white to pale yellowish crystalline powder. Edoxaban tosylate can exist in (b) (4) The drug substance, edoxaban tosylate, is synthesized using a (b) (4)

The drug substance quality is ensured through quality control of all starting materials, in-process controls throughout the manufacturing process, appropriate quality control of the isolated intermediates and the appropriate final drug substance specification. The drug substance acceptance specification includes tests and acceptance criteria for drug substance critical quality attributes, e.g., appearance, identification, assay, organic impurities, (b) (4) heavy metals, residue on ignition, water content, residual solvents and particle size distribution. The analytical procedures have been adequately described and validated to control the quality of the drug substance. The stability of the drug substance has been demonstrated through appropriate stability studies to support a retest period of (b) (4) months when stored (b) (4)

Drug product:

Savaysa (edoxaban) tablets are an immediate release product to be marketed in 15 mg, 30 mg and 60 mg strengths. The three strengths are dose proportional that use standard compendial excipients, e.g., mannitol, pregelatinized starch, crospovidone, hydroxypropyl cellulose, and magnesium stearate. The manufacturing process is a (b) (4) The manufacturing process has appropriate in-process controls to ensure the quality of the drug product. The product release testing is done through (b) (4) for most of the attributes. The product specification includes testing for appearance, identification, assay, uniformity of dosage units, related substances, and dissolution. All analytical procedures for the drug product are adequately described and validated. The provided stability data support the proposed 36-month expiration period for this product.

The drug product is stored at 25°C with excursions permitted 15-30ºC (59-86ºF).

Conclusion: Adequate from CMC perspective.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion: The application is recommended for **"Approval"** from CMC perspective pending a final overall "Acceptable" recommendation from the Office of Compliance about the manufacturing facilities.

Ramesh K. Sood, Ph.D.
Acting Director, DPA I/ONDQA

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

/s/

RAMESH K SOOD
10/07/2014

Memorandum

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

Date: 21-Aug-2014

From: Janice Brown, M.S.
CMC Lead
DNDQA I/ONDQA

Through: Ali Al-Hakim, Ph.D.
Chief, Branch II
New Drug Quality Assessment Division I1
ONDQA

To: NDA 206316
Edoxaban Tablets

Subject: Risk Assessment

As per a new policy, each NDA with GRMP dates on or after August 1, 2014 will include a risk assessment in the Executive summary. This will be based on an initial risk assessment that would be captured in all IQAs written for NDAs received on or after June 1, 2014. It was decided that the CMC Lead would perform a retrospective risk assessment for those NDAs received prior to June 1, 2014 that had GRMP dates after August 1, 2014.

The following IQA template was provided:

ONDQA Risk Assessment Template for Initial Quality Assessments of Original NDAs

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment

In an email dated 30-May-2014, Dr. Ramesh Sood provided follow-up guidance on how to fill out the required IQA template that is used to populate the NDA template. The guidance provided templates for the most common dosage forms.

This memo captures both the table that would normally be in the IQA and populates the first three columns of the NDA template that will be filled in by the primary CMC reviewer.

IQA RISK ASSESSMENT

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment	Risk
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	3	2	Release (1) Stability (3)	Release (6) stability (18)	Moderately Stable Drug: Single impurity > (b) (4) Total impurities <	L
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3 (Crystalline)	3 (BCS IV)	4	36		M
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	1 (b) (4)	3	4	12		L
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	1	2	5	10	OPS Micro will assess	L
Dissolution	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipment • Site	4	2	4	32	ONDQA BioPharm will assess	M

The evaluation from the IQA table was transferred to the following NDA table that can be used by the primary reviewer as a part of the NDA review.

NDA RISK ASSESSMENT TABLE

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations / Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L			
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M			
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L			
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L			
Dissolution	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipment • Site	M			

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

/s/

JANICE T BROWN
08/22/2014

ALI H AL HAKIM
08/22/2014

Submission Type: Standard; Type 1 submission
Recommendation: Pending

NDA 206316
Review 1
Review Date Sept 8, 2014

Drug Name/Dosage Form	Endoxaban / Immediate Release Tablets
Strength	15, 30 and 60 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Daichii Sankyo
US agent, if applicable	Doreen V. Morgan, Pharm D. Exe. Director, Regulatory Affairs Phone #: (732) 590-5198; Fax #: (732) 906-6652 Add: 399 Thornall Street, 10th floor, Edison, NJ 08837

Submission Reviewed	*Received Date*
Original NDA Submission	**08-Jan-2014**
Quality/Response To Information Request	**22-Jan-14**
Quality/Response To Information Request	**14-Feb-2014**
Quality/Response To Information Request	**03-Apr-2014**
Quality/Response To Information Request	**18-Apr-2014**
Quality/Response To Information Request	**23-Apr-2014**
Quality/Response To Information Request	**29-Apr-2014**
Quality/Response To Information Request	**30-Apr-2014**
Quality/Response To Information Request	**05-May-2014**
Quality/Response To Information Request	**09-May-2014**
Quality/Response To Information Request	**16-Jun-2014**
Quality/Response To Information Request	**07-Jul-2014**
Quality/Response To Information Request	**10-Jul-2014**
Quality/Response To Information Request	**24-Jul-2014**
Quality/Response To Information Request	**01-Aug-2014**
Quality/Response To Information Request	**18-Aug-2014**

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Debasis Ghosh	Branch II/ Division I
Drug Product	Akm Khairuzzaman	Branch I/ Division I
NIR Procedures	Yubing Tang	Branch VI/ Division II
Microbiology	Steve Donald	
Facility	Vibhakar Shah, Vipul Dholakia	
Biopharmaceutics	Sandra Suarez	
CMC Lead	Kasturi Srinivasachar (DCRP), Janice Brown (DHP)	
Project Manager	Yvonne Knight	

Technical Lead	Sharmista Chatterjee	
Laboratory (OTR)	John Kauffman, Jason Rodriguez	OTR/DPA
ORA Lead		
Environmental Assessment (EA)		

Quality Review Data Sheet

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

2. **RELATED/SUPPORTING DOCUMENTS:**
   A. DMFs:

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

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DATE
EOP2 CMC Only	IND 63266	01-Jul-2010
Pre-NDA Meeting	IND 63266	24-Sep-2013

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Division of Pharmaceutical Analysis/OTR	Completed	Methods are suitable for their intended use	5-Sep-2014	Dr. Jason Rodriguez

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Summary of Complete Response issues
Recommendation pending EES recommendation and response from the firm regarding concerns with dissolution method and (b) (4) proposal. Additionally, the applicant has committed to several changes in the drug substance specifications and change management of the drug product design spaces, but has not formally updated the NDA. These amendments will be captured in following reviews.

b. Action letter language, related to critical issues such as expiration date
These will be communicated with the final recommendation

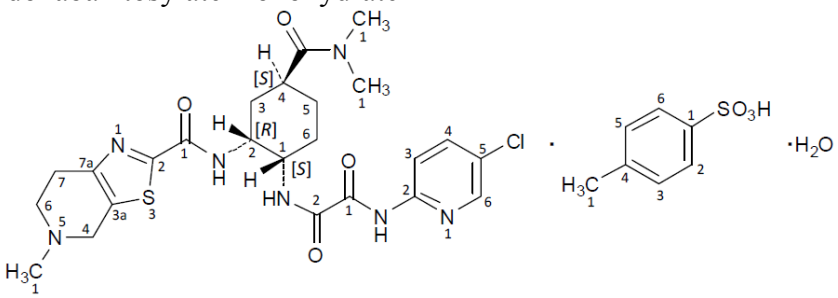
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The biopharmaceutics reviewer is in negotiations regarding a post-marketing commitment to develop a more discriminating dissolution method and associated acceptance criteria within one year of approval. This commitment has not yet been finalized.

