

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

220073Orig1s000

PRODUCT QUALITY REVIEW(S)



Template Revision: 03

Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



NDA Executive Summary

1. Application/Product Information

NDA Number.	220073
Applicant Name	Bristol Myers-Squibb Company (BMS)
Drug Product Name	ELIQUIS® (apixaban)
Dosage Form.	For suspension
Proposed Strength(s)	0.15 mg
Route of Administration	Oral
Maximum Daily Dose	0.6 mg (days 1 to 7 per labeling)
Rx/OTC Dispensed	Rx
Proposed Indication	• to reduce the risk of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation. • for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in adult patients who have undergone hip or knee replacement surgery. • for the treatment of DVT and PE, and for the reduction in the risk of recurrent • DVT and PE in adult patients following initial therapy. Treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE in pediatric patients from birth and older.
Drug Product Description	0.15 mg apixaban formulated as a white to pale yellow powder for oral suspension, in a yellow opaque capsule marked "898." The capsules are not to be swallowed, and the powder may be mixed with water or infant formula.
Co-packaged product information	N/A
Device information:	N/A



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Storage Temperature/ Conditions		20°C to 25°C	
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	N/A	N/A
	<i>Drug Product/ Labeling</i>	Rao Kambhampati	Theodore Carver
	<i>Manufacturing</i>	Zhouxi Wang	Feiyan Jin
	<i>Biopharmaceutics</i>	Parnali Chatterjee	Haritha Mandula
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Mickee Aguirre	
	<i>ATL</i>	Theodore Carver	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life of 36 months is granted for the drug product when stored at 20°C to 25°C.

b. Additional Comments for Action

See Postmarketing Commitment (PMC) [DARRTS, dated March 21, 2025] agreed to by the Applicant as follows:

For manufacturing the first few commercial batches of apixaban capsules for oral suspension, implement enhanced process controls to demonstrate the manufacturability and robustness of the commercial primary packing operation,



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e.g., capping and labeling steps, to ensure product quality. Demonstrate that the commercial manufacturing process performs as per FDA Guidance for Industry Process Validation: General Principles and Practices (2011).

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1.) Background

The Applicant, Bristol Myers Squibb, Inc., submitted NDA 220073, a 505(b)(1) new drug application, to market a pediatric formulation of apixaban for treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years of age after at least 5 days of initial anticoagulant treatment. This application relies on the approved NDA 202155, for which BMS is also the applicant, hence the Applicant has right of reference to the CMC information in NDA 202155, including the approved apixaban drug substance used to manufacture the drug product in NDA 220073, and no new drug substance information is included in NDA220073. Therefore, drug product, manufacturing, and biopharmaceutics review teams were assigned for review of this NDA.

2.) Drug Product

The drug product is a (b) (4) capsule filled with beads of (b) (4) % w/w apixaban, Hypromellose, and sugar spheres. The capsule is composed of a clear body with yellow opaque cap that is partially filled with a white to off white powder. All excipients are compendial and in acceptable amounts as determined in consultation with the nonclinical division, and the drug product specification includes appropriate tests to ensure the quality of the drug product. The drug product was found to contain a specified degradants that is not detected in the previously approved tablet formulation. The drug product reviewer, in consultation with the nonclinical division, determined that the control of this impurity and acceptance criteria based on the ICH Q3A guideline, are acceptable. The drug product was determined to have low risk of formation of potential nitrosamine impurities, based on the risk assessment and other information provided in the application. In-use stability data obtained in water and infant formula were provided to demonstrate adequate stability of the drug product for up to four hours, supporting the labeled in-use storage period of up to two hours. The long-term stability data were determined to be acceptable to support a shelf life of 36 months for storage of the drug product, based on 36 months real time and 6 months accelerated stability data.



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3.) Manufacturing

Process – The manufacturing process includes (b) (4)

(b) (4). No scale-up is proposed for commercial manufacturing. The review determined that the manufacturing process is adequate except for a proposed change from (b) (4) packaging operations for commercial manufacturing after approval of the application. The Process Performance Qualification (PPQ) batches were (b) (4) capped, sealed, and labeled at the commercial packaging site, (b) (4); however, the proposed commercial process will employ (b) (4) capping and labeling process. This change from (b) (4) packaging after approval deviates from the FDA recommendation that PPQ batches should be manufactured using the actual commercial facility, utilities, and equipment and with the commercial manufacturing process, control procedures, and components. In consultation with the OPMA policy group, a post-approval commitment was deemed appropriate to mitigate residual risk associated with this change. The Applicant agreed to a post-marketing commitment (PMC) to implement enhanced process controls to demonstrate the manufacturability and robustness of the commercial primary packing operation, e.g., capping and labeling steps, to ensure product quality, for the first few commercial manufacturing batches of the drug product.

Facilities – The review of the facilities recommended approval of all facilities based on previous inspection history.

4.) Biopharmaceutics

The biopharmaceutics review assessed the dissolution method development, including the selection of testing parameters, discriminating ability for the proposed dissolution method, and the acceptance criterion for dissolution testing of the 0.15 mg drug product. In addition, as the 0.15 mg granules were not administered in a clinical trial, this review assessed the bridging strategy proposed to bridge the 0.1 mg granule used in clinical studies to the proposed 0.15 mg granule. The biopharmaceutics review concluded that even though the drug product dissolved rapidly, that the dissolution method is the best quality test to include in the drug product specification. The dissolution method and proposed bridging were determined to be adequate.

5.) Quality Labeling

The Applicant initially proposed a capsule dosage form, (b) (4) but during review, it was determined that the capsule contents are best described as a powder based on the small diameter of the apixaban-



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(b) (4) beads. The capsules only serve as a container and are not to administered to the patients (sprinkle-only formulation). In accordance with FDA and USP recommendations, FDA proposed to revise the dosage form to 'for oral suspension' in the highlights and other parts of the labeling after approval of the proprietary name "ELIQUIS SPRINKLE", and the Applicant has agreed to this change. Other recommended revisions have been communicated to the Applicant and will be finalized in the labeling.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	-	N/A
Drug Product	-	Adequate
Quality Labeling	-	Adequate
Manufacturing	-	Adequate
Biopharmaceutics	-	Adequate
Microbiology	-	N/A

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments: None.

Comparability Protocols (PACMP): No

Comments: None.

Additional Lifecycle Comments:

See completed PMC template entered in DARRTS on March 21, 2025.



Theodore
Carver

Digitally signed by Theodore Carver

Date: 4/10/2025 08:58:13AM

GUID: 5d963967007fd4bc3c9fab2a6c3eade



Title:	NDA IQA Template CHAPTER IV-LABELING		
Document ID:	OPQ-ALL-TEM-0045		
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CHAPTER IV: LABELING

NDA 220073

NDA Number	220073
Assessment Cycle Number	1
Drug Product Name	Proposed by the Applicant: Eliquis® (apixaban) capsules for oral suspension, 0.15 mg

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	eCTD Seq# 0001
Medication Guide	Adequate	eCTD Seq# 0001
Container Labels	Adequate	eCTD Seq# 0001
Carton Labeling	Adequate	eCTD Seq# 0001

Brief Description of Outstanding Issues: The revised final documents will reflect all the recommended changes in this review.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
NDA 220073 eCTD# 0001	10/17/2024	USPI, Medication Guide, and Container and Carton Labels.

Note: This labeling review is based on the discussion and agreement between the representatives of the DPQA II, DMEPA, and OPPQ.

1.0 PRESCRIBING INFORMATION¹

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights² [21 CFR 201.57(a)(2)]		
Established name(s) ³	Inadequate	Proposed Name: ELIQUIS® (apixaban) (b) (4) Recommended Name: ELIQUIS® SPRINKLE (apixaban) for oral suspension
Route(s) of administration	Adequate	For oral use
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	2012
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s) ⁴ and strength(s) in metric system ⁵	Inadequate	Proposed: (b) (4) Comment: The dosage form should be changed to "For Oral Suspension: 0.15 mg in a yellow opaque capsule."

¹ [Labeling Review Tool \(LRT\) \(March 2022\)](#), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

² Draft guidance: [Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format](#) (January 2018)

³ Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

⁴ Draft guidance: [Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format](#) (January 2018); USP <1151>; USP Nomenclature Guideline

⁵ [Labeling Review Tool \(March 2022, page 13\)](#), include limited packaging information; USP <7>

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). ⁶	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored." ⁷	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. ⁸	N/A	

Assessment: *Adequate*

The above comments were communicated to the applicant and the final USPI will reflect the above recommended changes.

⁶ Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1

⁷ Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)

⁸ Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)⁹

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food ¹⁰ , storage conditions needed to maintain the stability of the reconstituted or diluted product).	Adequate	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	
For parenteral products: include statement: <i>"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i> ¹¹	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. ¹² Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the	N/A	

⁹ See § 201.57(c)(3); draft guidance: [Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format](#) (January 2023); Labeling Review Tool (March 2022, page 25)

¹⁰ Draft Guidance: [Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments](#)

¹¹ §201.57(c)(3)(iv)

¹² USP General Notices 2.30 Legal Recognition

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
patient and healthcare practitioner(s) who administer the drug		
For hazardous products, include the statement <i>"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x"</i> with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: Adequate

The above recommended changes were conveyed to the applicant and the final USPI will reflect those changes.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)¹³

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Inadequate	Proposed:  (b) (4) Comment: The above statement should be changed to "For Oral Suspension: 0.15 mg white to pale yellow powder in a yellow opaque capsule marked "898".
Strength(s) in metric system	Adequate	0.15 mg
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly state whether the strength is based on the active moiety (e.g., Tablets:	N/A	

¹³ See § 201.57(c)(4); [Labeling Review Tool \(March 2022, page 29\)](#)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: Adequate

The above recommended changes were communicated to the applicant and the final revised USPI will reflect the changes.

1.2.3 Section 11 (DESCRIPTION)¹⁴

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s) ¹⁵ [§ 201.57(c)(12)(i)(A)].	Inadequate	Proposed: ELIQUIS (apixaban)

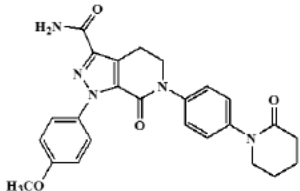
¹⁴ See § 201.57(c)(12); [Labeling Review Tool \(March 2022, page 56\)](#)

¹⁵ Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
		Recommended: ELIQUIS® SPRINKLE (apixaban)
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Inadequate	Proposed: (b) (4) (b) (4) Comments: Should be changed to ELIQUIS® SPRINKLE for oral suspension contain 0.15 mg apixaban and the following inactive ingredients: hypromellose and sugarspheres.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	N/A	
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order. ¹⁶ Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and	N/A	

the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

¹⁶ Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
statement of effect. [§ 201.100(b)(5)(iii)].		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class ¹⁷ [§ 201.57(c)(12)(i)(E)].	Adequate	
Chemical name ¹⁸ , structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	ELIQUIS (apixaban), a factor Xa (FXa) inhibitor, is chemically described as 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. Its molecular formula is C ₂₅ H ₂₅ N ₅ O ₄ , which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula: 
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	Apixaban is a white to pale-yellow powder. At physiological pH (1.2-6.8), apixaban does not ionize; its aqueous solubility

¹⁷ Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in [FDA's Labeling Resources for Human Prescription Drugs](#) for the most recent EPC list.

