

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

220073Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	04/16/2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 220073; NDA 202155/S-39 and NDA 202155/S-40
Product Name, Dosage Form, and Strength:	Eliquis Sprinkle (apixaban) for oral suspension 0.15 mg Eliquis (apixaban) tablets for oral suspension 0.5 mg Eliquis (apixaban) tablets 2.5 mg and 5 mg (currently marketed)
Applicant Name:	Bristol Myers Squibb
FDA Received Date:	April 15, 2025; April 16, 2025
TTT ID #:	2024-13438-2; 2024-11342-2
DMEPA 2 Safety Evaluator:	Shabana Rauf, PharmD
DMEPA 2 Director:	Danielle Harris, PharmD

1 PURPOSE OF MEMORANDUM

Bristol Myers Squibb submitted revised container labels and carton labeling received on April 15, 2025 for Eliquis tablets and Eliquis Sprinkle for oral suspension. The Division of Non-Malignant Hematology (DNH) requested that we review the revised container labels and carton labeling for Eliquis tablets and Eliquis Sprinkle for oral suspension (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

We note the revised container label and carton labeling for Eliquis Sprinkle (apixaban) for oral suspension 0.15 mg submitted on April 15, 2025 required further revision. The dosage form (b) (4) should instead read "for oral suspension". This recommendation was conveyed to the applicant on April 15, 2025, and as such, the revised carton labeling and container labels were submitted on April 16, 2025.

Bristol Myers Squibb implemented all of our recommendations and we have no additional recommendations at this time. The container labels and carton labeling Eliquis (apixaban) tablets for oral suspension (0.5 mg, 1.5 mg, and 2 mg) received on April 15, 2025, and the container labels and carton labeling for Eliquis Sprinkle (apixaban) for oral suspension 0.15 mg received on April 16, 2025 are acceptable from a medication error perspective.

^a Rauf, S. Memorandum Review of Revised Label and Labeling for Eliquis and Eliquis Sprinkle (NDA 220073; NDA 202155/S-39 and NDA 202155/S-40). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 Apr 10. TTT ID: 2024-13438-1; 2024-11342-1

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/s/

SHABANA RAUF
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DANIELLE M HARRIS
04/16/2025 02:27:49 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	April 10, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 220073; NDA 202155/S-39 and NDA 202155/S-40
Product Name, Dosage Form, and Strength:	Eliquis Sprinkle (apixaban) for oral suspension 0.15 mg Eliquis (apixaban) tablets for oral suspension 0.5 mg Eliquis (apixaban) tablets 2.5 mg and 5 mg (currently marketed)
Applicant Name:	Bristol Myers Squibb
FDA Received Date:	April 8, 2025
TTT ID #:	2024-13438-1; 2024-11342-1
DMEPA 2 Safety Evaluator:	Shabana Rauf, PharmD
DMEPA 2 Associate Director for Nomenclature and Labeling	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Bristol Myers Squibb submitted revised container labels and carton labeling received on April 8, 2025 for Eliquis. The Division of Non-Malignant Hematology (DNH) requested that we review the revised container labels and carton labeling for Eliquis (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The container labels and carton labeling are unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Bristol Myers Squibb in Section 3.

3 RECOMMENDATIONS FOR BRISTOL MYERS SQUIBB

- A. Carton Labeling and Container Label(s) Eliquis Sprinkle (apixaban) for oral suspension 0.15 mg
- The proprietary name "ELIQUIS SPRINKLE" was found to be conditionally acceptable on April 7, 2025. Replaces all instances of "ELIQUIS" with "ELIQUIS SPRINKLE" for oral suspension dosage form.
 - As currently presented the dosage form is presented as (b) (4) which is inconsistent with the dosage form presented in the prescribing information. To prevent confusion and for consistency we recommend revising the dosage form to "for oral suspension".
 - We recommend revising the format of established name "(apixaban)" to align to be under its proprietary name to prevent confusion and for consistency with all other dosage form labels and labeling.
- B. Carton Labeling and Container Label(s) Eliquis (apixaban) tablets for oral suspension 0.5 mg, 1.5 mg, and 2 mg
- As currently presented the dosage form is presented as (b) (4) which is inconsistent with the dosage form presented in the prescribing information. To prevent confusion and for consistency we recommend revising the dosage form to "tablets for oral suspension".
 -
- C. Container Label(s) Eliquis Sprinkle (apixaban) for oral suspension 0.15 mg
- As currently presented the placeholder for the expiration date is not indicated. A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors. Identify the expiration date location and format you intend to use. We recommend that the human-readable expiration date on the drug package label include

^a Rauf, S. Human Factors Study Report and Label and Labeling Review for Eliquis (NDA 220073; NDA 202155/S-39 and NDA 202155/S-40). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 Mar 03. TTT ID: 2024-11420; 2024-11342; 2025-13438.

a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a forward slash or a hyphen be used to separate the portions of the expiration date.

- As currently presented the placeholder for the lot number is not indicated. The lot number statement is required on the immediate container label per 21 CFR 201.10(i)(1). Revise the container label to include the lot number and ensure that there are no other numbers located in close proximity to the lot number where it can be mistaken as the lot number.⁸ Additionally, ensure the lot number is clearly differentiated from the expiration date.

D. Container Label(s) Eliquis (apixaban) tablets for oral suspension 0.5 mg, 1.5 mg, and 2 mg

- As currently presented the established name "apixaban" is inconsistent with the prescribing information and the carton labeling as the parenthesis around the established name is missing. For consistency we recommend revising the established name to "(apixaban)".
- We acknowledge your comment that the linear barcode was omitted due to concerns regarding physical space. However, the drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2). Add the product's linear barcode to each individual container label in accordance with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation). Or you may submit a barcode exemption request to the Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Silver Spring, MD 20993-0002.

E. Carton Labeling Eliquis (apixaban) tablets for oral suspension 0.5 mg, 1.5 mg, and 2 mg

- As currently presented, the net quantity statement (b) (4) consists of the term (b) (4) instead of "packets". It is inconsistent with the terminology in prescribing information. We recommend revising and replacing the term (b) (4) with "packets" to minimize confusion and ensure consistency with terminology used in PI and IFU.
- The color scheme used to highlight the 2 mg per packet for oral suspension strength is not clearly differentiated due to the similarity between the (b) (4) colors which also overlap with the color scheme of the 2.5 mg tablet carton labeling. Lack of adequate differentiation may contribute to wrong strength errors. Color differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme. We recommend you revise the color scheme to highlight the 2 mg per packet for oral suspension.