II. Summary of Quality Assessments

- **Drug Substance [USAN Name] Quality Summary**

a. Chemical Name or IUPAC Name/Structure
Endoxaban tosylate monohydrate



b. Properties/CQAs Relevant to Drug Product Quality
Solubility (acid soluble, base or water insoluble), hygroscopicity (non-hygroscopic), particle size and (b) (4) Chiral compound (no inversion of configuration). Based on NDA, edoxaban tosylate (b) (4) possibly (b) (4) (b) (4)

(b) (4)

c. List of starting materials & Suppliers of starting materials (site)

Chemical Name of Starting Material	Supplier
(b) (4)	Custom manufacturer
	Non pharmaceutical market and commercially available
	Non pharmaceutical market and commercially available
	Non pharmaceutical market and commercially available

The proposed starting materials are consistent with ICH Q11.

d. Summary of Synthesis

The drug substance, edoxaban tosylate monohydrate, is synthesized using a

(b) (4)

(b) (4)

e. Process

(b) (4)

f. Drug Substance Specification

Release and stability specification included tests for: appearance, identification, organic impurities, (b) (4) heavy metals, residue on ignition, water content, residual solvent, assay, particle size distribution. Though (b) (4) is important to drug product quality, supporting batch data was presented to show consistent generation of (b) (4) The justification for the exclusion of (b) (4) in the release and stability specifications is provided. It is acceptable.

g. Container Closure System
The drug substance is packaged in double low density polyethylene (LDPE) bags with twist ties and placed in a high density polyethylene (HDPE) drum.

h. Retest Period & Storage Conditions
The proposed (b) (4) months of retest period, when stored at long-term storage conditions (b) (4) in the proposed container closure system, is acceptable

- **Drug Product [Edoxaban tosylate, tablets] Quality Summary**

a. Strength
Available in three strengths, 15, 30 and 60mg

b. Description/Commercial Image

Item	15 mg tablets	30 mg tablets	60 mg tablets
Description (appearance)	Orange round-shaped film-coated tablets debossed with "DSC L15"	Pink round-shaped film-coated tablets debossed with "DSC L30"	Yellow round-shaped film-coated tablets debossed with "DSC L60"
Dosage form	Immediate release film-coated tablets	Immediate release film-coated tablets	Immediate release film-coated tablets
ID code (debossing)			
Tablet weight	105 mg	210 mg	420 mg

c. Summary of Product Design
Dose proportional formulation, manufactured using a (b) (4)

d. List of Excipients:
Mannitol, pregelatinized starch, crospovidone, hydroxypropyl cellulose, magnesium stearate, and film coating materials (b) (4) orange, pink and yellow). All ingredients are of USP grade and IIG limits of all excipients are well within limits used for commercial product manufacture.

e. Process Selection (Unit Operations Summary)
The drug product is manufacturing process by (b) (4)

(b) (4)

f. Drug product specifications

(b) (4) was proposed for almost all attributes with the exception of description that are included in the specification. This included:

(b) (4)

- (b) (4) proposed for dissolution as a function of some (b) (4). However, as detailed in the biopharmaceutics review this approach was found to be unacceptable. The biopharmaceutics has a verbal agreement with the applicant to remove the model supporting (b) (4) of dissolution, implementing release testing with the current dissolution method with associated acceptance criteria, and to commit to a post-marketing commitment to develop a more discriminating method.
- No microbial testing for routine release. This is supported by (b) (4) activity results that show finished product doesn't support microbial growth.
- (b) (4) is used as a backup method for (b) (4) It is also the regulatory analytical method. The method was validated using the (b) (4) mg strength, since other strengths are dose proportional. Validation data provided followed the requierments as outlined in ICH Q2(R1) and was found to be adequate

g. Container Closure

SAVAYSA Tablets will be packaged in all aluminum blisters as well as in HDPE bottles.

h. Expiration Date & Storage Conditions
Proposed shelf life is 36 months at long term storage conditions of 25ºC/60%RH. This is supported by 24 months of registration stability batch data and 48 months of clinical (phase 3) batch stability data. Batches used in the registration stability program were manufactured by the final commercial process at pilot-scale.

i. List of co-packaged components
NA

- **Summary of Drug Product Intended Use**

Proprietary Name of the Drug Product	Savaysa TM
Non Proprietary Name of the Drug Product	Edoxaban Tosylate
Proposed Indication(s) including Intended Patient Population	Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (DCRP) Treatment of deep vein thrombosis and pulmonary embolism (DHP) (b) (4)
Duration of Treatment	
Maximum Daily Dose	60 mg
Alternative Methods of Administration	NA

- **Biopharmaceutics Considerations**

(For additional details regarding biopharmaceutics considerations refer to the review by Sandra Suarez)

a. BCS Classification: lass IV
b. Specification: NLT (b) (4)% in 30 min
c. Biowaivers/Biostudies
   - Biowaiver Requests : NA
   - PK studies
   - IVIVC : None

- **Novel Approaches**

Applicant has proposed for (b) (4) for all quality attributes except for (b) (4)

Following (b) (4)

(b) (4)

However, this approach was found to be inadequate upon review. Also, change control protocols were included for managing post approval changes to (b) (4). Upon review, the applicant was asked to modify and resubmit the reporting categories for some potential changes as a protocol. The applicant agreed to the information request, and a comparability protocol was submitted in Amendment 08/01/2014 in Section 3.2.R. This only includes changes and maintenance of the (b) (4) the applicant has not yet sent a similar protocol for the drug product design spaces. No comparability protocol for design space is submitted in Section 3.2.R.

- **Any Special Product Quality Labeling Recommendations** NA

Lifecycle Knowledge Management

a) Drug Substance

From Initial Risk Identification				Review Assessment	
Attribute/ CQA	**Initial Risk Ranking***	**Justification**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Organic impurities including genotoxic impurities			(b) (4)	Acceptable	Limits for genotoxic impurities to be revisited if there is a change in drug substance processing conditions
Elemental impurities/residual solvents				Acceptable	Limits for residual solvents to be revisited if there is a change in drug substance synthesis or any of the starting materials Limits for elemental impurities to be revisited if there is a change in drug substance processing conditions
Particle size distribution				Acceptable	Evaluate adequacy of existing PSD specifications if there is a change in drug product manufacturing conditions or change in bulk excipient PSD (due to a change in supplier or grade)
Assay				Acceptable	None
Water content				Acceptable	Evaluate adequacy of existing water content specifications if there is a change in drug product manufacturing, e.g. change in type and amount of excipients
Stability				Acceptable	Stability data to be evaluated if there is a change in drug substance synthesis. A post approval stability protocol and stability commitment included in the application and are consistent with ICH Q1A

Note: Since initial risk ranking was not done for the drug substance, these cells are greyed out

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking ***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters •Scale/equipment • Site	L	(b) (4)		
Physical stability (solid state)	• Formulation • Raw materials • Process parameters •Scale/equipment • Site	M			
Content Uniformity	• Formulation • Raw materials • Process parameters •Scale/equipment • Site	L			
Microbial limits	• Formulation • Raw materials • Process parameters •Scale/equipment • Site	L			
Dissolution	API particle size, Granule characteristics, Moisture, Tab hardness and density, Disintegration, formulation components	M			

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

226 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

AKM KHAIRUZZAMAN
09/08/2014

DEBASIS GHOSH
09/08/2014
Responsible for Drug Substance Review only

YUBING TANG
09/08/2014

SHARMISTA CHATTERJEE
09/08/2014

OLEN M STEPHENS
09/08/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
1114 Market Street, Room 1002
St. Louis, Missouri 63101
Telephone (314) 539-3855
FAX (314) 539-2113

Date: September 5, 2014

From: Jason D. Rodriguez, Ph.D., Chemist, OPS/OTR/ DPA

To: Yubing Tang, OPS/ONDQA/DNDQAII/BRVI
Yvonne Knight, OPS/ONDQA

Through: John Kauffman, Ph.D., Deputy Director, OPS/OTR/ DPA

Subject: DPA Consult for NDA206316 Edoxaban Tablets

Background

The Division of Pharmaceutical Analysis reviewed the (b) (4) methods for NDA206316 with emphasis on the questions raised in the consult request from Yvonne Knight dated January 18, 2014 The methods described in the application employ both (b) (4)

Conclusion

In general the (b) (4) are well-described and seem to be appropriate for their application and use and we find the methods adequate as amended. The applicant has placed emphasis on several different hazards that are important in determining the performance of the methods. In general, the hazards cited are commonly known for (b) (4) and have been documented in literature for several decades. The models developed are based on well-known (b) (4) and references are provided throughout the document when necessary. Specific areas where more information would be helpful are identified in Attachment 1 in red and summarized below.

Areas Needing Clarification

- (b) (4) should be documented for all the models developed. All models follow the same general procedure and are claimed to be suitable for their intended purpose based primarily on the linear trend between the (b) (4) method and the reference methods.
- The section dealing the determination of the effective (b) (4) has few details to fully evaluate the conclusions reached in the application.