¹⁸ Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
		across the physiological pH range is ~0.04 mg/mL.
For oral prescription drug products, include gluten statement ¹⁹ (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: *Adequate*

The final USPI document will contain all the above recommended changes.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)²⁰

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Inadequate	Proposed: (b) (4) Comments: Should be changed to "For oral suspension".
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA	Adequate	0.15 mg

¹⁹ Draft guidance: [Gluten in Drug Products and Associated Labeling Recommendations \(December 2017\)](#)

²⁰ See § 201.57(c)(17); [Labeling Review Tool \(March 2022, page 70\)](#). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Guidance . Clearly state whether the strength is based on the active moiety. No equivalency statement.		
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	Bottles of 28
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	(b) (4) printed with "898"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. ^x " with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	Adequate	
Storage conditions. Where applicable, use USP storage range rather than storage at a	Adequate	Store ELIQUIS at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
single temperature. (see USP <659>).		and 30°C (59°F-86°F) [see USP Controlled Room Temperature].
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: <i>"Not made with natural rubber latex. Avoid statements such as "latex-free."</i> ²¹	N/A	
Include information about child-resistant packaging ²² (if chosen by manufacturer).	N/A	

Assessment: *Adequate*

The above recommended changes were communicated to the applicant, and they will be incorporated into the final USPI.

²¹ Guidance: [Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex](#) (December 2014)

²² Guidance: [Child-Resistant Packaging Statements in Drug Product Labeling](#) (August 2019)

1.2.5 Other Sections of Labeling: Not applicable

1.2.6 Manufacturing Information After Section 17 (for drug products)²³

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	Marketed by: Bristol-Myers Squibb Company Princeton, NJ 08543 USA and Pfizer Inc New York, NY 10001 USA

Assessment: *Adequate*

Above recommended changes will be included in the final USPI.

2.0 PATIENT LABELING:

Assessment of Medication Guide:

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²⁴	Inadequate	ELIQUIS® (ELL eh kwiss) (apixaban) tablets Comment: Should be revised by also including ELIQUIS® SPRINKLE (apixaban) for oral suspension
Special preparation instructions (if applicable).	Adequate	

²³ § 201.1(h)(5) and 201.1(i); [Labeling Review Tool \(March 2022, page 74\)](#)

²⁴ Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage and handling information (if applicable).	Adequate	Store ELIQUIS at room temperature between 68°F to 77°F (20°C to 25°C).
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	N/A	
Active ingredient(s) (if applicable).	Adequate	apixaban
Alphabetical listing of inactive ingredients (if applicable).	Inadequate	Presently shown as: (b) (4) (b) (4) Above should be changed to: ELIQUIS® SPRINKLE for oral suspension contains 0.15 mg of apixaban and the following inactive ingredients: hypromellose and sugar spheres.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	Marketed by: Bristol-Myers Squibb Company Princeton, NJ 08543 USA and Pfizer Inc New York, NY 10001 USA

Assessment: *Adequate*

The above comments were conveyed to the applicant and the final Medication Guide will reflect the recommended changes.

3.0 CONTAINER AND CARTON LABELING²⁵

²⁵ [Carton and Container Labeling Resources](#)

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

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name ²⁷ , (font size and prominence) [§ 201.10(g)(2)].	Inadequate	Yes	Proposed: Eliquis® (apixaban) Comments: Should be changed to ELIQUIS® SPRINKLE (apixaban)
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)]. ²⁸	Adequate	Yes	0.15 mg
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	For oral suspension
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	Yes	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)]. ²⁹	Inadequate	Yes	Proposed: 28 Capsules for opening Comments: Should be changed to "28 capsules and each capsule contains 0.15 mg Eliquis Sprinkle (apixaban) for oral suspension.
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	

²⁷ Established name = [Drug] [Route of Administration] [Dosage Form]

²⁸ Express as "XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See [Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors \(May 2022\)](#)

²⁹ § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).	N/A	Yes	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	Yes	
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Linear Bar code [§ 201.25(c)(2)]. ³⁰	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	N/A	Yes	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	Yes	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance	N/A	Yes	

³⁰ See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
criteria set forth in the relevant compendium, its difference shall be plainly stated on its label. ³¹			
And others if space is available.	N/A	Yes	

Assessment of Carton Labels and Container Labeling: *Adequate*

Above recommended changes were conveyed to the applicant and the final container and carton labels will reflect the changes.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

The comments listed in the above tables are communicated to the applicant and the final labeling documents will contain the recommended changes.

Primary Labeling Assessor Name and Date: Rao V. Kambhampati, Ph.D. 3/17/2025

³¹ USP General Notices 3.20 Indicating Conformance



Rao
Kambhampati

Digitally signed by Rao Kambhampati
Date: 3/20/2025 09:47:02AM
GUID: 508da72000029fd06e8c9283b7414189



Theodore
Carver

Digitally signed by Theodore Carver
Date: 3/20/2025 10:39:50AM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded



Office of Pharmaceutical Quality

New Drug Application (NDA)

Integrated Quality Assessment Template

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	Apixaban capsule for oral suspension, 0.15 mg, is an immediate-release, (b) (4) capsule filled with beads of (b) (4) % w/w apixaban, Hypromellose, and sugar spheres. The capsule is composed of a clear body with yellow opaque cap that is partially filled with a white to off white powder. The capsule cap has (b) (4) with "898" printed underneath with (b) (4).
NDA Number	220073
Assessment Cycle Number	Cycle 01
Drug Product Name/ Strength	Eliquis® (apixaban) Capsules for Oral Suspension, 0.15 mg
Route of Administration	Oral
Applicant Name	Bristol Myers-Squibb Company (BMS)
Therapeutic Classification/ OND Division	DNH/OCHEN
RLD/RS Number	NDA 202155 for Eliquis® (apixaban) film coated tablets, 2.5 mg, 5 mg (approved on 28/12/2012)
Proposed Indication	Eliquis® (apixaban) capsules for oral suspension is indicated for the treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years of age after at least 5 days of initial anticoagulant treatment.

Assessment Recommendation: Adequate

Assessment Summary:

Eliquis® (apixaban) Capsules for Oral Suspension, 0.15 mg, is a low-dose, immediate-release, (b) (4) capsule filled with beads/granules/powder of (b) (4) % w/w apixaban, Hypromellose, and sugar spheres indicated for the treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years of age after at least 5 days of initial anticoagulant treatment.

The instructions for use (IFU) in the label recommends the capsules are to be opened and the beads/powder are to be dispersed in a liquid vehicle to form a suspension. The suspension is administered orally, and the capsule shell should be discarded.

The highest recommended dose for the proposed product for the proposed indication is 4×0.15 mg capsules or 0.6 mg for pediatric patients with body weight $\geq$ 2.6 kg to (b) (4) kg.

The basis for approval of the proposed 0.15 mg Eliquis® (apixaban) capsules for oral suspension is the pivotal safety and efficacy Study CV185-325 that was conducted with 0.1 mg sprinkle granule product in pediatric subjects (N=152) from birth to <18 years requiring anticoagulation for the treatment of VTE.

The 0.1 mg sprinkle granules administered in the pivotal safety and efficacy Study CV185-325 are (b) (4) to the proposed 0.15 mg granules, except for the fill weight. (b) (4)

The objective of this assessment was to evaluate the dissolution data provided to support the selection of testing parameters and discriminating ability for the proposed dissolution method and acceptance criterion for dissolution testing of the 0.15 mg drug product. In addition, as the 0.15 mg granules were not administered in a clinical trial, this review assessed the bridging strategy proposed to bridge the 0.1 mg granule to the proposed 0.15 mg granule and to the 0.5 mg tablet.

Dissolution Method and Acceptance Criterion: Adequate

The 0.15 mg granule demonstrated pH-independent high solubility in <250 mL buffer solutions across the physiological pH range, 1.2-6.8. Therefore, a modified FDA guidance (2018) method [USP Apparatus II (paddle) at 50 rpm using 500 mL 0.05 M sodium phosphate buffer, pH 6.8 at $37.0 \pm 0.5^\circ\text{C}$] was proposed for dissolution testing of the 0.15 mg capsule product.

Approved dissolution method (M00004938) and acceptance criterion for dissolution testing of Eliquis® (apixaban) capsules for oral suspension

Apparatus	Rotation Speed (rpm)	Medium/Volume (mL)	Temperature	Acceptance Criterion
USP App 2 (paddle)	50 rpm	500 mL 0.05 M sodium phosphate buffer, pH 6.8	37°C	$Q = \frac{(b) (4)}{(4)}\%$ in 20 minutes

Dissolution data were provided to support the selection of testing parameters (dissolution media and rotation speed) for the proposed method. Commercial image batches demonstrated very rapid and similar dissolution (b) (4) and using the proposed method. Dissolution data provided for the variant batches demonstrated no discriminating ability of the method with respect to the (b) (4) and sugar sphere particle size within the parameters evaluated.

All clinical, registration stability, and commercial image batches for the 0.15 mg granule demonstrated very rapid dissolution (>90% in 10 mins) at release and on stability using the proposed method. Additionally, 0.15 mg commercial image batches prepared according to the IFU demonstrated very rapid and similar dissolution (b) (4) and using the proposed method.

The 0.1 mg clinical batches demonstrated very rapid (>90% in 10 mins) and similar dissolution at release using the proposed method.

The Applicant noted the proposed product forms a solution following reconstitution as per the labeling instructions (IFU). Since the product demonstrates very rapid dissolution (>90% in 10 mins), the Applicant was recommended to propose other critical quality attributes (CQAs) in lieu of dissolution testing. However, the Applicant noted other CQAs such as (b) (4)

and therefore proposed to retain dissolution testing as a quality control test.

Based on the overall dissolution data provided in the submission, the proposed dissolution method is adequate as a quality control test for the proposed product. The proposed dissolution acceptance criterion "Q=(b) (4) % in (b) (4) mins" was deemed inadequate for the drug product. The Applicant agreed to implement "Q=(b) (4) % in 20 minutes" as the acceptance criterion for the drug product at batch release and on stability.

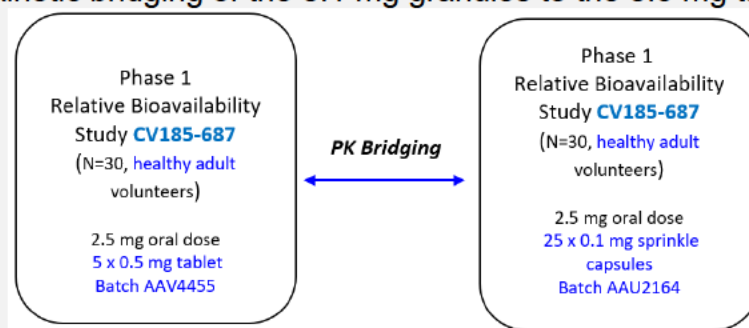
Bridging/Biowaiver of the 0.15 mg Granules/Powder for Oral Suspension to the 0.1 mg Granules and 0.5 mg Tablet Product: Adequate

The 0.1 mg sprinkle granules are (b) (4) to the proposed 0.15 mg granules, except for the fill weight. (b) (4)

➤ *Pharmacokinetic bridging of the 0.1 mg granules to the 0.5 mg tablet product*

In the Phase I relative bioavailability (rBA) Study CV185-687, 25×0.1 mg sprinkle granules batch AAU2164 were administered along with 5×0.5 mg tablets batch AAV4455 for a total oral dose of 2.5 mg. The 0.1 mg batch AAU2164 demonstrated equivalent apixaban exposure ($AUC_{0-\infty}$) to the 0.5 mg tablet batch AAV4455 in N=30 healthy adult subjects (see Office of Clinical Pharmacology Review for details). *Therefore, the 0.1 mg rBA batch is bridged to the 0.5 mg tablet rBA batch through equivalent exposure data.*

Pharmacokinetic bridging of the 0.1 mg granules to the 0.5 mg tablet product



➤ *Bridging the 0.1 mg granules to the to-be-marketed 0.15 mg granule product through dissolution testing*