- For the 1.5 mg and 2 mg tablets for oral suspension, the strength presentation does not specify that the designated strength (xx mg) is per tablet. We are aware of product selection and administration errors related to misunderstanding the number of units (i.e., tablets) required for a single dose. We recommend you prominently state the strength of the tablet. For example, For 1.5 mg per packet state, "1.5 mg per packet (3 x 0.5 mg tablets)." For 2 mg per packet state, "2 mg per packet (4 x 0.5 mg tablets)." For example,

1.5 mg per packet
(3 x 0.5 mg tablet)

2 mg per packet
(4 x 0.5 mg tablet)

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: March 26, 2025

To: Carleveva Thompson, MS
Senior Regulatory Project Manager
Division of Non-Malignant Hematology (DNH)

Through: Barbara Fuller, RN, MSN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Ruth Mayrosh, PharmD
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Melissa Khashei, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): ELIQUIS (apixaban)

Dosage Form and Route, Application Type/Number, Supplement Number: tablets, for oral use; NDA 202155/S-039 & S-040
capsules, for oral use; NDA 220073

Applicant: Bristol-Myers Squibb

1 INTRODUCTION

On October 17, 2024, Bristol-Myers Squibb submitted for the Agency's review an original New Drug Application (NDA) 220073 for ELIQUIS (apixaban) capsules, with proposed indication for the treatment of venous thromboembolism (VTE) and reduction in 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 purpose of this submission is to provide for a new capsule for oral suspension formulation.

On October 17, 2024, Bristol-Myers Squibb submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved NDA 202155/S-039 & S-040 for ELIQUIS (apixaban) tablets to support the newly proposed pediatric indication and a new age appropriate 0.5 mg film coated tablet for oral suspension formulation, respectively.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Non-Malignant Hematology (DNH) on November 19, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for ELIQUIS (apixaban) tablets and capsules.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFUs was completed on February 12, 2025.

2 MATERIAL REVIEWED

- Draft ELIQUIS (apixaban) tablets and capsules MG and IFUs received on October 17, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 13, 2025.
- Draft ELIQUIS (apixaban) tablets and capsules Prescribing Information (PI) received on October 17, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 13, 2025.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFUs documents using the Arial font, size 10.

In our collaborative review of the MG and IFUs we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the PI

- removed unnecessary or redundant information
- ensured that the MG and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFUs meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFUs is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFUs.

Please let us know if you have any questions.

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/s/

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BARBARA A FULLER
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: March 26, 2025

To: Carleveva Thompson, MS, Senior Regulatory Project Manager
Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, DNH

From: Melissa Khashei, PharmD, RAC Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ELIQUIS[®] (apixaban) capsules, for oral use; ELIQUIS[®] (apixaban) tablets, for oral use

NDA: 220073; 202155/S-039; 202155/S-040

Background:

In response to DNH's consult request dated November 19, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide/Instructions for Use (IFU), and carton and container labeling for the original NDA submission for ELIQUIS[®] (apixaban) capsules, for oral use and supplements 039 and 040 for ELIQUIS[®] (apixaban) tablets, for oral use. The original NDA introduces a new capsule form. The supplements introduce the indication of 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 and add a tablet for oral suspension.

PI/Medication Guide/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on March 13, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide/IFU, and comments will be sent under separate cover.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on October 17, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at 301-796-7818 or melissa.khashei@fda.hhs.gov.

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/s/

MELISSA KHASHEI
03/26/2025 09:11:29 AM

HUMAN FACTORS STUDY REPORT AND LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	03/25/2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 220073; NDA 202155/S-39 and NDA 202155/S-40
Product Type:	Single Ingredient Product
Product Name, Dosage Form and Strength:	Eliquis Sprinkle (apixaban) for oral suspension ^a 0.15 mg Eliquis (apixaban) tablets for oral suspension 0.5 mg Eliquis (apixaban) tablets 2.5 mg and 5 mg (currently marketed)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Bristol Myers Squibb
FDA Received Date:	10/17/2024; 11/22/2024
TTT #:	2024-11420; 2024-11342; 2025-13438
DMEPA 2 Safety Evaluator:	Shabana Rauf, PharmD
DMEPA 2 Team Leader:	Millie Shah, PharmD, BCPS
DMEPA 2 Associate Director for Human Factors:	Lolita Sterrett, PharmD
DMEPA 2 Associate Director for Nomenclature and Labeling	Hina Mehta, PharmD

^a The proposed proprietary name, Eliquis Sprinkle (apixaban) for oral suspension is pending under NDA 220073.

1 REASON FOR REVIEW

This review evaluates the human factors validation study (HFVS) report and labels and labeling for Eliquis (apixaban) for oral suspension 0.15 mg and tablets for oral suspension 0.5 mg.

The Applicant submitted, in parallel, the following:

- NDA 202155/S-039 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
- NDA 202155-S-040 for the addition of tablets for oral suspension
- NDA 220073 for the proposed Eliquis (apixaban) for oral suspension dosage form

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Section/Appendix
Product Information	Section 1.1
Relevant Regulatory History Related to the Proposed Product's Human Factor's Development Program	Section 1.2
Human Factors (HF) Validation Study Report and HF-Related Supporting Documents	Appendix A
Information Requests Issued During the Review	Appendix B
Labels, Labeling, and Packaging	Appendix C

1.1 PRODUCT INFORMATION

Table 2 presents relevant product information for Eliquis (apixaban) for oral suspension 0.15 mg and tablets for oral suspension 0.5 mg that Bristol Myers Squibb submitted on 10/17/2024.

Table 2. Relevant Product Information for Eliquis (apixaban) for oral suspension 0.15 mg and tablets for oral suspension 0.5 mg	
Initial Approval Date	December 28, 2012
Active Ingredient	apixaban
Indication	Approved: • Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation (NVAF)

	• Prophylaxis of Deep Vein Thrombosis (DVT), which may lead to Pulmonary Embolism (PE) following Hip or Knee Replacement Surgery • Treatment of DVT • Treatment of PE • Reduction in the Risk of Recurrence of DVT and PE Proposed: • 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
Route of Administration	Oral
Dosage Form	Approved: tablets Proposed: • For oral suspension • Tablets for oral suspension
Strength	Approved: 2.5 mg and 5 mg Proposed: • for oral suspension 0.15 mg • tablets for oral suspension 0.5 mg
Dose and Frequency	Approved: ○ Reduction of risk of stroke and systemic embolism in NVAf: 5 mg orally twice daily ○ Dose reduction: 2.5 mg orally twice daily in patients with at least two of the following characteristics: ▪ age greater than or equal to 80 years ▪ body weight less than or equal to 60 kg ▪ serum creatinine greater than or equal to 1.5 mg/dL ○ Prophylaxis of DVT following hip or knee replacement surgery: 2.5 mg orally twice daily ○ Treatment of DVT and PE: 10 mg taken orally twice daily for 7 days, followed by 5 mg twice daily. ○ Reduction in the risk of recurrent DVT and PE following initial therapy: 2.5 mg taken orally twice daily. Proposed: 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 The recommended dose of Eliquis is based on the patient's weight.