Overall Evaluation and Review Outcome:

The following Information Request was sent to the applicant on June 17, 2014:

1. *Provide technical details to show how mean areas were calculated by using* (b) (4)
2. *For figures 1.136 through 1.138 in section 3.2.P.2.3, provide the measured* (b) (4)
3. *Clarify whether batch samples used in method validations were representative of the expected process and material variability, and these samples were different from those used in the calibration set.*

On July 7, 2014 the applicant submitted an amendment addressing these areas as follows:

1. (b) (4)
2. The (b) (4) for the figures 1.136 through 1.138 are not given due to limitations of the software used for these identification tests. The Applicant provides a (b) (4)
3. The information from the Applicant clearly shows that the batch samples used in the validation are both different from the calibration samples and representative of expected material variability.

Evaluation: **Adequate as Amended**

The Division of Pharmaceutical Analysis has found the responses by the Applicant to the information request to be adequate.

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

MICHAEL L TREHY
09/05/2014

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

METHODS VALIDATION REPORT SUMMARY

TO: Akm Khairazzuman and Debasis Ghosh, CMC Reviewer

Office of New Drug Quality Assessment (ONDQA)
E-mail Address: akm.khairazzuman@fda.hhs.gov
Phone: (301)-796-3886 (Akm); (301) 796-4093 (Debasis)
Fax: (301)-796-9747

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-3815

Through: John Kauffman, Deputy Director
Phone: (314) 539-2168

SUBJECT: Methods Validation Report Summary

Application Number: 206316

Name of Product: Savaysa (edoxaban), Tablets 15, 30 amd 60 mg

Applicant: Daiichi Sankyo, Inc.

Applicant's Contact Person: Doreen V. Morgan, Pharm.D.; Executive Director, Regulatory Affairs

Address: 399 Thornall Street, 10th floor, Edison, NJ 08837

Telephone: (732) 590-5198 Fax: (732) 906-5562

Date Methods Validation Consult Request Form Received by DPA: Feb-28-2014

Date Methods Validation Package Received by DPA: Feb-28-2014

Date Samples Received by DPA: Apr-15-2014

Date Analytical Completed by DPA: June-24-2014

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: See attached memo for analysts' comments and data summary.

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-3852

Date: June 23, 2014

From: Changning Guo, Chemist (DPA)

To: Akm Khairazzuman and Debasis Ghosh, CMC Reviewers,
Kasturi Srinivasachar, CMC Lead
Office of New Drug Quality Assessment (ONDQA)

Through: John Kauffman, Deputy Director, Division of Pharmaceutical Analysis (DPA)

Subject: Method Validation for NDA 206316
Edoxaban Tablets, 15 mg, 30 mg, and 60 mg
Daiichi Sankyo, Inc

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

1. (b) (4)
(Daiichi Sankyo, Inc, 3.2.S.4.2)

2. (b) (4)
(Daiichi Sankyo, Inc, 3.2.S.4.2)

3. (b) (4)
(Daiichi Sankyo, Inc, 3.2.S.4.2)

4. (b) (4)
(Daiichi Sankyo, Inc, 3.2.P.5.2)

5. (b) (4)
(Daiichi Sankyo, Inc, 3.2.P.5.2)

6. Dissolution, Apparatus 2, 50 rpm, UV-VIS
(Daiichi Sankyo, Inc, 3.2.P.5.2)

The following method was not evaluated due to lack of the required sampling unit at DPA:

(b) (4)
(Daiichi Sankyo, Inc, 3.2.S.4.2)

Link to analyst's work sheets and data:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f88073196b

DPA has the following comments pertaining to the following methods.

(b) (4)
(Daiichi Sankyo, Inc, 3.2.P.5.2)

(b) (4)

2 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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

/s/

MICHAEL L TREHY
06/24/2014

JOHN F KAUFFMAN
06/25/2014

INSPECTIONAL ASSIGNMENT
(EMAIL TRANSMITTAL)

Date:	May 23, 2014
To:	*International* Division of Medical Products and Tobacco Inspections Office of Regulatory Affairs
Facility(ies):	Daiichi Sankyo Propharma Co., Ltd. (DSPP) Akita Plant, 1-10-1, Mukaihama, Akita-shi Akita, 010-1601, Japan **FEI No:** 3002806777 and Daiichi Sankyo Chemical Pharma Co., Ltd. (DSCP) Odawara Plant, 477, Takata, Odawara-shi, Kanagawa 250-0216, Japan **FEI No.:** 3003279188
Drug Name (dosage form, strength/concentration):	Edoxaban Tosylate Drug Substance
Profile Class:	(b) (4)
A/NDA No.:	NDA 206-316
Chemistry Reviewer	Debasis Ghosh, Ph.D. CDER/OPS/ONDQA/DNDQAI/BRII debasis.ghosh@fda.hhs.gov Tel: 310-796-4093
Microbiology Reviewer (if applicable)	N/A
OC Compliance Officer	Vipul Dholakia, Ph.D, CDER/OC/OMPQ HFD-320 vipul.dholakia@fda.hhs.gov Tel. 301-796-5065

CDER has identified specific area(s) for inspectional focus for drug substance manufacturing in connection with the NDA 206-316. In accordance with the API Process Inspection Compliance Program 7356.002F, PAIs provide for continuity in our pre-market review of drug product by focusing on areas in which data is questionable; drug

characteristics or sensitivities[1] indicate special scrutiny, the overall manufacturing and control strategy appears lacking; and potential manufacturing weaknesses may exist.

Summary of Drug Substance and Manufacturing Process

Edoxaban, an antithrombotic agent, is a member of the anti-factor Xa class of compounds. Edoxaban Tosylate is a white to pale yellowish-white powder and is a pure, stable crystalline solid which exhibits (b) (4) Edoxaban tosylate exists i (b) (4)

Edoxaban is a new molecular entity indicated to reduce the risk of stroke and systemic embolic events in patients with nonvalvular atrial fibrillation, and the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), (b) (4)

Manufacturing Process:

The manufacturing process for Edoxaban Tosylate (b) (4)

The manufacturing process for (b) (4)

The (b) (4) for manufacturing edoxaban tosylate are summarized below:

(b) (4)

(b) (4)

9 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

The following is a brief explanation of product or process specific issues that should receive follow-up during the inspection.

I. Chemistry Review

The chemistry reviewer, Debasis Ghosh did not have any major issue for inspectional coverage.

II. Microbiology Review

The microbiology reviewer, Steven Donald did not have any major issue for inspectional coverage.

III. Manufacturing

Edoxaban Tosylate (Daiichi Sankyo Propharma Co. Ltd.)

a. (b) (4)

b. (b) (4)

c. (b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

IV. Quality Control / Quality Assurance

a. Quality System**:**

i. Determine if all laboratory test instruments are adequate for their intended use (qualified). Review the HPLC analytical method used (b) (4) and determine if the HPLC method is validated.

ii. Determine if any OOS results or deviations or rejections have occurred during development or scale up, and report on adequacy of investigations.

b. Validation:

i. Review the process performance qualification protocol (if available), which specifies the procedures (and tests) to be conducted and the data to be collected. Determine if the validation protocol includes equipment qualification, an evaluation of the suitability of materials and evaluation of consistent adherence to pre-established process parameters and quality attributes. If process validation batches have been manufactured, review the data generated from these batches.

ii. Determine if the firm has integrated this drug into its (b) (4) approach for (b) (4) equipment and evaluate the (b) (4) program.

c. Stability

i. Review the stability data generated by the firm for this product to determine if the testing was conducted in accordance with the submitted stability protocol, whether stability samples were stored under appropriate storage conditions, whether the testing was conducted appropriately, and whether the stability test results meet all specifications. Include a review of pertinent raw test data.

d. Raw Materials:

i. Determine if there were any OOS results for any incoming raw materials used in the formulation. If so, verify the adequacy of investigations, and determine what corrective/preventive actions are implemented to address these OOS results.

ii. (b) (4)

e. Distribution Supply Chain:

i. (b) (4)

A pre-inspection briefing may be scheduled if additional clarification or background is needed. Should you have questions prior to or post inspection or for significant deficiencies observed during inspection, please contact the CDER officials identified above.

Please report your findings regarding these issues in the Establishment Inspection Report (EIR) under the heading, “ADDITIONAL INFORMATION” with the subheading, “Follow-up to CDER Questions.”