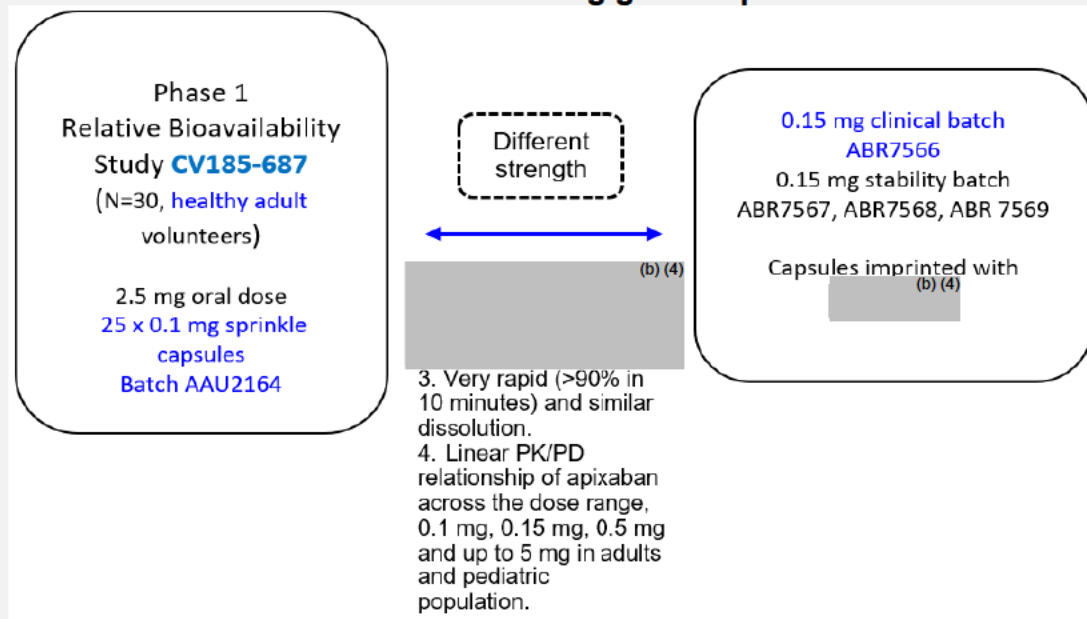
The proposed 0.15 mg sprinkle granule product is bridged to the 0.10 mg granules/powder for oral suspension based on (b) (4)

, (3) very rapid (>90% in 10

minutes) and similar dissolution between the 0.1 mg and 0.15 mg drug product, and (4) linear pharmacokinetics/pharmacodynamics relationship of apixaban across the dose range, 0.1 mg, 0.15 mg, 0.5 mg and up to 5 mg in adults and pediatric population (see Office of Clinical Pharmacology/Pharmacometric Review for details).

Dissolution of the 0.1 mg clinical batch AAU2164 administered in the rBA Study CV185-687 is very rapid (>90% dissolution in 10 mins) and similar to the 0.15 mg clinical, registration stability, and commercial image batches at release using the proposed dissolution method.

Bridging/Biowaiver of the 0.1 mg granules to the to-be-marketed 0.15 mg granule product



Bridging the 0.1 mg granules/powder batches administered in relative bioavailability studies and in the pivotal safety and efficacy studies: Adequate

Several 0.1 mg batches were administered in another relative bioavailability Study CV185-118 in pediatric subjects, to assess the single dose pharmacokinetics (PK) of apixaban. In addition, several 0.1 mg batches were administered in Phase 2 safety, efficacy and PK Study CV185-362 and in the pivotal safety and efficacy Study CV185-325 in pediatric population of varying age groups.

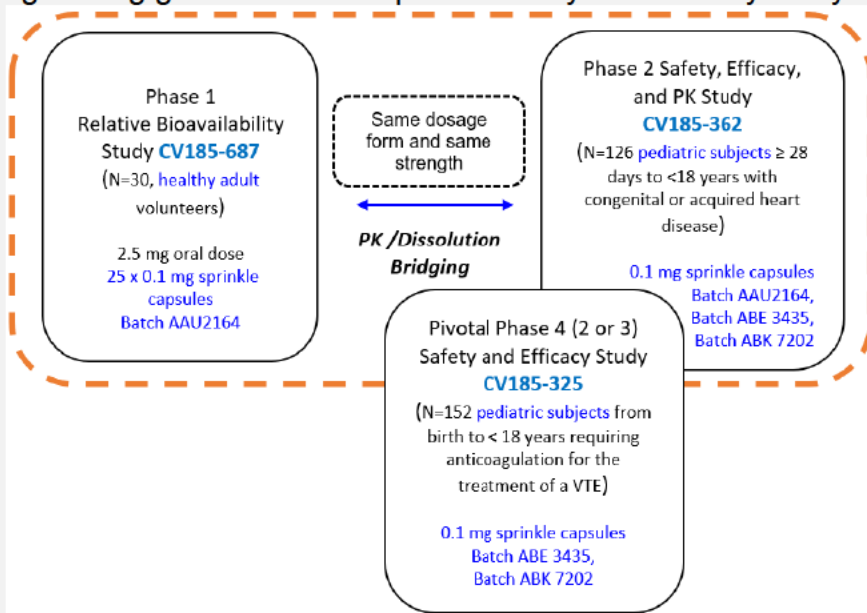
The 0.1 mg batches demonstrated similar exposures (AUC_{0-inf}) to the 0.5 mg and 5 mg tablet in adult and in pediatric population, except in patients <5 kg (see Office of Clinical Pharmacology Review for details).

Dissolution of the 0.1 mg clinical batch AAU2164 administered in the rBA Study CV185-687 and in supportive Phase 2 safety, efficacy, and PK Study CV185-362 is very rapid (>90% dissolution in 10 mins) and similar at release to other 0.1 mg clinical batches ABE 3435, ABK 7202 administered in the supportive Phase 2 safety, efficacy, and PK Study

CV185-362 and in pivotal Phase 4 (2 or 3) safety and efficacy study, CV185-325 using the proposed method.

Therefore, the 0.1 mg rBA and pivotal safety and efficacy study batches with different drug substance lots are bridged through PK and dissolution data.

Bridging 0.1 mg granule rBA and pivotal safety and efficacy study batches

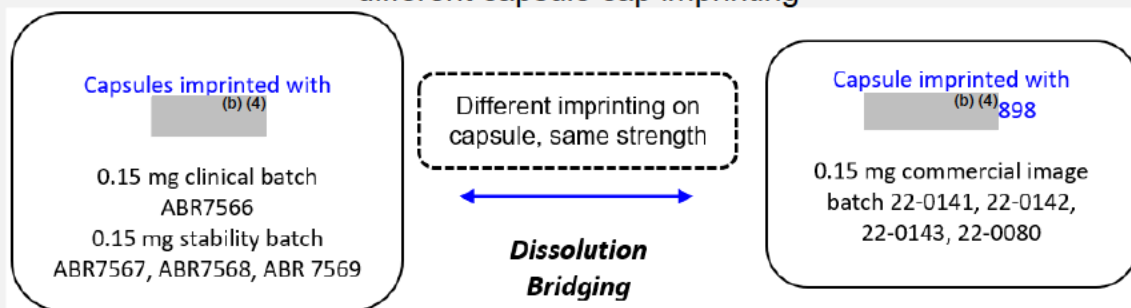


Bridging the 0.15 mg granules/powder batches due to changes in imprinting on the capsule cap and drug substance lots: Adequate

The 0.15 mg clinical batch ABR7566 and registration stability batches have capsule caps imprinted with (b) (4); whereas the TBM commercial image batches will have (b) (4) "898" printed underneath on the capsule cap.

Dissolution of the 0.15 mg clinical batch ABR7566, registration stability batches, and commercial image batches are very rapid (>90% dissolution in 10 mins) and similar with low unit-to-unit variability. *Therefore, the 0.15 mg batches with different imprinting are bridged through dissolution data.*

Bridging 0.15 mg granule clinical, stability, and commercial image batches due to different capsule cap imprinting



Risk Assessment:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #1	Comments
Dissolution Testing	Medium	Biopharmaceutics risk level was initially ranked as "Medium" as the TBM 0.15 mg product is a low dose product. Moreover, the product was not administered in any clinical study. The proposed dissolution method was deemed not optimal as very rapid dissolution (>90% in 10 mins) was observed and the method demonstrated no discriminating ability with respect critical manufacturing variables.	Low	Biopharmaceutics risk level has been mitigated from "Medium" to "Low" as additional justification was provided for retaining the originally proposed dissolution method based on high solubility of apixaban drug substance across the pH range 1.2-6.8 and very rapid dissolution (>90% in 10 mins) of the 0.1 mg and 0.15 mg granule product using the proposed method and in multi-pH dissolution medium, (b) (4) (b) (4) according to the IFU. In addition, other CQAs such as (b) (4) (b) (4) Therefore, the proposed dissolution method is retained as a quality control test and 'Q= (b) (4) % in 20 mins' is recommended as the

dissolution acceptance criterion for the 0.15 mg drug product.

List of Submissions Being Assessed:

Document(s) Assessed	Date Received
Original NDA 202155 for Eliquis® (apixaban) film coated tablets, 2.5 mg, 5 mg (approved on 28/12/2012) (\\CDSESUB1\EVSPROD\nda202155\0000\m1\us\coverletter.pdf)	28/09/2011
Original NDA 220073 for Eliquis® (apixaban) capsules for oral suspension, 0.15 mg. (\\CDSESUB1\EVSPROD\nda220073\0001\m1\us\coverletter.pdf)	10/17/2024
Supplemental NDA 202155/S039 for Eliquis® (apixaban) film coated tablets, 2.5 mg, 5 mg (approved on 28/12/2012) for new indication in pediatric population. (\\CDSESUB1\EVSPROD\nda202155\0290\m1\us\coverletter.pdf)	10/17/2024
Supplemental NDA 202155/S040 for Eliquis® (apixaban), 0.5 mg tablets for oral suspension (in unit dose sachets of 0.5 mg, 1.5 mg, and 2 mg), for new indication in pediatric population. (\\CDSESUB1\EVSPROD\nda202155\0291\m1\us\coverletter.pdf)	10/17/2024
Response to Information Request #1 (\\CDSESUB1\EVSPROD\nda220073\0013\m1\us\bms-562247-us-response-cmc-q1-q5.pdf)	01/29/2025
Response to Information Request #2 (\\CDSESUB1\EVSPROD\nda220073\0020\m1\us\bms-562247-us-response-cmc-q1-q2.pdf)	02/18/2025
Response to Information Request #3 (\\CDSESUB1\EVSPROD\nda220073\0023\m1\us\bms-562247-us-response-cmc-q1.pdf)	02/27/2025

Highlight Key Issues from Last Cycle and Their Resolution: Not Applicable

Concise Description of Outstanding Issues (list bullet points with key information and update as needed): Not Applicable

B.1 BCS DESIGNATION

Assessment: High Solubility/Low Permeability BCS Class III drug substance

Solubility: High

Apixaban is an un-ionizable, non-hygroscopic, crystalline (solid-state (b) (4)) drug substance [molecular formula is $C_{25}H_{25}N_5O_4$, molecular weight of 459.5 grams/mole]. Chemical structure of apixaban is provided in **Figure 1**.

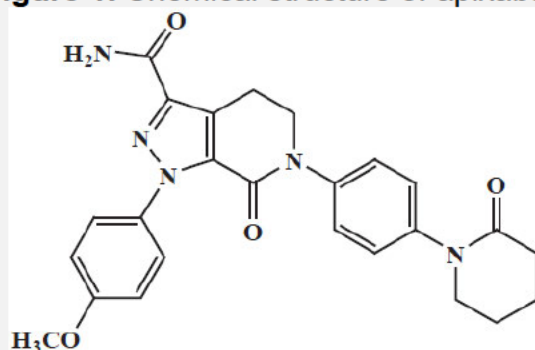
Aqueous solubility of apixaban drug substance in physiological buffer solutions, pH 1.2-6.8 at 37°C is provided in **Table 1**. The 0.15 mg dose strength of apixaban in the proposed product will be soluble in <250 mL buffer solutions across the pH range, 1.2-6.8 at 37°C. Therefore, apixaban demonstrates pH-independent, high solubility per Biopharmaceutics Classification System (BCS).