How Supplied	Approved				
	Strength	Dosage form/Description	Markings	Package Size	NDC Code
	2.5 mg	Tablet Yellow, round, biconvex	Debossed with "893" on one side and "2½" on the other side	Bottles of 60 Hospital Unit- Dose Blister Package of 100	0003-0893- 21 0003-0893- 31
5 mg	Tablet Pink, oval, biconvex	Debossed with "894" on one side and "5" on the other side	Bottles of 60 Bottles of 74 Hospital Unit- Dose Blister Package of 100 30-Day Starter Pack for Treatment of DVT and PE Containing 74 Tablets (1 blister pack of 42 tablets and 1	0003-0894- 21 0003-0894- 70 0003-0894- 31 0003-3764- 74	

				blister pack of 32 tablets)	
Proposed					
0.15 mg	Capsule Yellow, opaque	Printed with "898"	Bottles of 28	0003-0898-28	
0.5 mg	Tablet Pink, round	N/A	Carton of 28 packets 28 count tablet carton (1 tablet per packet) 84 count tablet carton (3 tablets per packet) 112 count tablet carton (4 tablets per packet)	0003-1028-28 0003-3084-28 0003-4112-28	
Storage	Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F) [see USP Controlled Room Temperature].				
Container Closure/ Device Constituent (including figure)	Approved: bottles, hospital unit-dose blister packs, 30-day starter pack Proposed: for oral suspension				

Intended Users	Proposed: Adults ages 18-65 (parent, grandparent, or caregiver)
Intended Use Environment	a nonclinical setting (home environment)

1.2 RELEVANT REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On November 7, 2024, we searched for previous DMEPA reviews and FDA/Applicant interactions relevant to this current review using the terms, "Eliquis", "apixaban", "IND 066106", and "NDA 202155". The identified reviews and FDA/Applicant interactions are provided below.

- On April 02, 2020, we provided written responses for the Applicant's Type C Meeting that included a question regarding the Applicant's proposed plan to introduce capsules for oral suspension (b) (4) 0.15 mg and tablets for oral suspension 0.5 mg to support the anticipated apixaban dosing regimen for the prevention and treatment of VTE in pediatric patients. We recommended the Applicant continue to apply the human factors engineering process principles to develop and optimize the proposed formulations and product labeling (i.e., Instructions for Use [IFU]). We also recommended that the Applicant submit a proactive risk assessment and proposed commercial IFU to the IND for Agency review to determine if additional human factors data is needed to support the supplement. On April 07, 2020, the Applicant responded to the Agency comments and canceled the Type C meeting but agreed to submit the proactive risk assessment and proposed commercial IFU to the IND for Agency review prior to submission of the sNDA^b.
- On April 12, 2024, the Applicant submitted their "Summary Report Apixaban Pediatric Human Factor Studies" and the proposed IFU for their proposed pediatric dosage forms under IND 066106. In the Human Factors General Advice letter, we advised that the Applicant submit the HF validation study report as part of the marketing application and that the acceptability of the HF study report and IFU will be a matter of review under the marketing application^c.
- On October 17, 2024, the Applicant submitted the HFVS results report and labels and labeling for Eliquis (apixaban) for oral suspension and tablets for oral suspension under NDA 220073 and NDA 202155/S-40, which is the focus of this review.

2 OVERALL ASSESSMENT OF HUMAN FACTORS STUDY DESIGN AND METHODOLOGY

This section provides a summary of the study design, and our evaluation of the study methodology to determine if the study has been appropriately designed to support the safe and effective use of the proposed product.

^b Hanan, E. Meeting Request-Written Responses for IND 066106, Eliquis (apixaban). Silver Spring (MD): FDA, CDER, OND, DHP (US); 2020 Apr 07.

^c Corbie, C. Human Factors General Advice Letter for Eliquis (apixaban). Silver Spring (MD): FDA, CDER, OND, DNH (US); 2024 July 15.

2.1 SUMMARY OF STUDY DESIGN

Table 3 presents a summary of the HF validation study (HFVS) design and our discussion of methodology concerns (as applicable). See Appendix A for more details on the study design.

The Applicant did not submit the HF validation study protocol for the Agency’s review prior to commencing the HF validation study. We identified several methodology concerns as described in Table 3 below. Despite the methodology concerns discussed below, in this instance, we evaluated the HFVS results and root cause analysis/participants’ subjective feedback to inform our recommendations, where applicable.

Table 3. Study Methodology for Human Factors (HF) Validation Study																							
Study Design Elements	DMEPA Discussion of Methodology Concerns																						
User Group(s) Total = 45 users There was one user group comprised of adults ages 18-65 (parent, grandparent, or caregiver of a child ages newborn – 6 years of age) who have had experience preparing or administering medicine to the child. <table border="1"> <thead> <tr> <th>User Group</th> <th>Planned Total N = 45</th> <th>Actual Total N = 45</th> </tr> </thead> <tbody> <tr> <td>Adults aged 18-65, parent, grandparent, or caregiver of a child ages newborn – 6 years of age.</td> <td>45</td> <td>45</td> </tr> <tr> <td>Scenario 1: Capsules with liquid</td> <td>15</td> <td>14</td> </tr> <tr> <td>Scenario 2: Sachets with liquid</td> <td>15</td> <td>15</td> </tr> <tr> <td>Scenario 3: Sachets with food</td> <td>15</td> <td>16</td> </tr> <tr> <td>Subgroup A: Older adults, ages 50-65</td> <td>9 (20%)</td> <td>9 (20%)</td> </tr> <tr> <td>Subgroup B: Targeted Limited Literacy</td> <td>~13 (30%)</td> <td>~13 (30%)</td> </tr> </tbody> </table> Criteria for Exclusion (partial list-see Appendix A for full inclusion/exclusion criteria) The user has participated in a market research study, product label study or clinical trial in the previous three (3) months.	User Group	Planned Total N = 45	Actual Total N = 45	Adults aged 18-65, parent, grandparent, or caregiver of a child ages newborn – 6 years of age.	45	45	Scenario 1: Capsules with liquid	15	14	Scenario 2: Sachets with liquid	15	15	Scenario 3: Sachets with food	15	16	Subgroup A: Older adults, ages 50-65	9 (20%)	9 (20%)	Subgroup B: Targeted Limited Literacy	~13 (30%)	~13 (30%)	Based on the exclusion criteria, it is unclear whether the HFVS included participants who may have participated in a previous formative study for the product at any point during the product development program. Inclusion of participants who have previously participated in an HF study for the proposed product may bias the HFVS results. Thus, the exclusion criteria should be considered when interpreting the HFVS results	
User Group	Planned Total N = 45	Actual Total N = 45																					
Adults aged 18-65, parent, grandparent, or caregiver of a child ages newborn – 6 years of age.	45	45																					
Scenario 1: Capsules with liquid	15	14																					
Scenario 2: Sachets with liquid	15	15																					
Scenario 3: Sachets with food	15	16																					
Subgroup A: Older adults, ages 50-65	9 (20%)	9 (20%)																					
Subgroup B: Targeted Limited Literacy	~13 (30%)	~13 (30%)																					
Training Participants were required to watch the training video (approximately 6 minutes) prior to the simulated use tasks.	We acknowledge that the Applicant lists the training video as a risk control measure in the use related risk analysis (URRA). However, the Applicant has not provided details to ensure that all users will consistently watch the training video. It is not guaranteed that all intended users will have access to the training																						