THIS ASSIGNMENT IS CONFIDENTIAL FDA CORRESONDENCE

cc:
HFD-320 (Division Chron File)
HFD-323 (New Drug Manufacturing Assessment Branch)
OC Doc. No.: KTM-2014-012

APPENDIX I

In-Process Controls for the Manufacturing of Edoxaban Tosylate

IPC No.	Stage	Purpose	Sample	Test Method	Acceptance Criteria
(b) (4)					

In-Process Controls for the Manufacturing of (b) (4)

IPC No.	Stage	Purpose	Sample	Test Method	Acceptance Criteria
(b) (4)					

APPENDIX II

Specifications for (b) (4)

Tests	Acceptance Criteria	Analytical Procedure
(b) (4)		

APPENDIX III

Release and Shelf-Life Specifications for Edoxaban Tosylate Drug Substance

Test	Acceptance Criteria	Analytical Procedure [Method No.]
Description (Appearance)	White to pale yellowish-white powder	(b) (4)
Identification	The spectrum from the sample and the reference spectrum exhibit similar intensities in absorption at the same wavenumbers.	
(b) (4) Impurities (b) (4)	Individual Unspecified NMT (b) (4) % Total NMT (b) (4) % (exclusive of the (b) (4) impurity)	
(b) (4) Impurities (b) (4)	(b) (4) NMT (b) (4) %	
(b) (4)	(b) (4) Report Value Report Value	
	(b) (4) Report Value	
Heavy Metals [a)]	Total NMT (b) (4) ppm NMT (b) (4) ppm	
Residue on Ignition [a)]	NMT (b) (4) %	
Water Content	(b) (4)	
Residual Solvent [a)]	(b) (4) NMT (b) (4) ppm	
Assay (b) (4)	(b) (4)	
Particle Size Distribution [a)]	(b) (4) NMT (b) (4) µm	

a) (b) (4) NMT= Not more than

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

/s/

VIPULCHANDRA N DHOLAKIA
05/23/2014

MAHESH R RAMANADHAM
05/23/2014

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

I. Review Cover Sheet

1. OMPQ Reviewer: Vipul Dholakia, Ph.D. (Drug Substance)
Vibhakar Shah, Ph.D. (Drug Product)

2. NDA/BLA Number: 206316
Submission Date: 01/08/2014
21st C. Review Goal Date: 09/09/2014
PDUFA Goal Date: 01/08/2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Savaysa (Proposed)
Established or Non-Proprietary Name (USAN) and strength:	Edoxaban Tosylate Tablet (15 mg, 30 mg, and 60 mg)
Dosage Form:	Tablet

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	Daiichi Sankyo, Inc.
Responsible Organization (OND Divisions):	DCRP and DHP

II. Application Detail

1. INDICATION: Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; treatment of venous thromboembolism including DVT and PE, (b) (4)

2. ROUTE OF ADMINISTRATION: Oral

3. STRENGTH/POTENCY: 15 mg, 30 mg and 60 mg

4. Rx/OTC DISPENSED: ☒Rx ☐OTC

5. ELECTRONIC SUBMISSION (yes/no)? ☒ Yes ☐ No

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		X		
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			QbD and (b) (4) approaches are indicated for the manufacture, control and release of the DP
10.	Other (e.g., expedited for an unlisted reason)		X		

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:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	**Yes**	**No**	**Comment**
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		All sites involved in the manufacture of drug substance and product are stated to be ready on the FDA form 356h.
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	 X X	CMC reviewer is interested in participating on the PAI of the DP mfg facility.

*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.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
16.	Have any Comparability Protocols been requested?		X	

IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
17.	Does this application fit one of the EES Product Specific Categories?	X		NME
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.	**From a CGMP/facilities perspective, is the application fileable?** 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	(b) (4)	PAT	Drug/Device Combo
☐	/☒	☒	☐
PET	Design Space	Continuous Mfg	Naturally derived API
☐	☒	☐	☐
Other (explain):	Quality by Design approach to drug product manufacture		

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	(b) (4) is manufactured at Daiichi Sankyo chemical pharma site. The final drug product, Edoxaban Tosylate tablet is manufactured at Daiichi Sankyo Propharma site.

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?	X		Applicant has proposed implementation of (b) (4)

3. Facility-Related Risks or Complexities (e.g., number of foreign sites, large number of sites involved, etc.)

Drug substance, edoxaban tosylate is manufactured by Daiichi Sankyo Propharma Co. Ltd (DSPP), Akita, Japan and the (b) (4) used in the manufacture of drug substance is manufactured by Daiichi Sankyo Chemical Pharma Co. Ltd., Odawara, Japan. Release and stability testing are also performed at the respective sites.

Additional information on Manufacturing issues or Complexities

Drug Substance Manufacturing Process (see eCTD Section 3.2.S.2.2)

Manufacturing Stages and Reaction Steps for Edoxaban Tosylate

Manufacturing Stage	Description
	(b) (4)

Manufacturing Stages (b) (4)

Manufacturing Stage	Description
	(b) (4)

Drug Product:

Daiichi Sankyo Propharma Co., Ltd. (FEI # 3010164826), located in Hiratsuka, Kaganawa, Japan is identified as the manufacturer of the drug product. The applicant has indicated to employ an "enhanced" QbD approach in developing the manufacturing process, controls and quality assurance for Edoxaban tablets.

As part of the controls strategy, applicant has proposed to (b) (4)

Applicant has proposed to implement (b) (4)

Refer to the process flow chart for in-process controls and critical in-process controls relating to (b) (4) .

Additional information on Manufacturing issues or Complexities:

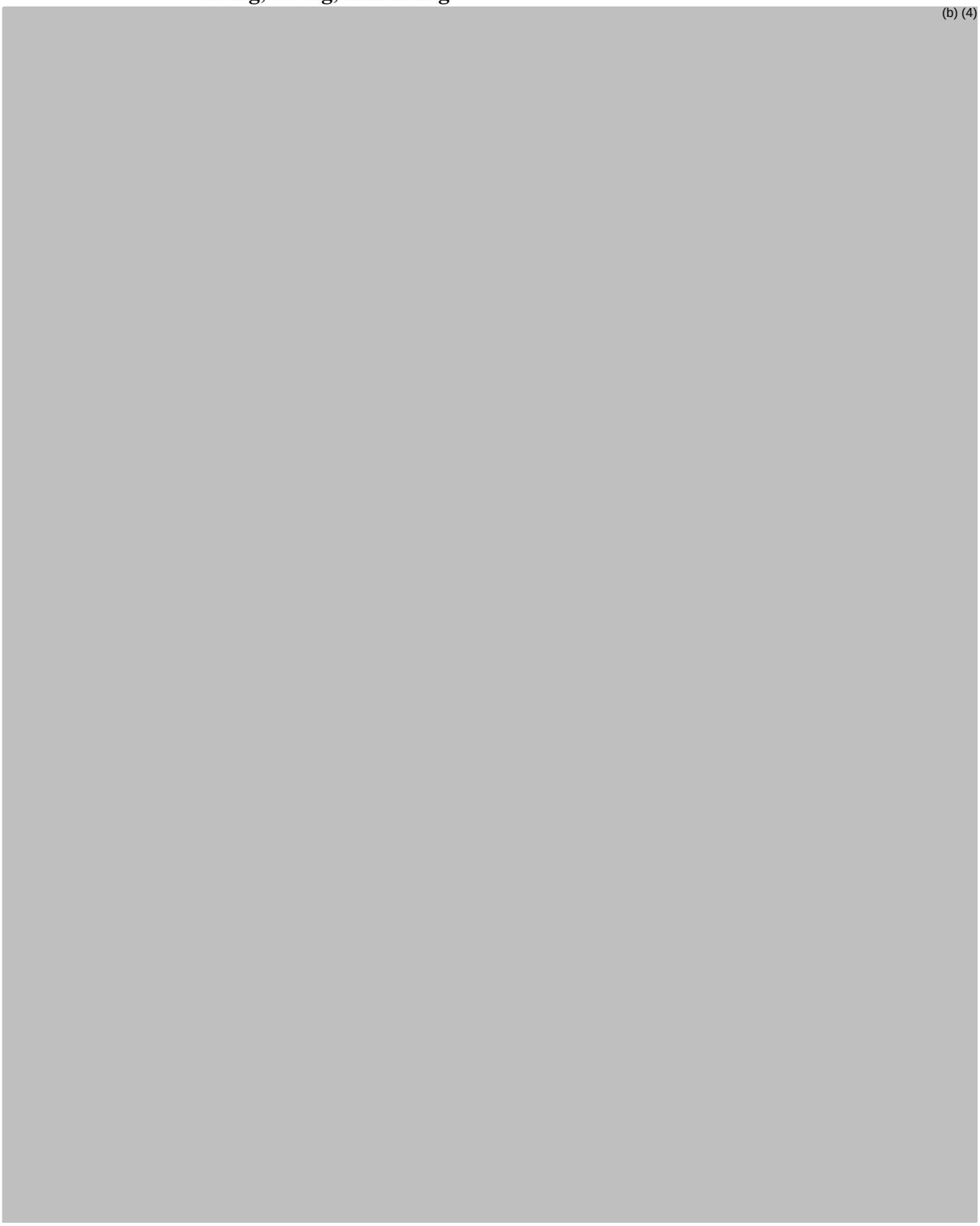
Drug Product Manufacturing Process (see eCTD Section 3.2.P.3.2.3)