Table 1. Aqueous solubility of apixaban drug substance in physiological buffer solutions, pH 1.2-6.8 at 37°C

pH	Buffer/Media	Solubility (mg/mL)	(Dose Strength × # of Capsules)/250 mL ^a			Solubility/Conc. for 1 cap (4 cap)
			0.1 mg × 1	0.15 mg × 1	0.15 mg × 4	
1.2	0.1 N HCl	0.041	0.0004	0.0006	0.0024	68 (17)
4.5	0.05 M Sodium Acetate	0.041	0.0004	0.0006	0.0024	68 (17)
6.8	0.05 M Sodium Phosphate	0.038	0.0004	0.0006	0.0024	63 (16)

^a Result should be less than solubility.

Figure 1. Chemical structure of apixaban



Permeability: Low

Absolute oral bioavailability of apixaban is approximately 50% for doses up to 10 mg. About 25% of the administered dose is eliminated in urine (27%) and feces as metabolites. Apixaban demonstrates dose linear pharmacokinetics across the adult therapeutic dose range, 2.5 mg to 10 mg. At doses >25 mg, apixaban demonstrates dissolution-rate-limiting absorption and hence reduced bioavailability. The time to reach maximum concentration (T_{max}) is 3-4 hrs following dosing. Apixaban has a total clearance of ~3.3 L/h and an apparent half-life of ~12 hours following repeated oral administration. There is no food effect on the bioavailability of apixaban. It is a substrate of P-gp and BCRP. Based on the available information, apixaban is a low permeable drug substance.

Dissolution:

Apixaban capsule for oral suspension, 0.15 mg, is an immediate-release, (b) (4) capsule filled with active beads of (b) (4) % w/w drug load, hypromellose, and sugar spheres for administration in pediatric patients with body weight (b) (4) kgs. The instructions for use

(IFU) in the label recommend the capsules to be opened and the beads/powder are to be dispersed in a liquid vehicle to form a suspension. The suspension is administered orally, and the capsule shell is not ingested.

In the [Dissolution Method Development Report](#) a modified FDA guidance (2018) dissolution method for drug products containing highly soluble drug substances is proposed [*USP Apparatus II (paddle) at 50 rpm using 500 mL 0.05 M sodium phosphate buffer, pH 6.8 at 37.0 ± 0.5°C*] for dissolution testing of the 0.15 mg capsule product.

Dissolution of the 0.15 mg product development batch BREC-1931-130, clinical and commercial image batches of the capsule product is very rapid (>90% in 10 mins) using the proposed dissolution method (see **Figure 2a** and **Figure 2b**).

Reviewer's Assessment of BCS Designation:

Solubility data provided in the current submission indicates apixaban is a pH-independent, highly soluble drug substance, per BCS. At doses up to 10 mg, the absolute bioavailability of apixaban is low (~50%). Therefore, the Applicant designated apixaban as a BCS Class III drug substance, which is adequate.

Figure 2a. Dissolution profile data for 0.1 mg and 0.15 mg capsule product (0.15 mg dose) using the proposed dissolution method

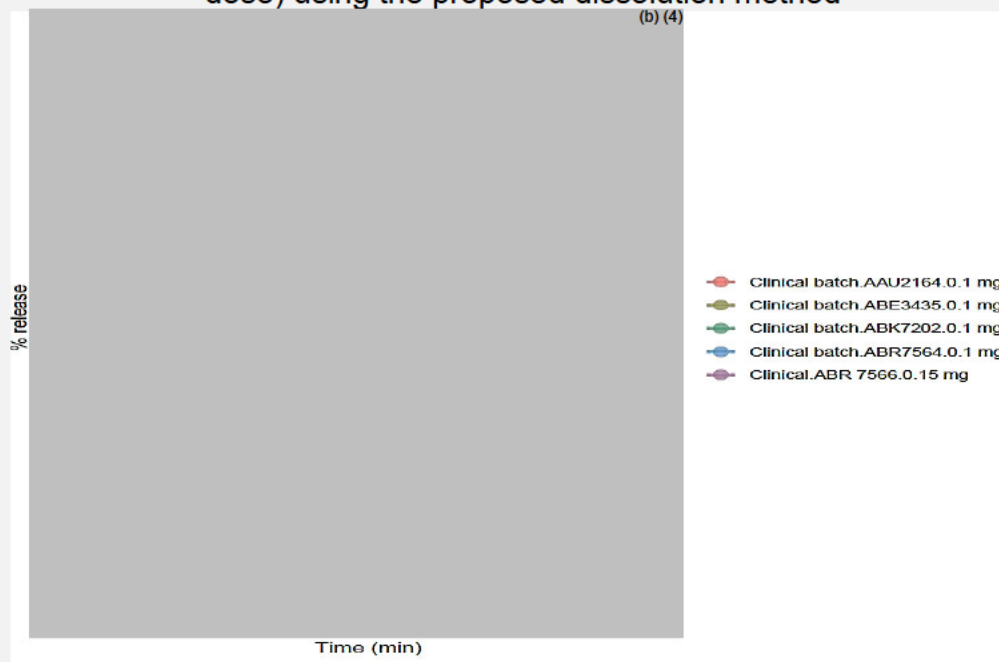
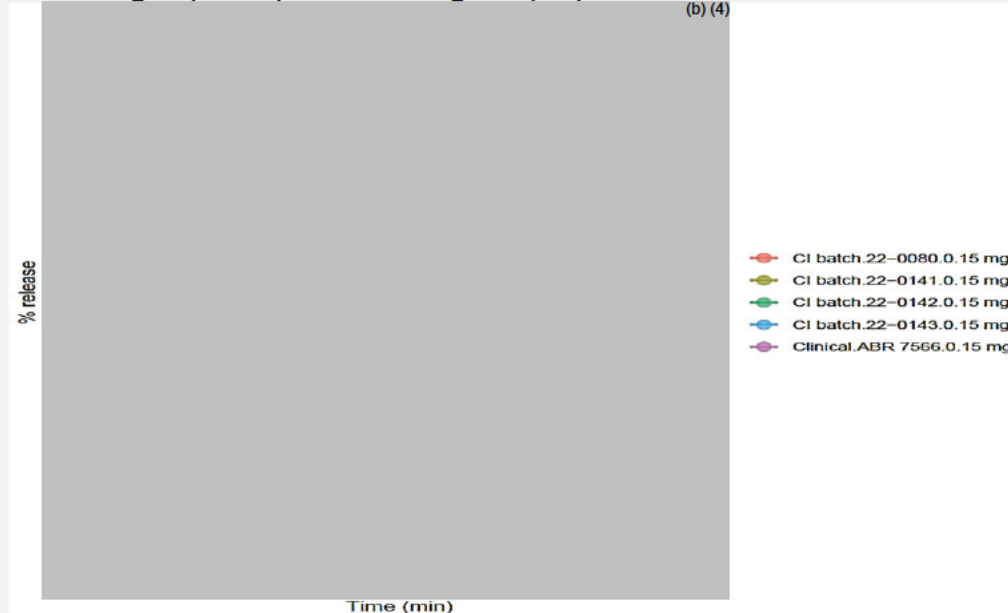


Figure 2b. Dissolution profile data for clinical and commercial image batches of the 0.15 mg capsule product using the proposed dissolution method



B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: **Adequate**

The proposed product is a low-dose (0.15 mg) bead/powder/granules for oral suspension. Dissolution was identified as a critical quality attribute (CQA) that could have an impact on the quality and in vivo performance of the drug product.

As the highest strength (0.15 mg) of apixaban in the capsule drug product demonstrated pH-independent high solubility in <250 mL buffer solutions across the physiological pH range, 1.2-6.8 (see **Table 1**), in the [Dissolution Method Development Report](#), a modified FDA guidance (2018) dissolution method for drug products containing highly soluble drug substances [*USP Apparatus II (paddle) at 50 rpm using 500 mL 0.05 M sodium phosphate buffer, pH 6.8 at 37.0 ± 0.5°C*] is proposed for dissolution testing of the 0.15 mg capsule product for oral suspension (see **Table 2a**).

Table 2a. Proposed dissolution method (M00004938) and acceptance criterion for dissolution testing of Apixaban capsule for oral suspension, 0.15 mg

Apparatus	Rotation Speed (rpm)	Medium/Volume (mL)	Temperature	Acceptance Criterion
USP App 2 (paddle)	50 rpm	500 mL 0.05 M sodium phosphate buffer, pH 6.8	37°C	Q = (b) (4) % in (b) (4) minutes

Initial dissolution method development was conducted

(b) (4)

(b) (4)

Discriminating Ability of the Proposed Dissolution Method:*Manufacturing process for the proposed product:*

(b) (4)

(b) (4) The composition of the 0.15 mg proposed product is provided in

Table 3a.

The capsules are to be opened prior to administration and the beads are to be dispersed in a liquid vehicle to form a suspension. The suspension is to be administered orally. The capsule shell is not ingested and discarded.

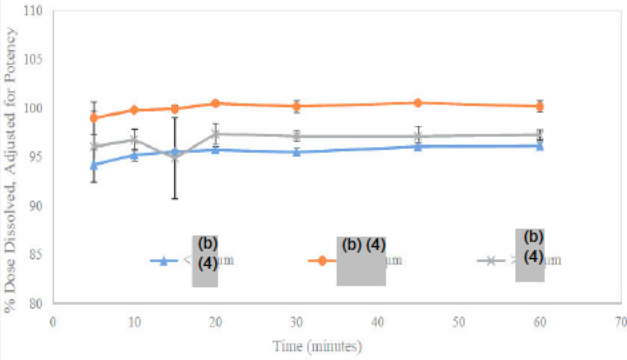
(b) (4) and particle size distribution (PSD) of the sugar spheres were identified as critical material attributes (CMAs) that could have an impact on the CQA and in vivo performance (critical bioavailability attribute, CBA) of the drug product.

Table 3a. Composition of the proposed 0.15 mg and 0.1 mg drug product

Component	Quality Standard	Function	Quantity per Capsule	
			0.1 mg strength	0.15 mg strength
			% w/w	mg
Apixaban Drug Substance (BMS-562247-01)	In-house ^a	Active	(b) (4)	0.1
Hypromellose ^b	USP, Ph.Eur.			(b) (4)
Sugar Spheres ^c	NF, Ph.Eur.			(b) (4)
Total Weight of Beads ^f				(b) (4)
CAPSULE SHELL				(b) (4)
(b) (4) capsule shell ^g , (b) (4)	In-house	Capsule		
(b) (4) capsule shell ^g , clear body, yellow opaque cap	In-house	Capsule		
Total Weight of Filled Capsule				(b) (4)

To support the specificity/selectivity of the proposed dissolution method for the proposed product, effect of (b) (4) and PSD of the sugar spheres were evaluated on the dissolution of the variant batches using the proposed method (see **Table 3b**). However, neither (b) (4) nor PSD of sugar spheres had any impact on the dissolution of the variant batches. The proposed method demonstrates no discriminating ability with respect to either material attributes or formulation variables.

Table 3b. Dissolution data to support discriminating ability of the proposed dissolution method

Testing Parameter	Dissolution Profile Data	Comments
(b) (4)		
PSD of the sugar spheres		PSD of sugar spheres up to (b) (4) μm had no impact on the dissolution of the variant batches as >90% dissolution was observed in 10 mins for all variant batches with different PSD of sugar spheres.
Variant batches with apixaban and		
(b) (4)		
sugar spheres with varying PSD		
(b) (4)		
and evaluated.		
Optimized PSD of sugar spheres		
(b) (4)		
(b) (4) are to be between (b) (4) μm and (b) (4) μm.		