Table 3. Study Methodology for Human Factors (HF) Validation Study

	video (e.g. lack of internet, lack of smart phone, lack of devices to view video). Therefore, if the training is optional or the provision of training cannot be ensured, then the HFVS should have included both trained and untrained users or only untrained users to represent a higher-risk scenario. Thus, it is not reasonable to consider the training video could be used as a mitigation to address risk of use errors for all intended users. Inclusion of all trained participants who watched the video should be considered when interpreting the HFVS results.
Moderator Script The moderator’s script includes the following statements: • “Take your time to review the product, labeling and animated video demonstration at your own pace.” • “Instruct the participant to take the information for use document out of the Rx bag or sachet box and play the instructions for use video demonstration. Allow participant to read through the instructions for use and view video demonstration.” • “You may refer back to the instructions or animated video demonstration at any time during your demonstration.” • “Now prepare a dose for your child mixed in liquid using the packets (called sachets).” • “Please remember that what we would like for you to do is familiarize yourself with the instructions and demonstrate how you would use this medication.” • “Take as much time as you need.” • “Talk out loud to describe what you are thinking or doing.”	The moderator script includes leading and prompting statements. Leading/prompting language can bias the study participants’ performance in the HF validation study and confound the results. As such, the leading language used by the moderator should be considered when interpreting the HFVS results. Also, the HFVS design includes using a “Talk out loud” approach. The talk out aloud approach is not an appropriate methodology for an HF study. It is not representative of actual use, as it interrupts the natural sequence and flow of events. Additionally, it may bias the study results by affecting how the participant completes the task. Thus, the talk out loud approach should be considered when interpreting the HFVS results.

Table 3. Study Methodology for Human Factors (HF) Validation Study

Test Environment & Materials

- Instructions for Use (IFU)
- The testing room was set up to simulate a kitchen (pantry items, measuring devices, table/counter, and a sink).
- Cup simulating child’s mouth (on counter to right)
- Premixed baby formula bottle (on kitchen cabinet to left)
- The room had lighting like a home environment.
- The room was also equipped with a 1-way mirror for observing as well as a camera and audio equipment for recording and video streaming.
- Training video available on an iPad for viewing

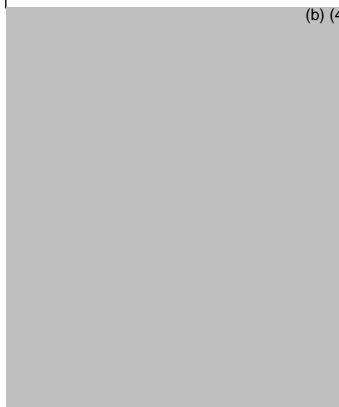
Scenario 1 Setup: Eliquis for oral suspension



- Capsule for oral suspension 0.1 mg bottle with placebo inside prescription bag

IFU Format:

The format of the IFU for tablets for oral suspension in the HFVS is different from the intend-to-market IFU the Applicant submitted. The IFU in the HFVS included side-by-side format (see image below); whereas the proposed IFU submitted presents the liquid mixing method first followed by food mixing method within the IFU (see Appendix C).



Thus, we sent an information request (IR) to clarify the format for the intend-to-market IFU. Based on the IR response, the intend-to-market format of the IFU presents the liquid mixing method first followed by food mixing method (see Appendix B).

Generally, we recommend the Applicant uses the intend-to-market IFU format in the HFVS as differences in formatting and location of information have the potential to impact the performance of critical tasks. However, from a medication error perspective, we do not think the differences in format preclude our ability to review the HFVS results in this instance.

For oral suspension 0.1 mg strength:
The HFVS included the 0.1 mg for oral suspension strength; however, the Applicant

Table 3. Study Methodology for Human Factors (HF) Validation Study

Scenario 2 & 3 Setup: Tablets for oral suspension  • Sachet (packet) box with sachets (packets) containing placebo. • Scissors	proposes the 0.15 mg strength for commercialization. According to the Applicant, the apixaban 0.1 mg capsules were developed and used in the clinical studies to treat neonates. The results suggested an apixaban dosage of 0.3 mg twice daily for 7 days followed by 0.15 mg twice daily thereafter for VTE treatment. Therefore, only the apixaban 0.15 mg capsules are proposed for commercialization. Since the apixaban 0.1 mg and 0.15 mg capsules use the same capsule shell and differ only in the amount of capsule fill and capsule shell color and markings, the HFVS results are applicable to either capsule strength, 0.1 mg, and 0.15 mg. Although, we generally expect the HFVS evaluate the final intend-to-market product, the tasks and the number of capsules participants need to use remain the same for both strengths (i.e., 4 capsules). Specifically, 4 x 0.15 mg capsules are needed for the 0.6 mg dose and 4 x 0.1 mg capsules were used in the HFVS. As such, we find that the difference in the oral suspension strength does not preclude our ability to review the HFVS results in this instance.
Sequence of Study All participants completed the Rapid Estimate of Adult Literacy in Medicine (REALM-SF) at the beginning of their study session to assess their level of health literacy and signed the informed consent form. A brief study overview presented by study staff followed by user viewing the video for the assigned dosing scenario on a tablet device. • Scenario #1: Performance tasks for mixing capsules for oral suspension in liquid.	[Redacted content]

Table 3. Study Methodology for Human Factors (HF) Validation Study

• Scenario #2: Performance tasks for mixing tablets for oral suspension in liquid. • Scenario #3: Performance tasks for mixing tablets for oral suspension in food. • Knowledge-based Task Questions (comprehension interview) • Debriefing Interview/ Root Cause Analysis (RCA)	

3 RESULTS AND ANALYSIS

The HF validation study showed issues with the tasks evaluated by simulated use (performance task) listed below in this section.