Figure 1.1 Overview of the Batch Size for Each Unit Operation

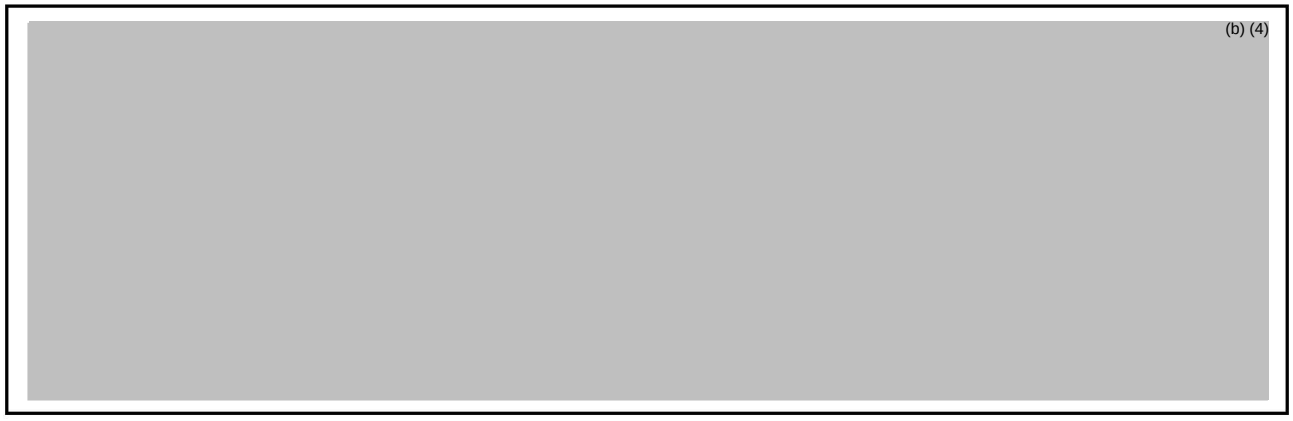
(b) (4)

Edoxaban Tablet Manufacturing Process Flow Chart

Figure 1.2 Commercial Scale Manufacturing Flow Chart for Edoxaban Tablets 15 mg, 30 mg, and 60 mg



Edoxaban Tablet Manufacturing Process Flow Chart



4. Establishment Evaluation Status
Drug substance and Drug product Manufacturing Facilities
GMP Compliance Status Chart
(as of March 5, 2014)

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Facts Assignment ID	Inspection Start -End Date	Most Recent Milestone	Most Recent EER Compliance Status	Comment
Daiichi Pharmaceutical Co., Ltd.	3002806777	ROW	JPN	(b) (4)	CSN	**CSN** [**AC**, 07/30/2009]	9168316	6/2-6/2014	INSPECTION Scheduled	**PN**	DS is NME
Daiichi Sankyo Chemical Pharma Co., Ltd.	3003279188	ROW	JPN		CSN	No prior GMP history	9216817	6/16-20/2014	INSPECTION Scheduled	**PN**	(b) (4)
Daiichi Sankyo	3003673570	PHI	USA		TCM	**TCM,** (b) (4) [**AC**, 04/20/2012] (b) (4) [**AC**, 04/14/2009]	-	-	OC Recommendation	**AC**	Based on Profile 23-Jan-2014 EER-ReEval by: 20-APR-2016
Daiichi Sankyo Propharma Co., Ltd. (DSPP) Hiratsuka Plant	3010164826	ROW	JPN		TCM	No prior GMP history	9168315	6/9-13/2014	INSPECTION Scheduled	**PN**	(b) (4)

DS: Drug Substance**, DP:** Drug Product**; AC**: Acceptable; **NA**: Not Applicable; **TBD**: To be determined; **PN**; Pending; NME: New Molecular Entity

V. Overall Conclusions and Recommendations

Is the application fileable?	**Yes**
At this time, is a KTM warranted for any PAI? To facilitate the pre-approval inspections of both the drug substance and the drug product manufacturing facilities, Knowledge Transfer Memoranda are recommended.	**Yes**
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities?	**No**
Comments for 74 Day Letter	**None**
1.	
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.

/s/

VIBHAKAR J SHAH
03/05/2014

VIPULCHANDRA N DHOLAKIA
03/05/2014

MAHESH R RAMANADHAM
03/05/2014

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: Michael Trehy
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Akm Khairazzuman and Debasis Ghosh, CMC Reviewers
Kasturi Srinivasachar, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: akm.khairazzuman@fda.hhs.gov; debasis.ghosh@fda.hhs.gov
Phone: (301)-796 3886 (Akm); (301)-796 4093 (Debasis)
Fax.: (301)-796 9747

Through: Olen Stephens, Acting Branch Chief
Phone: (301)-796 3901
and
Youbang Liu, ONDQA Methods Validation Project Manager
Phone: (301)-796 1926

SUBJECT: Methods Validation Request

Application Number: NDA 206316

Name of Product: Savaysa (edoxaban), Tablets, 15, 30 and 60 mg

Applicant: Daiichi Sankyo, Inc.

Applicant's Contact Person: Doreen V. Morgan, Pharm.D., Executive Director, Regulatory Affairs

Address: 399 Thornall Street, 10th floor, Edison, NJ 08837

Telephone: 732-590-5198 Fax: 732-906-5562

Date NDA Received by CDER: **1-8-14**

Date of Amendment(s) containing the MVP: **1-8-14**

DATE of Request: **2-28-14**

Requested Completion Date: **5-28-14**

PDUFA User Fee Goal Date: **1-8-15**

Submission Classification/Chemical Class: NME

Special Handling Required: No

DEA Class: N/A

Format of Methods Validation Package (MVP)

☐ Paper X Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as descr bed 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 # 206316

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

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION
Upon FDA request, four representative samples of the drug substance and drug product will be provided to perform each test described in the application three times by the Agency. Reference standards will also be provided upon request to complete the testing.		

⇒ 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 / 3.2.S.4.2
Specifications/Methods for Finished Dosage Form(s)	3.2.P.5.1 / 3.2.P.5.2
Supporting Data for Accuracy, Specificity, etc.	3.2.S.4.3 / 3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms	3.2.S.4.4 / 3.2.P.5.4
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
Drug Substance EDX_QB06	(b) (4)	3.2.S.4.2	**0**	
Drug Substance EDX_QB12		3.2.S.4.2	**0**	
Drug Substance EDX_QB12		3.2.S.4.2	**0**	
Drug Substance EDX_QB11		3.2.S.4.2	**0,4**	
Drug Product 400081-5 (15 mg) 400082-5 (30 mg) 400083-5 (60 mg)		3.2.P.5.2	**0**	
Drug Product 400081-6 (15 mg) 400082-6 (30 mg) 400083-6 (60 mg)		3.2.P.5.2	**0**	(b) (4)

Drug Product 400081-3 (15 mg) 400082-3 (30 mg) 400083-3 (60 mg)	Dissolution, Apparatus 2, 50 rpm, UV-VIS	3.2.P.5.2	**0**	

Additional Comments: **The Applicant has proposed** [redacted] (b) (4) **It is also proposed to omit the** [redacted] (b) (4) **However, the conventional methods will be used for stability testing of the product.**