Proposed Dissolution Acceptance Criterion:**Dissolution Data for the Clinical and Commercial Image Batches of the 0.15 mg Drug Product at Release:**

Dissolution of the 0.15 mg clinical and commercial image batches of the capsule product at release is very rapid (>90% in 10 mins), similar with low unit-to-unit variability using the

proposed dissolution method (see **Figure 3a**) and would meet the proposed acceptance criterion " $Q = \frac{(b)}{(4)}\%$ in $\frac{(b)}{(4)}$ minutes".

Dissolution Data for the Clinical and Commercial Image Batches of the 0.15 mg Drug Product on Long-Term Stability:

Dissolution of the 0.15 mg registration stability batches of the drug product on long-term stability is very rapid ($>90\%$ in 10 mins), similar with low unit-to-unit variability using the proposed dissolution method (see **Figure 3b**). However, no dissolution data was provided for the batches at $\frac{(b)}{(4)}$ minutes sampling time-point. The Applicant was recommended to implement " $Q = \frac{(b)}{(4)}\%$ in 20 minutes" as the acceptance criterion for the 0.15 mg drug product at release and on stability.

In the Information Request response (02/27/2025), the Applicant agreed to implement the recommended acceptance criterion " $Q = \frac{(b)}{(4)}\%$ in 20 minutes". All registration stability batches would meet the recommended acceptance criterion at 20 minutes on long-term stability for up to 36 months (see **Figure 3b**).

Figure 3a. Dissolution of the 0.15 mg clinical and commercial image batches of the drug product at release using the proposed dissolution method

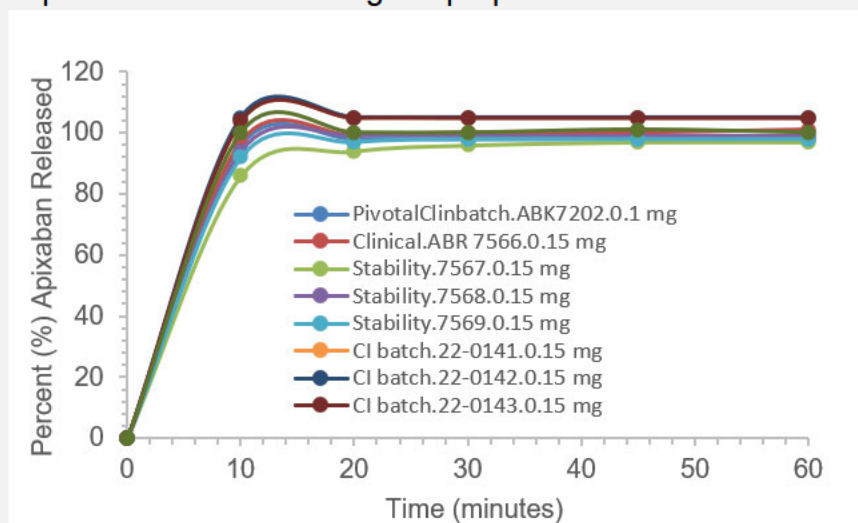
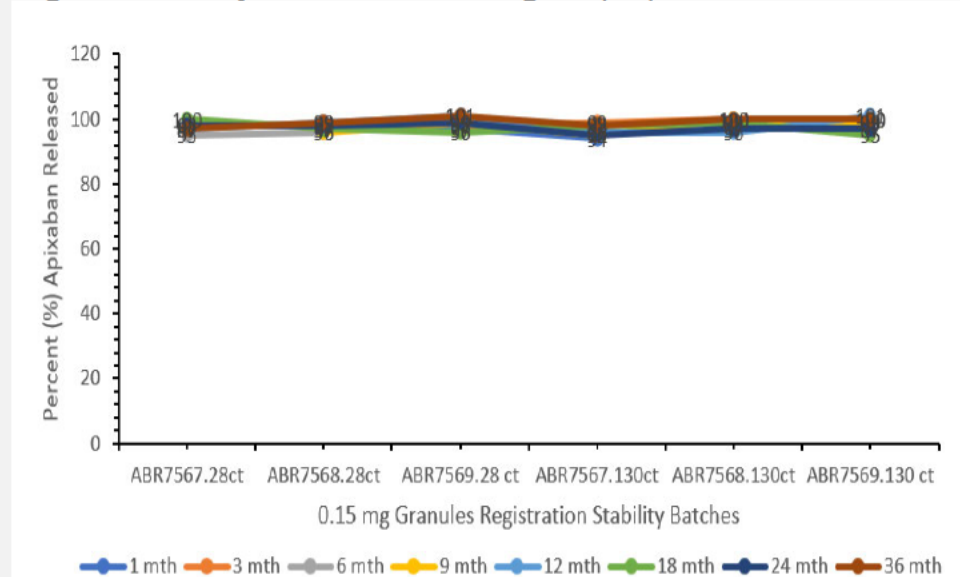


Figure 3b. Dissolution of the 0.15 mg registration stability batches of the drug product on long-term stability at 20 minutes using the proposed dissolution method



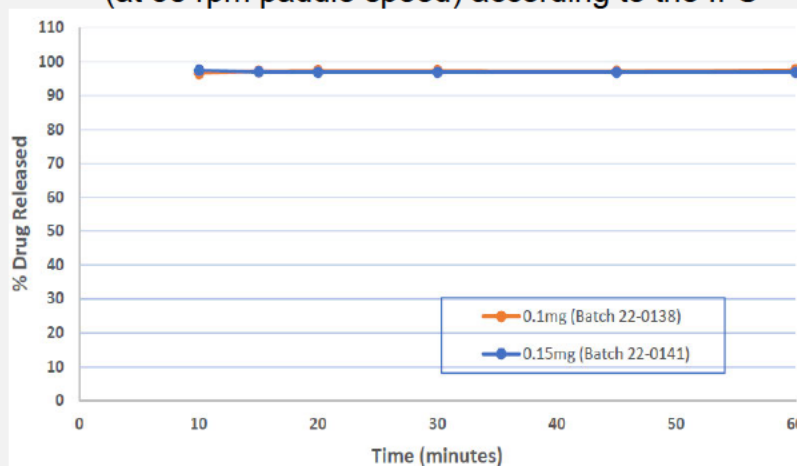
Reviewer's Assessment of the Proposed Dissolution Method and Acceptance Criterion:

Because the proposed product is a bead/powder/granules for oral suspension, no information could be located if dissolution testing of the product was conducted according to the labeling "[Instructions for Use \(IFU\)](#)" that states the proposed product should be mixed with 5 mL water or infant formula prior to administration.

Moreover, the commercial image and clinical batches of the drug product demonstrated very rapid dissolution (>95% in 10 minutes) at 50 rpm paddle speed and may not be optimal for dissolution testing of the drug product. Because the proposed product is an oral suspension, the Applicant was recommended to provide complete dissolution data at lower paddle speeds of (b) (4) rpm, using the labeling instructions in the IFU.

In the *Information Request* response (dated 01/29/2025), dissolution data were provided for the 0.1 mg batch 22-0138 and 0.15 mg registration batch 22-0141 using samples prepared according to the IFU at (b) (4) rpm and 50 rpm paddle speed (see **Figure 4a** and **Figure 4b**).

Figure 4a. Dissolution profile data for the 0.1 mg batch 22-0138 and 0.15 mg registration batch 22-0141 using the proposed dissolution method (at 50 rpm paddle speed) according to the IFU



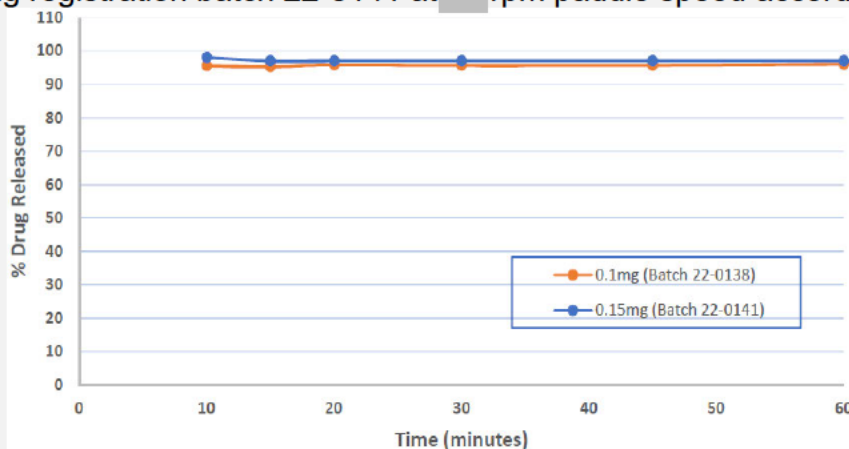
The 0.1 mg batch 22-0138 and 0.15 mg registration batch 22-0141 demonstrated very rapid (>90% in 10 mins) and similar dissolution using the proposed dissolution method and at lowered (b) (4) rpm paddle speed with samples prepared according to the IFU (see **Figure 4a** and **Figure 4b**). Therefore, the Applicant proposed to retain the originally proposed dissolution method without preparing the samples according to the IFU.

The proposed product contains apixaban a highly soluble drug substance. On reconstitution with 5 mL water or other liquid according to the IFU, the 0.15 mg product forms a solution. Moreover, the proposed product demonstrates very rapid (>90% in 10 minutes) dissolution using the proposed method and in multi-pH dissolution medium with low unit-to-unit variability. The proposed method demonstrates no discriminating ability as the solubility boundary for apixaban in proposed dissolution media and in multi-pH media is very wide. The Applicant was recommended to propose other critical quality attributes (CQA) that could be discriminating towards critical manufacturing attributes.

In a response (dated 01/29/2025), the Applicant noted other CQAs such as (b) (4) and therefore proposed to retain dissolution testing as a quality control test.

From Biopharmaceutics perspective, the risk due to dissolution failure is considered as low. The proposed dissolution method and acceptance criterion 'Q= (b) (4) % in 20 mins' are adequate for dissolution testing of the 0.15 mg drug product.

Figure 4b. Dissolution profile data for the 0.1 mg batch 22-0138 and 0.15 mg registration batch 22-0141 at (b) (4) rpm paddle speed according to the IFU



B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Assessment: Adequate

Apixaban is a highly soluble, low permeable, BCS Class III drug substance. The proposed product is a bead/granule/powder for oral suspension containing 0.15 mg apixaban for the treatment of VTE in pediatric patients from birth to less than 18 years of age.

A modified FDA guidance (2018) dissolution method for drug products containing highly soluble drug substances [USP Apparatus II (paddle) at 50 rpm using 500 mL 0.05 M sodium phosphate buffer, pH 6.8 at $37.0 \pm 0.5^{\circ}\text{C}$] is proposed for dissolution testing of the 0.15 mg granule for oral suspension. The proposed method is adequate for dissolution testing of the 0.15 mg proposed product.

The 0.15 mg granule for oral suspension was not administered in the relative bioavailability (rBA) study CV185-687 and CV185-118. (b) (4)

(b) (4) with different fill weight, 0.1 mg sprinkle granule product was administered in the Phase 1 relative bioavailability study CV185-118 to assess the single dose pharmacokinetics (PK) of apixaban in N=49 male and female pediatric subjects, neonates to <18 years and in rBA study in CV185-687 in N=30 healthy adult subjects.

The 0.1 mg sprinkle granule product was also administered in the Phase 2 safety, efficacy, and PK study CV185362 to assess apixaban PK in N=126 pediatric subjects ≥ 28 days to <18 years with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.

Dissolution of the 0.15 mg and 0.1 mg clinical batches of the granule for oral suspension are very rapid (>90% in 10 minutes) and similar using the proposed method (see **Figure 5a** and **Figure 5b**).