- Scenario # 1: 0.4 mg dose (4 x 0.1 mg for oral suspension) Age range 0 to 3 months. Mix in liquid.
 - Step 1: Prepare Supplies
 - Step 3: Tap Capsule
 - Step 4: Open Capsule -Sprinkle Medicine into Cup (Hold)
 - Step 4: Open Capsule - Sprinkle Medicine into Cup (Check)
 - Step 4: Open Capsule –Sprinkle Medicine into Cup (Sprinkle)
 - Step 4: Open Capsule - Sprinkle Medicine into Cup (Throw)
 - Step 6: Give Medicine -Pull Up Liquid Mixture with the Oral Syringe
 - Step 6b: To Ensure All of the Medicine is Given (Pour)
 - Step 6b: To Ensure All of the Medicine is Given (Mix)
 - Step 7: Wash

- Scenario # 2: 1 mg dose (2 x 0.5 mg tablets for oral suspension) Age 4 months and older who cannot eat solid food. Mix in liquid.
 - Step 1: Prepare Supplies
 - Step 3: Tap and Open Sachet (Packet) -Tap
 - Step 4: Empty the Sachet (Packet)- Empty
 - Step 4: Empty the Sachet (Packet)- Ensures all contents are in cup.
 - Step 5: Mixing - Stir Until Dissolved
 - In the HFVS results, some participants provided feedback that the tablets for oral suspension took longer than 7 minutes to dissolve in liquid. The IFU states (b) (4) Thus, we notified OPQ of this issue on 01/14/2025 and defer to OPQ to determine whether the tablet dispersion time stated in the IFU is accurate.
 - OPQ concluded that the drug substance is not completely soluble; therefore, the term “dispersed” or “uniformly dispersed” may be more appropriate

than (b) (4). Thus, we provide a recommendation in Table 5 below to replace (b) (4) with “dispersed” in the IFU.

- Step 6: Giving Medicine (Pull Up Mixture)
 - Step 6b: To Ensure All of the Medicine is Given (Pour)
 - Step 6b: To Ensure All of the Medicine is Given (Mix)
 - Step 6b: To Ensure All of the Medicine is Given (Use)
 - Step 6b: To Ensure All of the Medicine is Given (Give)
 - Step 7: Wash
- Scenario # 3: 1 mg dose (2 x 0.5 mg tablets for oral suspension) Age 9 months and older who can eat solid food. Mix in food.
 - Step 1: Prepare Supplies
 - Step 2: Preparing for Mixing
 - Step 3: Tap and Open Sachet (Packet)- Tap
 - Step 3: Tap and Open Sachet (Packet)- Open
 - Step 4: Empty the Sachet (Packet)- Ensures all contents are in the bowl.
 - Step 5: Mixing: Food Method
 - Step 7: Wash

For each observed issue, we considered the participants’ subjective feedback, the Applicant’s URRR, RCA, our evaluation of the overall residual risks, the implementation of best practice standards and the Applicant’s proposed mitigations (including any post-HFVS changes to the user interface). As a result, in this particular instance we find the proposed user interface has been appropriately designed and we did not identify recommendations to address the identified issues with these tasks.

In Table 4 below, we provide a summary of the use-related events supplied by the Applicant along with our detailed analysis of use-related events that resulted in recommendations and document our points of dissent with the Applicant’s findings.

Table 4. Detailed Analysis of Use Related Events and DMEPA’s Recommendations		
Legend: UE = use error; CC = close call; UD = use difficulty; URRR = use-related risk analysis; RCA = root cause analysis; HFVS = Human Factors Validation Study; Rx = prescription		
	Summary of Information Supplied by Applicant	DMEPA’s Identified Areas of Dissent and Recommendations
1.	Scenario #2: Performance tasks for mixing tablets for oral suspension in liquid. Task: ● Step 2: Prepare for Mixing- add liquid to medicine cup (Success criteria: Adds approximately 10 mL of liquid to medicine cup) ● Step 4: Empty the Sachet (packet)	

Table 4. Detailed Analysis of Use Related Events and DMEPA's Recommendations

Legend: UE = use error; CC = close call; UD = use difficulty; URRRA = use-related risk analysis; RCA = root cause analysis; HFVS = Human Factors Validation Study; Rx = prescription

Summary of Information Supplied by Applicant		DMEPA's Identified Areas of Dissent and Recommendations								
<table border="1"> <tr> <td>Reported Issues:</td> <td>Participant ID #</td> </tr> <tr> <td>UE: Step 2 (n=3) Step 4 (n=3)</td> <td>(b) (6)</td> </tr> <tr> <td>CC (n=0)</td> <td></td> </tr> <tr> <td>UD (n=0)</td> <td></td> </tr> </table>	Reported Issues:	Participant ID #	UE: Step 2 (n=3) Step 4 (n=3)	(b) (6)	CC (n=0)		UD (n=0)			
Reported Issues:	Participant ID #									
UE: Step 2 (n=3) Step 4 (n=3)	(b) (6)									
CC (n=0)										
UD (n=0)										
*Participant made 2 errors while performing the same task Observed event(s): - Added too much liquid, 30 mL first then changed to 20 mL after reviewing IFU. (b) (6) - Added 20 mL liquid and thought instructions meant 10 mL per sachet. (b) (6) - Used 1 sachet and did not empty all the contents in the cup. (b) (6)										
Potential harm associated with issues for this task: Lack of therapeutic effect (underdose)										
Relevant RCA/Subjective Feedback: Step 2 <u>Cognition:</u> Added 30 mL liquid (error 1), then changed to 20 mL (error 2) after reviewing IFU. The participant got confused by the video because it said to use 10 mL, but on the paper, it has at the top on the medication cup in parenthesis 30 mL, so the participant got confused and decided to use 20 mL because that was in the middle. They stated, "put it by the picture of the cup and say 'use 10mL' near where it says 30 mL or take the 30 mL off of there." (b) (6) Another participant added 20 mL and thought instructions meant 10 mL per sachet. The participant stated that the instructions were little confusing and there should be something on the instructions to make it clear. Also indicated that "by looking at the picture, there was only one sachet pictured, and so I thought, I need to add 10 mL more for the 2nd sachet, but then when administering it, couldn't pull it all up in the syringe at one time, so then I thought I should have been able to give all the medication at one time, so then I thought I shouldn't have added the 10 mL more, but I'm still not sure; so it should specify whether the										

Table 4. Detailed Analysis of Use Related Events and DMEPA's Recommendations

Legend: UE = use error; CC = close call; UD = use difficulty; URRRA = use-related risk analysis; RCA = root cause analysis; HFVS = Human Factors Validation Study; Rx = prescription