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

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

/s/

KASTURI SRINIVASACHAR
02/28/2014

OLEN M STEPHENS
02/28/2014

YOUBANG LIU
02/28/2014

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

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 206316

2. DATES AND GOALS:

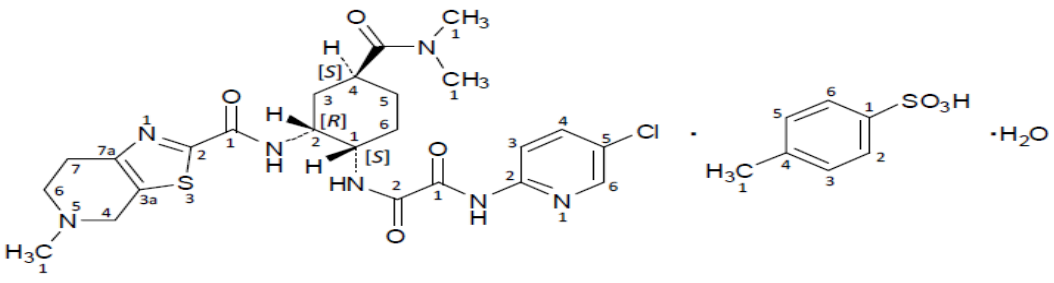
Letter Date: Jan. 8, 2014	Submission Received Date : Jan. 8, 2014
PDUFA Goal Date:	Jan. 8, 2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Savaysa (proposed)
Established or Non-Proprietary Name (USAN):	Edoxaban
Dosage Form:	Tablets, immediate release
Route of Administration	Oral
Strength/Potency	15, 30 and 60 mg
Rx/OTC Dispensed:	Rx

4. INDICATION: 1) To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; 2) for the treatment of venous thromboembolism including DVT and PE; (b) (4)

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



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

Daiichi Sankyo, Inc.

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 1, NME
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	Division of Cardiovascular and Renal Products and Division of Hematology Products

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		If needed by reviewer for genotoxic impurities
Methods Validation	X		
Environmental Assessment		X	
CDRH		X	
Other	X		Microbiology

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?
Yes

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?
No
CMC Comments for 74-Day Letter:
1.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?
Yes
Biopharmaceutics Filing Issues:
1.

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?
Yes
Biopharmaceutics Comments for 74-Day Letter:
Refer to page 12.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?
Yes

Steven Donald: Micro Reviewer

1. Based on the information provided, the application is fillable from a microbiology point of concern. However, issues remain that must be addressed by the applicant.
2. The applicant proposes to perform [redacted] (b) (4) for microbial limits testing (bioburden) for product release. The applicant proposes to perform [redacted] (b) (4) of drug product at release.
3. [redacted] (b) (4) All release tests must be performed for every lot.
4. However, Microbial Limits Testing may be omitted from the product release specifications if process control is demonstrated, from a microbiological standpoint. The reviewer has determined that adequate information is most likely available to qualify the application for reduced microbial limits testing, if the applicant so chooses.

5. The post-approval and annual stability protocols and their acceptance criteria are acceptable, from a microbiological standpoint.

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	Yes	No	(b) (4)

Is a team review recommended? Yes
Suggested expertise for team: This is a fairly complicated QbD submission with (b) (4) proposed (b) (4) A team with a drug substance reviewer trained in (b) (4) and a drug product reviewer with a thorough understanding of QbD concepts is recommended. In addition, since the (b) (4) someone with expertise in this area should also be included in the team.

Summary of Critical Issues and Complexities

Drug Substance:

- Has adequate justification been provided for the designation of (b) (4) as starting materials? Are the specifications for these materials, particularly (b) (4) acceptable?
- Since the only potential genotoxins controlled in the drug substance are (b) (4) have other possible genotoxic impurities from the synthesis been adequately controlled (b) (4) Pharm/Tox consult may be needed for some aspects of genotoxic impurity controls.
- A (b) (4) procedure is proposed for both the (b) (4) if specifications are not met. Has the Applicant shown that (b) (4) did not have to undergo this procedure? Have any constraints been placed on how large the deviation from the specifications have to be (b) (4)?
- Has it been conclusively established that (b) (4)
- The (b) (4) and their applicability to commercial scale should be evaluated.
- Regarding the specification –
  - There is no separate ID or assay for the (b) (4) Is this acceptable?
  - The Applicant was recommended to propose a (b) (4) particle size distribution in the pre-NDA meeting but chose to (b) (4) Have they provided an adequate justification for this?
- Since only 6 months' data have been provided for the site-specific batches, is there any need to request additional data from the on-going studies in order to grant the (b) (4) month retest period proposed?
- Is there a discussion of possible degradation pathways for edoxaban tosylate

Drug Product

- Since it is claimed that an enhanced QbD approach was used for the drug product, all aspects of formulation and manufacturing process development need to be critically evaluated:
    - Are design spaces for (b) (4) acceptable? This is not in accordance with ICH Q8 as discussed with the Applicant at meetings during drug development. It is claimed that using this approach the (b) (4) Does this imply that the firm can make changes to these factors without submitting post-approval supplements?
    - Has equivalence of the results calculated using (b) (4) and those obtained using conventional testing been established for batches manufactured at commercial scale?
    - Are the analytical methods for (b) (4) been adequately validated?
    - The specification table for (b) (4) lists (b) (4) methods for (b) (4) tests. Has it been clearly delineated under what circumstances (b) (4) methods would be employed? How will failure of a (b) (4) method be handled?
    - Table 1.13 in Section 3.2.P.3.4 lists the proposed regulatory filing categories for post-approval changes to (b) (4) – are these acceptable?
- Are the master batch records sufficiently detailed and do they include the proposed design spaces?
- Is the justification for not performing the (b) (4) adequate?
- An equivalency protocol for post-approval changes to container closure materials of construction has been submitted and should be evaluated, with input from the Post-Marketing Division, if needed.
- Is the (b) (4) in the registration stability batches acceptable?
- The post-approval stability commitment protocol for the first 3 commercial batches includes a (b) (4) proposal for the (b) (4) . This is contrary to ICH Q1A which states that the protocol for the full-scale commitment batches should be the same as the pilot scale registration batches.
- Is the proposed matrix for testing the marketed presentations in the annual stability program acceptable?

Initial Quality Assessment

This is a 505(b)(1) application for Savaysa (edoxaban) tablets, 15, 30 and 60 mg. A single NDA has been submitted for the following indications in two clinical divisions:

- To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (Division of Cardiovascular and Renal Products [DCRP]).
- For the treatment of venous thromboembolism including deep vein thrombosis and pulmonary embolism, (b) (4) (Division of Hematology Products [DHP]).

Edoxaban tosylate, an antithrombotic agent, is an NME which belongs to the anti-factor Xa class of compounds. It was developed under INDs 63266 (DHP) and 77254 (DCRP). Three major CMC related meetings were held with the Applicant during the development of this drug – an EOP2 on Nov. 6, 2008, a Type C Guidance meeting on June 2, 2010 to discuss Daiichi's QbD strategy and a pre-NDA meeting on May 17, 2013. The main focus of the EOP2 meeting was the designation of starting materials for the synthesis of edoxaban tosylate, the adequacy of the drug substance and drug product specifications, the general outline of Daiichi's QbD strategy, and the acceptability of the (b) (4) stability designs for the registration drug product batches. The Agency response to questions in these area was that, in general, Daiichi's approach seemed reasonable but that more information/data were needed for review either later in development or in the NDA to make a final determination. The Guidance meeting in 2010 provided details of the Applicant's QbD strategy, including their (b) (4) proposal. (b) (4)

The Pre-NDA meeting in 2013 included a comprehensive discussion of drug substance, drug product and dissolution issues. Regarding the drug substance, the most controversial issue was the designation of (b) (4) as a starting material in the synthesis of edoxaban tosylate. Daiichi had misinterpreted the Agency advice at the EOP2 meeting as agreement with this designation and were surprised that the Agency's current response was an unequivocal 'no' (b) (4) Post-meeting, Daiichi filed an official protest to re-iterate that the Agency was not consistent in its response regarding (b) (4) The Applicant was overruled and (b) (4) was deemed by the Agency (b) (4) Daiichi proposed that they could designate (b) (4) The Agency agreed to this proposal but Daiichi decided not to avail of this offer and has designated (b) (4) as a starting material in the original NDA.

Other drug substance issues related to the completeness and acceptability of the specification. The Agency recommended the inclusion of an (b) (4) or justification for their exclusion. The pharm./tox reviewer provided input on the control strategy for potential genotoxic impurities.