Figure 5a. Dissolution profile data for the 0.1 mg and 0.15 mg clinical batches using the proposed dissolution method not following the IFU

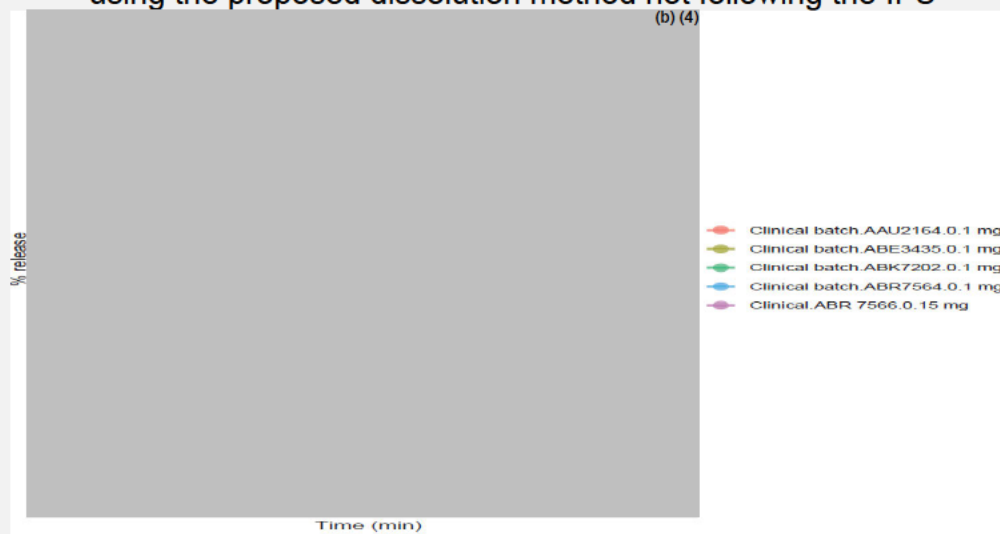
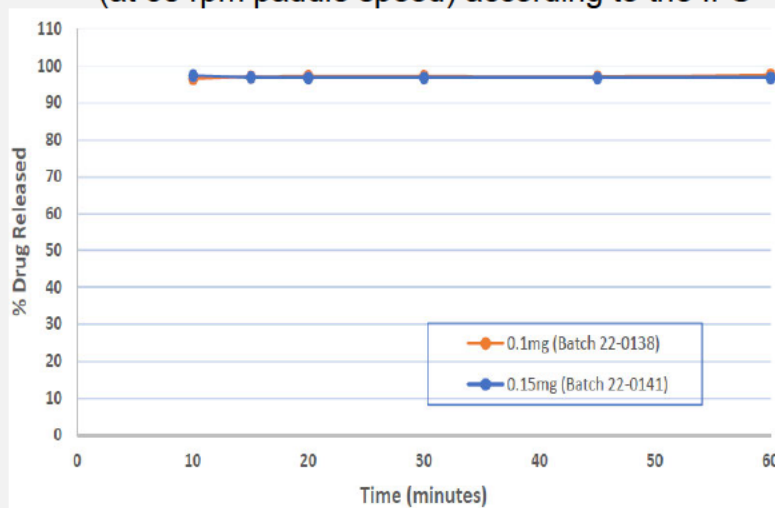


Figure 5b. Dissolution profile data for the 0.1 mg batch 22-0138 and 0.15 mg registration batch 22-0141 using the proposed dissolution method (at 50 rpm paddle speed) according to the IFU



In the rBA study in CV185-687 (in n=30 healthy adult subjects), the time to reach peak apixaban plasma concentration (T_{max}) from 0.1 mg sprinkle granule product was 1 hr (0.50, 2.00) as compared to the 0.5 mg tablet formulation. The F_{rel} or relative bioavailability of the 0.1 mg sprinkle granule product was 110% of the tablet formulation. Because the 0.1 mg powder/granule product demonstrates rapid absorption (~1 hr) and rapid dissolution (>90% in 10 mins), and the 0.1 mg and 0.15 mg products demonstrate rapid and similar dissolution, the proposed method is bio-relevant.

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: Adequate

The proposed bead/granule/powder for oral suspension contains low load (0.15 mg) of drug, apixaban a highly soluble, low permeable, BCS Class III drug substance. The proposed dissolution method demonstrates no discriminating ability within the parameter ranges evaluated for the identified critical material attributes for the drug product i.e., (b) (4) and PSD of the sugar spheres (up to < (b) (4) μm to > (b) (4) μm) as apixaban is a highly soluble drug substance and dissolution is not rate-limiting for this product. None of the product variants with changes in material attributes or formulation variables had an impact on the dissolution of the drug product (b) (4)

B.12 BRIDGING OF FORMULATIONS

Assessment: Adequate

Several formulation changes were made during product development of the proposed bead/granule/powder for oral suspension containing low drug load (0.15 mg), highly soluble apixaban drug substance. The 0.15 mg granule product was not administered in any clinical trial. However, the 0.1 mg granule product was dosed in several Phase I rBA study; Phase II safety, efficacy, and PK study; and in pivotal safety and efficacy study in pediatric subjects.

A. Bridging the 0.15 mg Granules/Powder for Oral Suspension to the 0.1 mg Granules and 0.5 mg Tablet Product:

- *Pharmacokinetic bridging of the 0.1 mg granules to the 0.5 mg tablet in the relative bioavailability study, CV 185-687*

Initially, 0.1 mg granule/powder for oral suspension (composition provided in **Table 3a**) was developed and administered in the rBA studies; Study CV185-687 in N=30 healthy adult subjects to assess the single dose pharmacokinetics (PK) of apixaban and in Study CV185-118 in N=49 male and female pediatric subjects, neonates to <18 years to assess the single dose pharmacokinetics (PK) of apixaban.

Bridging of 0.1 mg clinical batches administered in Phase 1 rBA study CV 185-687 to the 0.5 mg tablet product is based on PK bridging (see **Figure 6a**).

In the rBA Study CV185-687 in healthy adult subjects, 25×0.1 mg batch AAU2164 was administered as treatment B along with 5×0.5 mg tablet product batch AAV4455 was dosed as treatment A for a total oral dose of 2.5 mg. Mean plasma concentration vs. time profile of apixaban in linear and semi-logarithmic scale is provided in **Figure 6b** and geometric mean ratios of the pharmacokinetic parameters, C_{max} and AUC_{0-inf} is provided in **Table 4a**.

Figure 6a. Pharmacokinetic bridging of the 0.1 mg granules to the 0.5 mg tablet product in the relative bioavailability study, CV 185-687

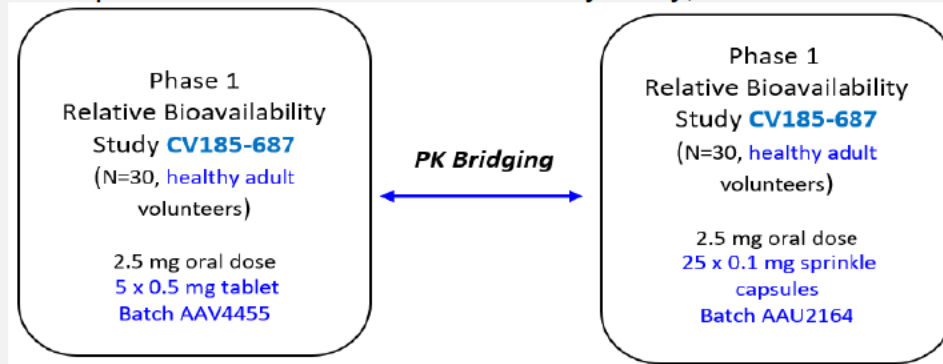
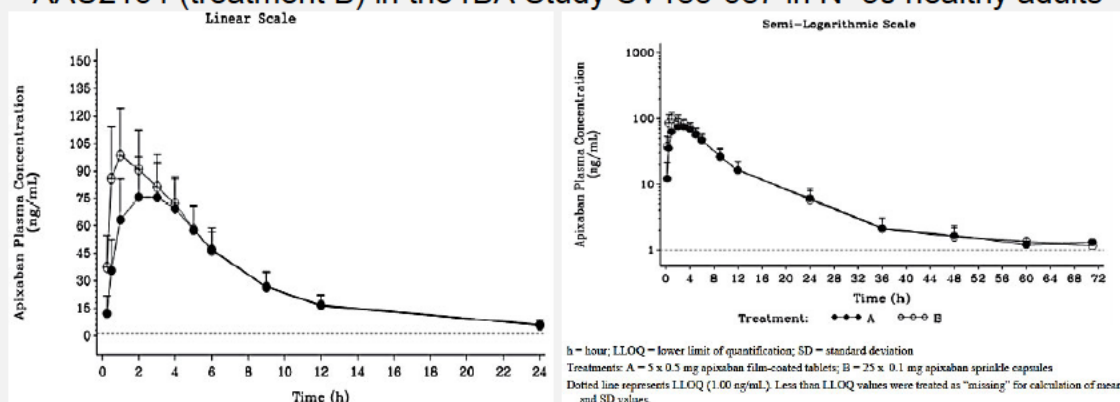


Figure 6b. Mean plasma concentration vs. time profile of apixaban following administration of 5×0.5 mg tablet product (treatment A) and 25×0.1 mg batch AAU2164 (treatment B) in the rBA Study CV185-687 in N=30 healthy adults



The geometric mean ratios for the pharmacokinetic parameters, C_{max} and $AUC_{0-\infty}$ for apixaban following administration of 25×0.1 mg batch AAU2164 (treatment B) vs. 5×0.5 mg tablet product (treatment A) in the rBA Study CV185-687 in healthy adult subjects would meet the 80-125% bioequivalence (BE) criteria for $AUC_{0-\infty}$ [90% CI for $AUC_{0-\infty}$ ($ng \cdot hr/mL$) = 1.071-1.135] for treatment B vs. treatment A. For C_{max} , geometric mean ratios for treatment B vs. treatment A is slightly higher (1.283), with 90% CI for C_{max} (ng/mL) = 1.222-1.136 (see **Table 4a**). Therefore, 0.1 mg batch AAU2164 demonstrated equivalent apixaban exposure ($AUC_{0-\infty}$) to the 0.5 mg tablet batch AAV4455 in N=30 healthy adult subjects (see Office of Clinical Pharmacology Review for details). *Therefore, the 0.1 mg rBA batch is bridged to the 0.5 mg tablet rBA batch through equivalent exposure data.*

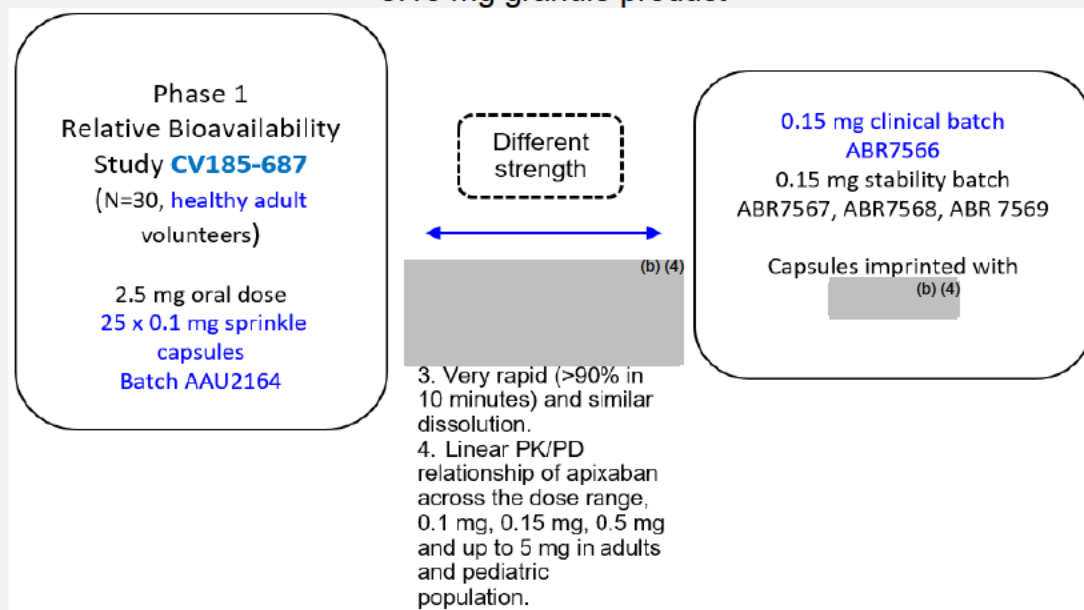
Table 4a. Geometric mean ratios of the pharmacokinetic parameters, C_{max} and AUC_{0-inf} for apixaban following administration of 5×0.5 mg tablet product (treatment A) and 25×0.1 mg batch AAU2164 (treatment B) in the rBA Study CV185-687 in N=30 healthy adult subjects