	Summary of Information Supplied by Applicant	DMEPA's Identified Areas of Dissent and Recommendations
	instructions are 'per sachet' or if it's 10 mL 'per dose.' Explained that the instructions should say something like "no matter the number of sachets you are using, just use 10 mL"; maybe say read the following instructions, these instructions are meant to be followed, no matter the number of sachets prescribed, at the top, and then under step one, again say you might have been prescribed 1 sachet up to i.e. 5 sachets, but 10 mL will be the amount of liquid you add; also add something about should leave the cup on the table when stirring so you don't spill any drops." (b) (6) Step 4 • Cognition: used 1 sachet, spilled contents (not all in cup) and did not fully read the instructions. The participant assumed it's for 4-month-old and didn't remember seeing any instructions for the age and stated, "I didn't read any of the words I just looked at the pictures". Also indicated that the words need to be more black/bold on the box itself. (b) (6) Another participant used 1 sachet and did not read the Rx box and therefore, did not know how many sachets to use. The participant indicated "I think you should make that one of the steps in the instructions - step: parent needs to look at the dose on the Rx box, for the recommended dose for your child, make that its own step, near the beginning of the instructions". (b) (6) • Behavior- Override: only used one sachet and thought child should be given second sachet later and stated, "I would do one pack in the morning and the other one in the evening, so as not to give the baby too much medicine". Also, suggested the Rx instructions to "say 2 packets, twice a day, or 4 packets once a day, so you would know to do both packets at a time, instead of splitting it up". (b) (6)	
	Applicant's Comments and Proposed Post-HFVS Mitigations: • No mitigation recommended.	Some participants did not prepare the correct dose because they did not refer to pharmacy label for the prescribed dose and therefore did not use the correct

Table 4. Detailed Analysis of Use Related Events and DMEPA's Recommendations

Legend: UE = use error; CC = close call; UD = use difficulty; URRRA = use-related risk analysis; RCA = root cause analysis; HFVS = Human Factors Validation Study; Rx = prescription

	Summary of Information Supplied by Applicant	DMEPA's Identified Areas of Dissent and Recommendations								
		number of packets. Our review of the IFU indicates that adding a step after Step 4 to check the prescription label and to repeat the steps, if necessary, may minimize the risk for this error. Although not explicitly stated by the Applicant, our comparison of the IFU evaluated in the HFVS report with the submitted proposed IFU indicates that the Applicant has removed "30 mL" from under the image of medicine cup in Step 1. We acknowledge the Applicant implemented a post HFVS-mitigation to remove "30 mL" from under the image of medicine cup but we disagree that no further mitigation is needed. Specifically, the figure of the medicine cup in Step 2 of the IFU can be improved to clearly show the mL needed for capsules/tablets for oral suspension (i.e., 5 mL for Eliquis for oral suspension and 10 mL for tablets for oral suspension). Additionally, our review of the HFVS results and subjective feedback finds that improvements can be made to the IFU to improve clarity that the mL of liquid is for all packets/capsules and not per packet/capsule. As such, we provide IFU recommendations 1 and 2, in Table 5 below. In this particular instance, we find these revisions can be implemented without submission of additional HF validation data.								
2.	Scenario #3: Performance tasks for mixing tablets for oral suspension in food. Task: Step 6b: To Ensure All of the Medicine is Given – Give <table border="1" data-bbox="245 1642 748 1835"> <thead> <tr> <th>Reported Issues:</th> <th>Participant ID #</th> </tr> </thead> <tbody> <tr> <td>UE (n=3)</td> <td>(b) (6)</td> </tr> <tr> <td>CC (n=0)</td> <td></td> </tr> <tr> <td>UD (n=0)</td> <td></td> </tr> </tbody> </table> Observed event(s): Does not give the remaining medicine in the bowl with the applesauce. (b) (6) Potential harm associated with issues for this task:	Reported Issues:	Participant ID #	UE (n=3)	(b) (6)	CC (n=0)		UD (n=0)		
Reported Issues:	Participant ID #									
UE (n=3)	(b) (6)									
CC (n=0)										
UD (n=0)										

Table 4. Detailed Analysis of Use Related Events and DMEPA's Recommendations

Legend: UE = use error; CC = close call; UD = use difficulty; URRRA = use-related risk analysis; RCA = root cause analysis; HFVS = Human Factors Validation Study; Rx = prescription

Summary of Information Supplied by Applicant	DMEPA's Identified Areas of Dissent and Recommendations
Lack of therapeutic effect (underdose)	
Relevant RCA/Subjective Feedback: <u>Behavior- Override</u>: did not give the rest of the applesauce in the container but would have given all mixture to child in real life setting. When asked if anything in instructions about giving all the mixture, the participant stated, "no, all it says it add approximately 1 tablespoon of food; oh, let me see, it does say give all food, to ensure all med is given". When asked to suggest, then indicated that the instructions would have to say to "give dose first with the food, and then let the child eat the rest of the applesauce, to make sure they are taking the medicine." (b) (6) Another participant gave two tablets from the mixture and didn't believe it was necessary to add more food and stated, "would give the remainder of what the child would want to eat." Also indicated "I emptied out the 2 packets and saw 2 little capsules, and gave the child the two bites, with the 2 capsules so I know the med is in my child's body, and then I would just have given whatever the rest my child would eat." (b) (6) <u>Cognition</u>: Did not comprehend instructions and thought you only needed to give one tablespoon of mixture. The participant stated, "based off the video it looked like after you mix everything, just give one spoonful. Oh, now I see on instructions it says to give all the food mixture, and I don't remember if it said give all the food in the video, and if it did, I didn't catch it; so was going based on memory from the video and not reading the instructions at that point." and suggested to make sure the video is saying exactly what the instruction say. (b) (6)	
Applicant's Comments and Proposed Post-HFVS Mitigations: No mitigation recommended.	Based on the subjective feedback and RCA, we find the IFU can be further improved by enhancing prominence of the entire statement, "Ensure ALL medicine and food have been given so no medicine is left in the bowl." in Step 6. Thus, we provide a recommendation # 1 in Table 5 below under "Instructions for Use (Eliquis 0.5 mg tablets for oral suspension)". We find the recommendation can be

Table 4. Detailed Analysis of Use Related Events and DMEPA's Recommendations

Legend: **UE** = use error; **CC** = close call; **UD** = use difficulty; **URRA** = use-related risk analysis; **RCA** = root cause analysis; **HFVS** = Human Factors Validation Study; **Rx** = prescription

	Summary of Information Supplied by Applicant	DMEPA's Identified Areas of Dissent and Recommendations
		implemented without the submission of additional HF data.

4 LABELS AND LABELING

We note the Office of Pharmaceutical Quality (OPQ) has determined the dosage form for the proposed 0.15 mg strength that is packaged in capsules is "For oral suspension". Additionally, OPQ determined that the appropriate term for the container for the tablets for oral suspension is "packet" not (b) (4).

Tables 5 and 6 below include the identified medication error issues with the submitted product samples, packaging, label and labeling, our rationale for concern, and our proposed recommendations to minimize the risk for medication error.