Concerning drug product stability, the Option 2 (b) (4) proposal was deemed reasonable and also recommended for the annual stability batches. Acceptance of the proposal (b) (4) was considered a review

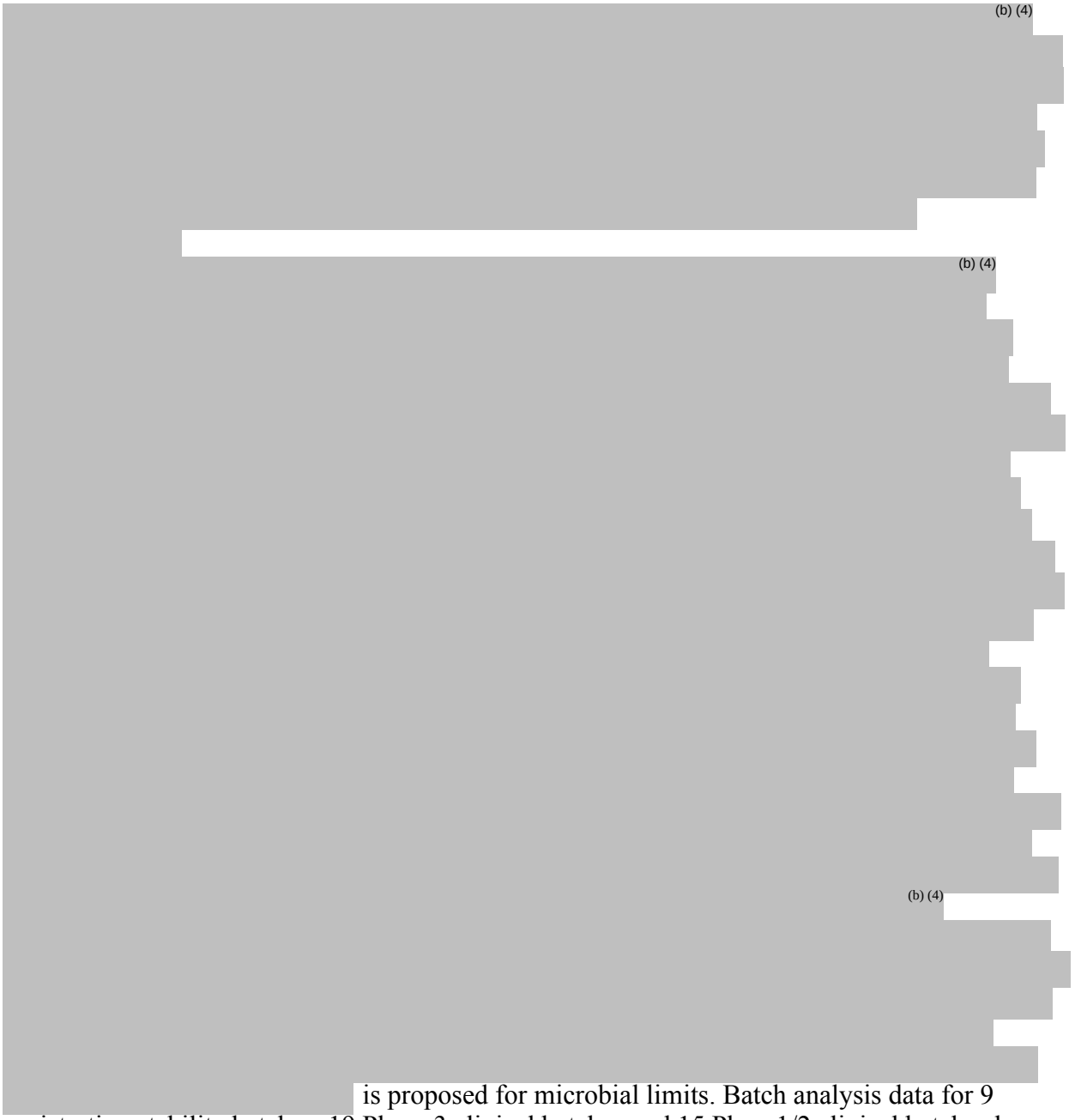
issue since insufficient information was submitted in the briefing package. The Applicant was recommended to consolidate (b) (4) Since an extensive QbD program is proposed, the Agency indicated that definitive answers to many of the questions posed could only be give after in-depth review of all supporting data in the NDA. However, some general guidelines and concerns were provided to Daiichi – (b) (4)

Drug Substance: Edoxaban tosylate is a white to pale yellowish-white crystalline powder, mp ~ 249 ˚C with decomposition. It has 3 asymmetric centers and is synthesized as a (b) (4) The exact stereochemistry at the 3 stereogenic centers has been established by (b) (4) It is obtained as a monohydrate. The solubility of edoxaban tosylate is pH dependent—slightly soluble in water, pH 3,4, and 5 buffers, very slightly soluble at pH 6 and 7 and practically insoluble at pH 8 and 9. (b) (4) It exists in (b) (4) The drug substance is synthesized at (b) (4)

Specifications for the drug substance are proposed based on release data from 24 lots, ranging from pilot to commercial scale (b) (4) Kg), used in toxicology, clinical and registration stability studies. Test attributes are appearance, identification, (b) (4) impurities (b) (4) impurities, assay, heavy metals, residue on ignition, water content, (b) (4) and particle size distribution. Batch analysis data to support the proposed acceptance criteria have been submitted.
Stability studies have been conducted on 3 primary, pilot scale registration batches manufactured at Hiratsuka and 3 site-specific commercial scale batches manufactured at Akita. The pilot scale batches were approx. (b) (4)% of the commercial scale of (b) (4) Kg. 36 months' long term registration batch stability data and 6 months of data at accelerated conditions have been submitted and show no change from the initial time point for any of the test attributes. Similarly, studies at ICH elevated temperature and humidity conditions showed no change in any stability indicating or quality parameters after 6 months. The site-specific stability data on commercial scale batches confirm these results although only 6 months' data are currently available. Photostability testing under ICH conditions on one lot again showed no change from the initial time point. Based on these results the Applicant has proposed a (b) (4) month retest period for the drug substance stored in (b) (4)

Drug Product: Edoxaban tosylate drug product is an immediate release, round- shaped , film coated, unscored debossed tablet in 3 strengths, 15, 30 and 60 mg. The tablet strengths are based on edoxaban free base and are differentiated by size, weight, color and debossed information. Standard compendial excipients are used in the manufacture of the tablets – mannitol, pregelatinized starch, crospovidone, hydroxypropyl cellulose, and magnesium stearate. The film coating agents, (b) (4) orange, pink and yellow are non-compendial but comprised of compendial ingredients. The proposed commercial formulations of edoxaban 15 and 30 mg tablets are identical to the Phase 3 clinical formulation with the exception of colors. It is claimed that bioequivalence has been demonstrated between the 60 mg tablet and two 30 mg tablets. All 3 strengths are manufactured from (b) (4) and are dose proportional.
The commercial manufacture of the (b) (4) requires the manufacture o (b) (4) . This commercial batch size yields (b) (4) tablets for the 15 mg strength, (b) (4) tablets of the 30 mg strength and (b) (4) 60 mg tablets. The manufacturing process consists of (b) (4)

The Applicant claims to have developed edoxaban tablets using an "enhanced" QbD approach based on the principles of experimental design, quality risk management, prior knowledge and manufacturing experience. This was implemented by (b) (4)



is proposed for microbial limits. Batch analysis data for 9 registration stability batches, 19 Phase 3 clinical batches and 15 Phase1/2 clinical batches have been provided. Primary stability data have been submitted for the registration batches, manufactured by the commercial process at pilot scale and packaged in the proposed commercial configurations, HDPE bottles and (b) (4) /Aluminum blisters. 24 months' long term and 6 months' accelerated data are available. A 36 month expiration dating period is proposed based on these data for all 3 strengths of edoxaban tablets.

Additional Comments:
Categorical exclusion from Environmental Assessment has been requested based on 21CFR 25.31 (b). Facilities for inspection have been entered in the EES database. Since this is an NME, Method Validation will be requested shortly from FDA laboratories in St. Louis.

Biopharmaceutics Assessment

Biopharmaceutics Critical Issues or Complexities

Submission: Edoxaban tosylate drug product is an immediate release, round-shaped, film-coated, unscored, debossed tablet. The tablets are available in three strengths, 15mg, 30mg, and 60mg. The three strengths of edoxaban tablets are manufactured from (b) (4) and are dose proportional to one another.

The pivotal Phase 3 clinical trials in atrial fibrillation (AF) and venous thromboembolism (VTE) indications used 15 and 30 mg strength tablets. The proposed commercial strengths include 15, 30 and 60 mg tablets to provide maximum flexibility for dose adjustment. A BE Study (A-U142) was conducted to bridge between the 30 mg and 60 mg tablets.