Adjusted Geometric Mean and Ratios [N] (90% CI)			
Pharmacokinetic Parameter (Unit)	Treatment A	Treatment B	Treatment B vs Treatment A
C _{max} (ng/mL)	77.4 [30]	99.3 [30]	1.283 [30]
	(71.3, 84.1)	(92.1, 107)	(1.222, 1.346)
AUC(0-T) (ng·h/mL)	696 [30]	769 [30]	1.105 [30]
	(639, 758)	(714, 829)	(1.074, 1.138)
AUC(INF) (ng·h/mL)	715 [30]	788 [30]	1.102 [30]
	(657, 778)	(733, 847)	(1.071, 1.135)

Treatments: A = 5 × 0.5 mg apixaban film-coated tablets; B = 25 × 0.1 mg apixaban sprinkle capsules
Abbreviations: AUC(0-T), area under the plasma concentration-time curve from time zero to time of last quantifiable concentration; AUC(INF), area under the plasma concentration-time curve from time zero extrapolated to infinite time; CI, confidence interval; C_{max}, peak serum concentration; N, number of participants or subjects

➤ *Bridging the 0.1 mg granules to the to-be-marketed 0.15 mg granule product:*
Later during product development, (b) (4) 0.15 mg sprinkle granule product with different fill weight was developed (composition provided in **Table 3a**). (b) (4)
(b) (4). The 0.15 mg sprinkle granule product was not administered in any rBA study; however, the Applicant proposes to administer it in an on-going clinical study.

Figure 6c. Bridging of the 0.1 mg granules to the to-be-marketed 0.15 mg granule product



The 0.1 mg granules is bridged to the to-be-marketed 0.15 mg granule product based on the following information/data:

(b) (4)

(2) The 0.1 mg and 0.15 mg drug product (b) (4) (see **Table 4b**),

Table 4b. (b) (4)

Function	Composition		
	% w/w	0.1 mg strength (mg/capsule)	0.15 mg strength (mg/capsule)
(b) (4)	(b) (4)		
Apixaban DS		0.1	0.15
(b) (4) (hypromellose			(b) (4)
			(b) (4)
			(b) (4)
Theoretical Total Weight of Beads			(b) (4)
Capsule (b) (4) sprinkle capsule)			(b) (4)
			(b) (4)

(3) Dissolution of the 0.1 mg pivotal batch ABK7202 and other 0.1 mg clinical batches is very rapid (>90% in 10 minutes) and similar to the 0.15 mg clinical batch, registration stability batches, and TBM commercial image batches with low unit-to-unit variability using the proposed dissolution method (see **Figure 6d**).

(4) Linear pharmacokinetics (PK)/pharmacodynamics (PD) relationship (of apixaban concentration and anti-FXa activity across the dose range, 0.1 mg, 0.15 mg, 0.5 mg and up to 5 mg in adults and pediatric population in the pivotal safety, efficacy and PK Study CV185-325 (see **Figure 6e** and **Table 4d**).

In the pivotal Study CV185-325, 5 mg tablets, 0.5 mg tablets (<5 years, 4 kg to < 35 kg), 0.1 mg sprinkle capsules (<5 years, 4 kg to < 35 kg), and 0.4 mg/mL solution for oral administration (≥5 years of age) were dosed in the pediatric patients <5 yrs (neonates) to <18 years (adults).

The geometric mean of the pharmacokinetic parameters and simulated steady-state exposures (AUC_{ss}) for subjects in the pivotal safety and efficacy study CV185-325 according to the body weight is provided in **Table 4c**.

Additional information on the studies can be found in the Office of Clinical Pharmacology/Pharmacometrics Review.

Figure 6d. Dissolution profile data for the 0.1 mg clinical batches and 0.15 mg clinical, registration, and TBM batches using the proposed dissolution method

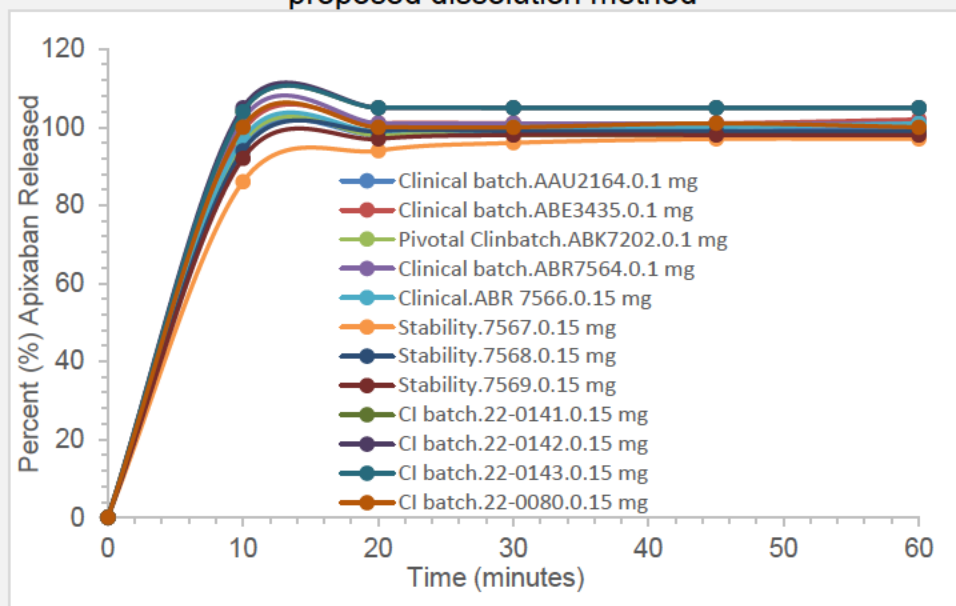
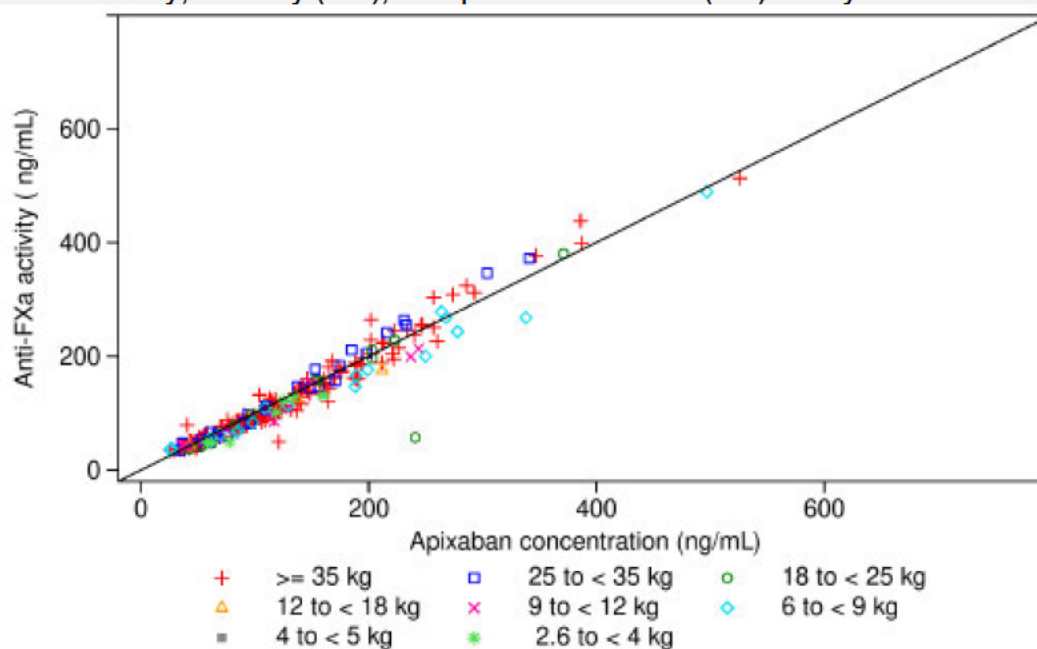


Figure 6e. Observed linear pharmacokinetic (apixaban concentration)-pharmacodynamic (anti-FXa activity) relationship across body weight in the pivotal safety, efficacy (PD), and pharmacokinetic (PK) Study CV185-325



KIWI Version 4 2024R1 - File ID: 2892882 - Scatterplot Profile: 6378

Source: Figure 3.3.2.4.4 of the CV185325 Pharmacometric Report⁸

Note: There were no subjects in the 4 to < 5 kg body weight category that were included for PK/PD analyses.

Table 4c. Geometric mean of the pharmacokinetic parameters and simulated steady-state exposures (AUC_{ss}) for subjects in the pivotal safety and efficacy study CV185-325 according to the body weight

PK Parameter	2.6 to <4 kg (n=9)	4 to <5 kg (n= 1)	6 to <9 kg (n= 2)	9 to <12 kg (n= 6)	12 to <18kg (n=2)	18 to <25kg (n=6)	25 to <35 kg (n = 14)	≥35 kg (n = 95)	Overall (n = 144)
AUC _{ss} (fAU) (ng·h/mL)	643(25.3)	485 (NA)	1200 (59.2)	1080 (317)	1240 (6.45)	1530 (34.4)	1400 (28.5)	1080 (38)	1090 (42.1)
CUF(1/h)	0.164 (26.1)	0.22(NA)	0.835 (59.2)	138 (316)	1.58(6.42)	189 (34.2)	2.68 (28.6)	4.27 (38)	2.59 (126)
C _{max} ss (ng/mL)	65.3(25)	49.3 (NA)	159 (53.1)	156 (25.7)	176(12.1)	211 (25.6)	180 (26.7)	134 (34.5)	137 (42.7)
C _{min} ss (ng/mL)	40 (26.1)	30.3 (NA)	45.7(84.1)	34.7 (63.1)	43.8 (6.64)	57.6 (55.8)	59.2 (36.3)	48.6 (52.5)	48.1 (53.3)

Table 4d. Slopes and 95% confidence interval for the PK/PD model for Anti-FXa activity in pediatric and adult population based on Studies CV185-118, CV185-325, and CV185-362

Parameter	Pediatric (CV185118) PK/PD Analysis	Adult PK/PD Analysis
Slope (IU/ng)	0.0155	0.0159
95% CI	0.0151, 0.016	0.0157, 0.0161

Source: SCP [adults] in NDA202155, SN0096, 24-Oct-2013; Section 3.2.2 pediatric (CV185118)

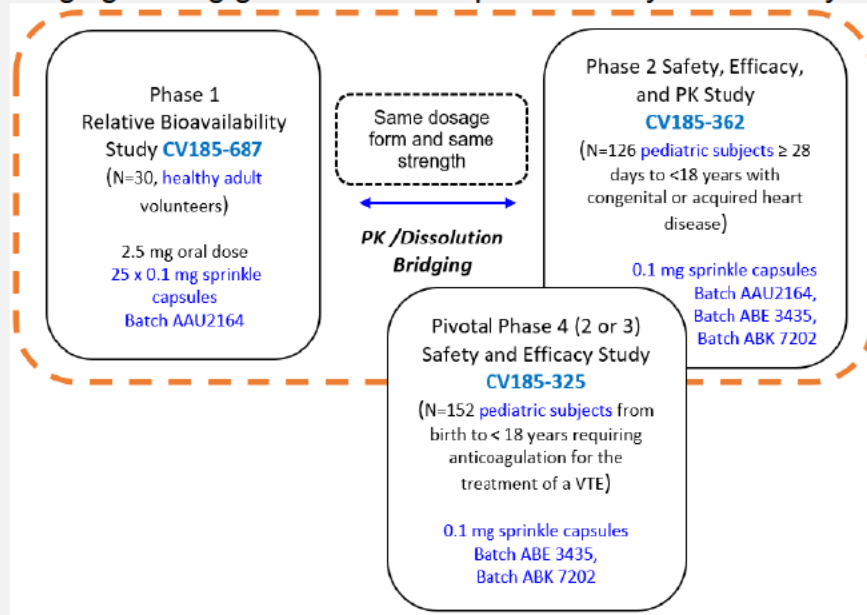
Based on the overall dissolution data, the 0.1 mg clinical batches administered in the clinical studies are adequately bridged to 0.15 mg clinical, registration, and TBM batches.