Table 5. Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	As currently presented, under "Dosage Forms and Strength" section, the 0.15 mg capsule strength does not state the determined dosage form.	Failure to provide this information may lead to administration errors.	We recommend revising to the appropriate dosage form as determined by OPQ. Revise to "For oral suspension".
2.	As currently presented, under "Dosage Forms and Strengths" section, the proposed tablet for oral suspension 0.5 mg is listed on the same bullet as the 2.5 mg, and 5 mg tablets.	We are concerned that including the tablet for oral suspension 0.5 mg on the same bullet as the tablets for oral use, may cause confusion and results in overdosing (For example, 0.5 mg tablet intended for oral suspension may be misinterpreted as a 5 mg tablet for oral use.)	We recommend the tablet for oral suspension 0.5 mg be listed as a separate bullet from the 2.5 mg and 5 mg tablets.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, the error prone symbols "<" and "≥" are utilized in section 2.2.	Error prone symbols may lead to misinterpretation and medication error.	We recommend replacing the symbols with their intended meaning. For example, revise "< 4" to "less than 4", and "≥ 35" to "greater than or equal to 35", and so forth.

Table 5. Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The tablet strength in section 2.2, Table 1 is presented with a trailing zero (i.e., 5.0 mg).	Trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed (i.e., 5.0 mg is seen as 50 mg)	We recommend revising the tablet strength in Table 1 to remove the trailing zero (i.e., 5 mg).
3.	In section 2.2: Recommended Dose in Pediatric Population, the inclusion of the (b) (4) column in Table 1 seems redundant, given that the dose is consistently twice daily (BID).	Redundant information may lead to clutter and important information may be overlooked.	Remove the column (b) (4) from Table 1.
Instructions for Use Eliquis (apixaban) for oral suspension 0.15 mg and Eliquis (apixaban) tablets for oral suspension 0.5 mg			
1.	The sequence of steps for the "Liquid mixing method" for capsule and packet can be improved. As currently presented, Step (b) (4) Add liquid to medicine cup occurs (b) (4).	We are concerned the current sequence of steps may result in administration errors. For example: • Users may spill the liquid if trying to crush the tablets in liquid. • Users may be unsure how to verify if the tablets are fully crushed when mixed with infant formula if tablets are crushed after adding the liquid.	Relocate Step (b) (4) "Add Liquid to Medicine Cup" (b) (4) to "tap and open" for capsule and "tap and open packet" and "empty the packet" for the packet, and the new step to check the prescription label for the prescribed dose such that users are instructed to open and sprinkle capsules and crush the number of tablets prescribed before adding infant formula, water, or apple juice.
The following revisions are from the above recommendation #1.			
Eliquis (apixaban) for oral suspension (b) (4)			

Table 5. Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Eliquis (apixaban) tablets for oral suspension (b) (4)		
2.	The root cause analysis (RCA) and subjective feedback in the human factors validation study (HFVS) indicate that participants were confused about the number of capsules for oral suspension/tablets for oral	Confusion regarding the correct number of capsule or packets might result in wrong dose errors.	We recommend adding a step that is prominently displayed (using color, bolding, boxing, or some other means) after Step (b) (4) (previously Step (b) (4)) as follows:

Table 5. Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	suspension to use in Scenario 1 Step 4, "Open Capsule –Sprinkle Medicine into Cup" and Scenario 2 Step 4, "Empty the Sachet (packet)" whereby they did not indicate that mixing and administration of more than one capsule for oral suspension or tablet for oral suspension is required to complete the dose.		For oral suspension 0.15 mg, "Check the prescription label for the number of capsule(s) to use per dose. Repeat Step (b)(4) and Step (b)(4) using the number of capsule(s) needed for the prescribed dose". For tablets for oral suspension 0.5 mg state, "Check the prescription label for the number of packets to use per dose. Repeat Step (b)(4) and Step (b)(4) using the number of tablet(s) needed for the prescribed dose".
The following revisions are from the above recommendation #2.			

Table 5. Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Eliquis (apixaban) for oral suspension (b) (4)		
3.	The RCA and subjective feedback in the HFVS indicate that participants were confused about the amount of liquid needed per packet or dose in Scenario 2 Step 5 (previously Step (b) (4) "Add liquid to medicine cup".	Confusion regarding amount of liquid to mix and administer might result in wrong dose errors.	The figure of the medicine cup in Step 5 (previously Step (b) (4) can be improved to show that the liquid is at 5 mL for the capsule and 10 mL for the tablets in the medicine cup.

Table 5. Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Additionally, the figure of the medicine cup in Step 5 (previously Step (b) (4)) can be improved to show the exact mL needed.		We recommend that the IFU clearly specify that the amount of liquid needed is not per capsule or packet. For example, for oral suspension 0.15 mg state, "The total amount of liquid required is 5 mL (1 teaspoon), regardless of the number of capsule(s) prescribed." and for tablets for oral suspension 0.5 mg state, "The total amount of liquid required is 10 mL (2 teaspoons), regardless of the number of packet(s) prescribed."
The following revisions are from the above recommendation #3.			
Eliquis (apixaban) for oral suspension			
(b) (4)			

Table 5. Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Eliquis (apixaban) tablets for oral suspension (b) (4)		
4.	The RCA and subjective feedback in the HFVS indicate the instructions in the training video were different than the Instructions for Use (IFU).	Inconsistent instructions may contribute to medication error.	We recommend revising the training video to align with IFU.
5.	As currently presented, the Important Information section in the IFU is missing important statements and is not comprehensive.	Missing important statements in the IFU could cause confusion and lead to administration errors.	We recommend adding the following statements to the “Important Information” section: • Always give this medicine exactly as your child’s doctor or pharmacist has told you. • If your child vomits or spits up within 30 minutes after taking ELIQUIS, repeat the dose. If a child vomits or spits up more than 30 minutes after taking ELIQUIS, do not repeat the dose. • Contact the doctor if your child repeatedly vomits or spits up after taking ELIQUIS.

Table 5. Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
6.	The location of the following statements appears at the end of the preparation steps and can be improved to be at the beginning of the IFU: For oral suspension 0.15 mg: "Be sure to give the medicine immediately or at the latest within 2 hours of preparation." For tablets for oral suspension 0.5 mg (in liquid): (b) (4) 2 hours of preparation." For tablets for oral suspension 0.5 mg (in food): (b) (4)	Including important information at the end of the IFU may result in users' overlooking the information.	We recommend relocating the statements under Important Information section as users may need to know this information before preparing the capsule or tablet for oral suspension. For oral suspension 0.15 mg: "(b) (4) 2 hours of preparation." For tablets for oral suspension: "If given with Liquid, give the medicine i (b) (4) or (b) (4) within 2 hours of preparation." "If given with Food, give the medicine i (b) (4) ."
The following revisions are from the above recommendations #5 and #6.			