Product Manufacturing: According to the Applicant, the manufacturing process development of edoxaban tablets was conducted according to a QbD approach (b) (4)

Review: The Biopharmaceutics review will focus on the evaluation and acceptability of the following:

- The conventional dissolution method
- The proposed dissolution acceptance criterion
- The proposed (b) (4)
- The BE study A-U-142 conducted to bridge the 30 mg and 60 mg tablets

Some biopharmaceutics information/data needed for the review of this NDA was not provided. The following comments and requests for information should be conveyed to the Applicant in the 74-Day letter or before.

Comments to be conveyed to the Applicant:

1. Provide dissolution profile comparisons in the proposed QC dissolution method for the batches tested in BE studies A-U140, A-U142 (e.g. one 30 mg tablet vs. one 60 mg tablet for all the batches tested).
2. Provide dissolution profile comparisons including statistical testing (e.g. f2 similarity testing) between the 15 mg, 30 mg and 60 mg commercial batches using the QC dissolution method. The dissolution testing for each strength should be done using only one tablet per vessel (n=12).
3. Provide explanation as to why the coated tablets from BA study DU176b-PRT012 (b) (4) from BA study DU176-E-PRT001) (refer to Figure 1.1 section 3.2.P.5.6).
4. As per ICH Q6A guidance, it is recommended that you use dissolution testing to monitor for the amount/type of (b) (4) at release and on stability. For this purpose, provide information/data showing that your proposed dissolution testing methodology and proposed acceptance criterion are able to reject batches with inadequate amount/type of (b) (4) Submit dissolution profiles as a function of (b) (4) (e.g (b) (4). In addition, the setting of an acceptable specification limit of (b) (4) allowed by the dissolution acceptance criterion should be supported by clinical information (i.e., bioavailability, exposure-response, etc.).
5. Alternatively, monitor the (b) (4) content at release and on stability using a (b) (4) In addition, the setting of an acceptable limit of the (b) (4) allowed by (b) (4) specification should be supported by clinical information (i.e., bioavailability, exposure-response, etc.).
6. Submit the following data for verification of the dissolution model:
7. Step by step model development procedure, including the statistics for all the models tested (the p-values, estimated coefficients and their standard errors of the final model).
8. Raw data including both model inputs and outputs used for model development and validation
9. Provide available data showing that the model can predict failed batches (i.e. batches that failed the dissolution acceptance criterion). This data are needed since dissolution was (b) (4)% for all the batches used for model validation. In addition, dissolution data used in the construction of the model (e.g. (b) (4) are (b) (4)% and there were values for which dissolution was (b) (4)%. Also, evaluate the predictive power of the model by using batches that failed in vivo BE, if available.
10. In order to verify the proposed design space (e.g. same in vitro and in vivo performance) provide dissolution profiles comparisons (with statistical data) and/or in vivo data (e.g. PK data) among the batches manufactured at the extremes of the design space using the target (clinical batches) as the reference.

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:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
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		

B. FACILITIES*				
*	**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.**			
	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

	Parameter	Yes	No	Comment
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 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		

	Parameter	Yes	No	Comment
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: • 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		

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

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		(b) (4)
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

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?	X		Master Batch Record submitted
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		Executed batch records provided
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		(b) (4)
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	X		(b) (4)

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

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

H. 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?	X		See table below

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	IV		(b) (4)	2-23-2011	
	IV			4-9-2013	
	III			3-20-2012	
	III			5-7-2013	
	III			5-8-2013	
	III			2-12-2013	
	III			6-4-2013	
	III			5-3-2013	
	III			2-7-2013	
	III			5-2-2013	
	III			4-20-2012	
	III			3-30-2012	

(b) (4)	III	(b) (4)	5-3-2013	
	III		3-20-2012	
	III		4-9-2012	

I. 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		

J. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
34.	Does the application contain dissolution data?	☒	☐	The following dissolution method was found acceptable during the IND stage: USP 11, 50 rpm, citrate/phosphate buffer pH 6. (refer to \\cdsesub1\evsprod\NDA206316\0000\m2\27-clin-sum under summary-biopharm, section 1.4
35.	Is the dissolution test part of the DP specifications?	☒	☐	The proposed acceptance criterion is: Q (b) (4)% at 30 min (\\cdsesub1\evsprod\NDA206316\0000\m3\32-body-data\32p-drug-prod\edoxaban-tablets\32p5-contr-drug-prod\32p56-justif-spec). Note that although a conventional dissolution method was developed, the Applicant is proposing a (b) (4) The manufacturing controls for edoxaban tablets will be conducted (b) (4) to assure the target dissolution rate at 30 minute.
36.	Does the application contain the dissolution method development report?	☒	☐	\\cdsesub1\evsprod\NDA206316\0000\m3\32-body-data\32p-drug-prod\edoxaban-tablets\32p2-pharm-dev
37.	Is there a validation package for the analytical method and dissolution methodology?	☒	☐	The CMC review team will evaluate the validation data.
38.	Does the application include a biowaiver request?	☐	☒	

39.	Does the application include data supporting the biowaiver?	☐	☒	
40.	Does the application include an IVIVC model?	☐	☒	
41.	Is information such as BCS classification mentioned, and supportive data provided?	☐	☒	
42.	Is information on mixing the product with foods or liquids included?	☐	☒	
43.	Is there any in *vivo* BA or BE information in the submission?	☒	☐	BE study A-U-142 was conducted to bridge the 30 mg and 60 mg tablet. This Study will be reviewed by ONDQA (refer to \\cdsesub1\evsprod\NDA206316\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\du176b-a-u142
44.	Is the to-be-marketed formulation the same as that used in pivotal clinical trials?	☒	☐	➢ The proposed commercial formulations of 15 mg and 30 mg tablets are identical to the Phase 3 tablets. ➢ The 60 mg tablet was developed for commercial use and confirmed as BE to the 30 mg Phase 3 tablets. There were some major changes implemented to the Phase 1 and Phase 2 formulation. Additional data may be needed to bridge across these phases depending on the impact the results of these studies in the product labeling. This issue will be discussed with the OCP reviewer.
45.	Is In vitro Release identified as a **CQA** and as a measured response for DOE in defining Design Space and control strategy?	☒	☐	\\cdsesub1\evsprod\NDA206316\0000\m3\32-body-data\32p-drug-prod\edoxaban-tablets\32p2-pharm-dev under pharmaceutical-development-manufprocdev.pdf
46.	Has the risk assessment been performed for the criticality of the in vitro release?	☒	☐	\\cdsesub1\evsprod\NDA206316\0000\m3\32-body-data\32p-drug-prod\edoxaban-tablets\32p2-pharm-dev under product-development-drugproduct.pdf
47.	Does the QbD approach contain RTRT elements? Is a dissolution model for RTRT purposes being proposed?	☒	☐	\\cdsesub1\evsprod\NDA206316\0000\m3\32-body-data\32p-drug-prod\edoxaban-tablets\32p2-pharm-dev Section 1.7.1.4.1

FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
48.	**IS THE BIOPHARMACEUTIC SECTIONS OF THE APPLICATION FILEABLE?**	☒		

49.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A (fileable)
50.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A (fileable)
51.	Are there any potential review issues identified?	☒	☐	➢ The dissolution acceptance criterion is not supported by the data (requesting additional information) ➢ The discriminating ability of the dissolution method is uncertain (requesting additional information) ➢ The (b) (4) steps for the dissolution model did not include data to demonstrate the ability of the model to (b) (4) (requesting additional data). ➢ Need additional data to support the approval of the 15 mg strength
52.	Are there any filing comments to be conveyed to the Applicant?	☒	☐	➢ See Biopharmaceutics comments in page12.
53.	Are there any comments to be conveyed to other review disciplines?	☒	☐	**Comments Conveyed to the OCP Review Team on 02/20/14**: There were major changes implemented to the drug product tested in Phase 1 and Phase 2 studies that may require additional data to support the bridging. The need for these data will be determined by the impact/relevance of the PK studies conducted in early phases of the development to the product labeling.

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page}
Kasturi Srinivasachar, Ph.D
CMC-Lead or
Division I, Branch 1
Office of New Drug Quality Assessment

{See appended electronic signature page}
Sandra Suarez, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

{See appended electronic signature page}
Olen Stephens, Ph.D.
Acting Branch Chief
Division I, Branch 1
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/

KASTURI SRINIVASACHAR
02/24/2014

SANDRA SUAREZ
02/24/2014

ANGELICA DORANTES
02/24/2014

OLEN M STEPHENS
02/24/2014