B. Bridging the 0.1 mg granules/powder batches administered in relative bioavailability studies and in the pivotal safety and efficacy Study CV185-325:

Several 0.1 mg batches were administered in another relative bioavailability Study CV185-118 in pediatric subjects to assess the single dose pharmacokinetics (PK) of apixaban. In addition, several 0.1 mg batches were administered in Phase 2 safety, efficacy and PK Study CV185-362 and in the pivotal safety and efficacy Study CV185-325 in pediatric population of varying age groups.

The 0.1 mg batches demonstrated similar exposures (AUC_{0-inf}) to the 0.5 mg and 5 mg tablet in adult and in pediatric population, except in patients <5 kg (see **Figure 6e**, **Table 4c** and **Table 4d**).

Dissolution of the 0.1 mg clinical batch AAU2164 administered in the rBA Study CV185-687 and in supportive Phase 2 safety, efficacy, and PK Study CV185-362 is very rapid (>90% dissolution in 10 mins) and similar at release to other 0.1 mg clinical batches ABE 3435, ABK 7202 administered in the supportive Phase 2 safety, efficacy, and PK Study CV185-362 and in pivotal Phase 4 (2 or 3) safety and efficacy study, CV185-325 using the proposed method (see **Table 4c** and **Table 4d**).

Figure 6f. Bridging 0.1 mg granule rBA and pivotal safety and efficacy study batches

Based on the overall dissolution data for the 0.1 mg rBA and pivotal safety and efficacy study batches with different drug substance lots, the 0.1 mg batches are bridged through PK and dissolution data.

C. Bridging the 0.15 mg Clinical Batch, Stability Batches to the 0.15 mg To-Be-Marketed (TBM), Commercial Image Drug Product Due to Change in Drug Substance Lot and Imprinting:

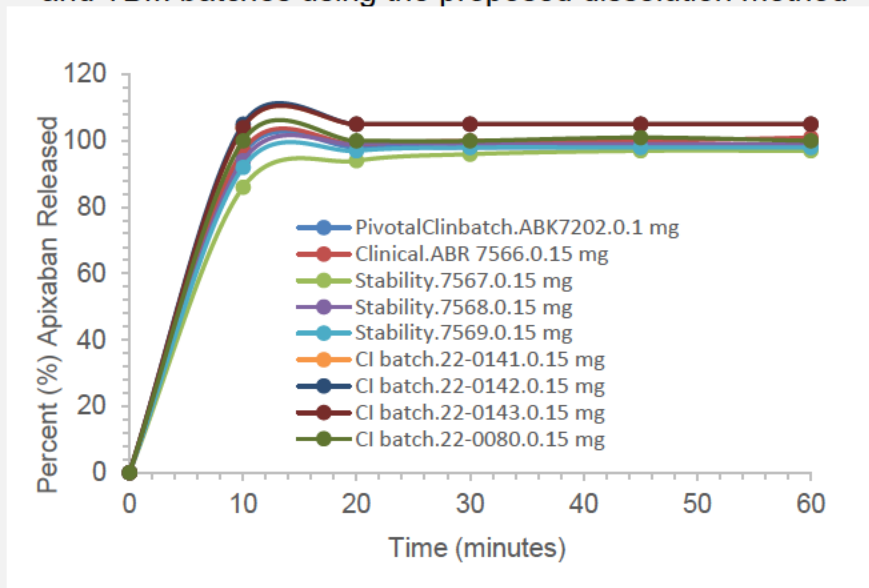
The 0.1 mg clinical batch ABK7202 administered in the pivotal clinical trial CV185-325 (see **Figure 6a**) and 0.15 mg clinical batch ABR 7566 were manufactured using drug substance Lot AAW2407. However, many other drug substance lots were used to manufacture the 0.15 mg stability batches and commercial image batches.

Dissolution of the 0.1 mg pivotal batch ABK7202 manufactured using drug substance Lot AAW2407 is very rapid (>90% in 10 mins) and similar to the 0.15 mg clinical batch, registration stability batches, and TBM commercial image batches manufactured with other drug substance lots with low unit-to-unit variability using the proposed dissolution method (see **Figure 6e**).

In addition, the 0.15 mg clinical batch ABR 7566 and the registration stability batches are imprinted with (b) (4) on the capsule cap TBM drug product. However, the TBM does not have (b) (4) imprinted on the capsule cap. Rather, the capsule cap for the TBM is imprinted with (b) (4) "898" underneath.

Dissolution of the 0.15 mg clinical batch ABR 7566, registration stability batches, and TBM commercial image batches are very rapid (>90% in 10 mins) and similar with low unit-to-unit variability using the proposed dissolution method (see **Figure 6e**).

Figure 6e. Dissolution profile data for the 0.1 mg pivotal batch ABK7202 manufactured using drug substance Lot AAW2407 and 0.15 mg clinical batch ABR 7566, registration, and TBM batches using the proposed dissolution method



Considering the overall dissolution data, the 0.15 mg clinical, registration, and TBM batches are adequately bridged due to changes in drug substance lots and changes in imprinting using the proposed dissolution method.

B. 13 BIOWAIVER REQUEST

Assessment: Adequate

Initially, 0.1 mg granule/powder for oral suspension (composition provided in **Table 3a**) was developed and administered in the rBA studies, Study CV185-687 in adults and in Study CV185-118 in pediatric subjects to assess the single dose pharmacokinetics (PK) of apixaban, and in several including pivotal safety, efficacy, and PK Studies, Studies CV185-118, CV185-325, and CV185-362.

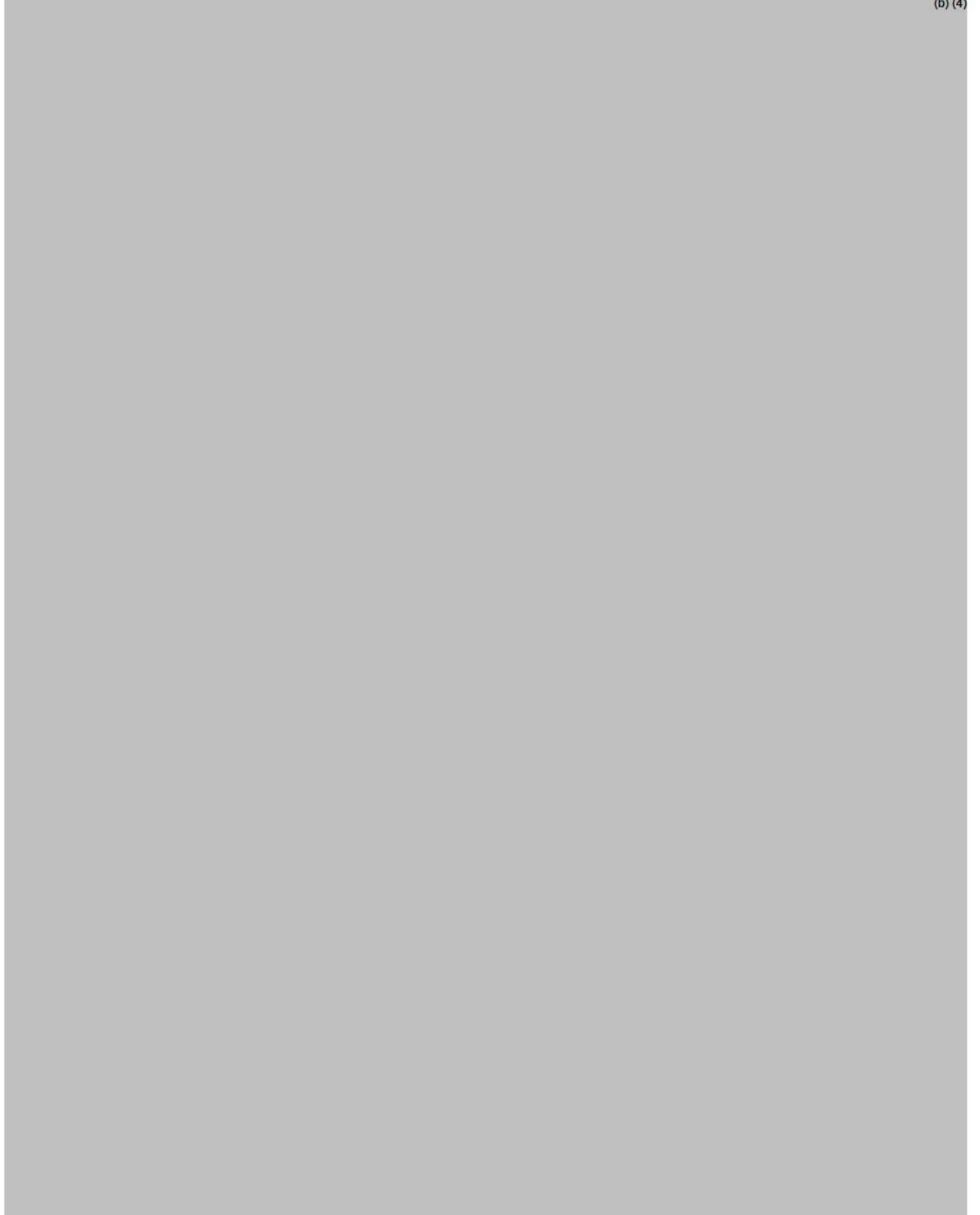
Later during product development, a (b) (4) 0.15 mg sprinkle granule product with different fill weight was developed (composition provided in **Table 3a**). (b) (4)

The 0.15 mg sprinkle granule product was not administered in any clinical study.

Though the Applicant did not request a biowaiver for the proposed 0.15 mg granule product, a bridging strategy was proposed for the 0.15 mg granule (see **Section B.12 Bridging of Formulations**). The bridging strategy (see **Figure 6a** and **Figure 6c**) for the 0.15 mg granule to the 0.1 mg granule and 0.5 mg tablet for suspension can be used to grant biowaiver for the proposed 0.15 mg granule product.

R. REGIONAL INFORMATION**BIOPHARMACEUTICS LIST OF DEFICIENCIES**

(b) (4)





Parnali
Chatterjee

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Date: 2/28/2025 02:29:30PM

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Haritha
Mandula

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Date: 2/28/2025 02:42:38PM

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Theodore
Carver

Digitally signed by Theodore Carver

Date: 4/10/2025 09:10:39AM

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THEODORE E CARVER
04/10/2025 09:23:11 AM