Table 5. Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
(b) (4)	7. The location of the following statement that currently appears in Important Information section can be improved to be within the related step: "For patients with fluid restrictions, (b) (4) 2.5 mL."	We are concerned that users may overlook the important statement, resulting in medication errors.	We recommend relocating the statement "For patients with fluid restrictions, (b) (4) to 2.5 mL." to appear in Step 5 (previously Step (b) (4))
8.	"Step 1: Prepare Supplies" does not clearly identify the	Lack of clarity may lead to users missing the necessary	We recommend revising the Prepare Supplies section to

Table 5. Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	supplies not included with the product.	supplies to prepare and administer the product.	identify the supplies not included with the product.
9.	In Step (b) (4) previously Step (b) (4): Part 2 (b) (4), the word "Repeat" lacks prominence.	Lack of prominence may lead to users missing important information, which may result in dosing errors.	Increase the prominence of the statement in Step (b) (4) (previously Step (b) (4)) through the use of boxing, bolding, or some other means.
Instructions for Use Eliquis (apixaban) for oral suspension 0.15 mg			
1.	As currently presented, the statement (b) (4) under important information section is located after " (b) (4) and is not salient.	We are concerned that users may overlook the important statement, resulting in administration errors.	We recommend relocating the statement related to "Open the capsule and sprinkle the entire contents of the capsule in water or infant formula to administer." to be the first bullet in this section. We also recommend adding "Do not swallow capsule" after the above statement and as a note in Step (b) (4) (previously Step (b) (4)).
2.	As currently presented, in Step (b) (4) previously Step (b) (4). Mixing states, (b) (4) However, if using infant formula, it is unclear how users will be able to determine that the medicine (b) (4).	We are concerned users may have difficulty determining that the medicine is (b) (4) if using infant formula. Unclear instructions can lead to confusion.	We recommend clarifying how users should determine the medicine is (b) (4) if using infant formula.
Instructions for Use Eliquis (apixaban) tablets for oral suspension 0.5 mg			
1.	The RCA and subjective feedback in the HFVS indicated that the	Lack of prominence may lead to users missing important information,	Increase the prominence of the statement, "Ensure ALL medicine and food have been given so no

Table 5. Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	information in Scenario 3 Step (b) (4) for “Ensure ALL medicine and food have been given so no medicine is left in the bowl.” lacks prominence.	which may result in administration errors.	medicine is left in the bowl.” in Step (b) (4) by bolding the entire statement.
2.	As currently presented, the image in the IFU for “Food mixing method for packet” in Step (b) (4) has an inconsistent number of tablets in the bowl of food when compared to image in Step (b) (4). Also, the image of tablets shown in the IFU is inconsistent with the number of tablets (i.e., the packets contain 1, 3 or 4 tablets but Step (b) (4) shows an image of (b) (4) tablets in the bowl).	Inconsistent use of images may lead to confusion.	Revise the image in Step (b) (4) to show 1 tablet remaining in the bowl of food to be consistent with the number of tablets shown in the image for Step (b) (4). Also, we recommend images of tablets shown in these steps be consistent with the number of tablets (i.e., the tablet(s) packaged in a packet consist of 1, 3 or 4 tablets but the image shows (b) (4) tablets).
3.	Based on participant subjective feedback from the HFVS for the liquid mixing method for tablets, the text in Step (b) (4) (previously Step (b) (4)) does not specify how to confirm the tablets are completely dispersed if infant formula is used.	We are concerned that not including information on how to determine whether the tablets are dispersed in infant formula may result in administration error.	We recommend specifying in Step (b) (4) previously Step (b) (4) how to confirm the tablets are dispersed if infant formula is used.
4.	As currently presented, the IFU states (b) (4) in Step (b) (4) previously Step (b) (4). The statement should be	Unclear instructions can result in confusion and wrong technique preparation medication errors.	We recommend revising the statement to state, (b) (4)

Table 5. Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	revised for clarity and accuracy.		
Instructions for Use and Medication Guide			
1.	As currently presented, The IFU and medication guide are located at the end of the PI.	We are concerned that presenting the IFU and medication guide at the end of the PI may result in patients being confused by the PI information that is not intended for them.	We recommend providing the IFU and medication guide on separate documents from the PI.

Table 6. Identified Issues and Recommendations for Bristol Myers Squibb (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling Eliquis (apixaban) tablets for oral suspension 0.5 mg, 1.5 mg, and 2 mg			
1.	As currently presented, the word "per packet" is missing next to the total strength on the principal display panel.	Failure to clearly express the product strength as "per packet" may lead to misinterpretation resulting in medication errors.	We recommend that the labels and labeling clearly and prominently express the total strength "per packet" (for example, "2 mg per packet").
2.	As currently presented, the format for the expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are

Table 6. Identified Issues and Recommendations for Bristol Myers Squibb (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).
3.	The PDP is missing the correct administration method.	Not including the correct administration method on the container labels and carton labeling may lead to wrong route of administration errors. See Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors (April 2016).	We recommend adding the statement "Mix tablets prior to ingestion. Do not swallow tablet" on the principal display panel of the carton labeling and "Mix tablets prior to ingestion" on the container label.
Container Label(s) and Carton Labeling Eliquis (apixaban) for oral suspension 0.15 mg and Eliquis (apixaban) tablets for oral suspension 0.5 mg, 1.5 mg, and 2 mg			
1.	As currently presented, the container label or carton labeling does not state, "For Pediatric Use".	Failure to include the important statement on carton and container label(s) may lead to medication errors.	We recommend adding the statement "For Pediatric Use" on Eliquis 0.15 mg for oral suspension and 0.5 mg, 1.5 mg, and 2 mg tablets for oral suspension carton and container labels.

Table 6. Identified Issues and Recommendations for Bristol Myers Squibb (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	As currently presented, strength is presented in close proximity to the proprietary name, which could lead to confusion.	The strength located in close proximity to the proprietary name may be mistaken as the modifier.	We recommend relocating the strength below the dosage form. Consider removing (b) (4) for placement of strength below the dosage form.
Container Label(s) Eliquis (apixaban) tablets for oral suspension 0.5 mg, 1.5 mg, and 2 mg			
1.	On the container labels for the 1.5 mg and 2 mg tablets for oral suspension, the designated strength per tablet in the packet (i.e., 0.5 mg is per tablet) is unclear.	Failure to clearly express the product strength "0.5 mg per tablet" may lead to wrong dose errors.	We recommend revising the strength statement as follows: For 1.5 mg tablet for oral suspension- (b) (4) to state, "3 tablets (0.5 mg per tablet)." For 2 mg tablet for oral suspension- (b) (4) to state, "4 tablets (0.5 mg per tablet)" to make it clear that the designated strength is per unit so there is no confusion as to how much product is contained in a single unit as compared to the total contents of the packet.
2.	As currently presented, the container label of 0.5 mg, 1.5 mg, and 2 mg tablet for oral suspension does not include the assigned NDC number or placeholder.	The human readable NDC is often used for product verification and identification prior to dispensing or administering a drug. It is an important safety feature that is recommended to be prominently displayed on the principal display panel of the container label.	We request that you include the NDC number or placeholder on the principal display panel of the container label per 21 CFR 201.2.
3.	A 2D machine-readable barcode is included on the container label; however, the linear barcode is missing.	The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should	We request you remove the 2D machine-readable barcode from the container label and add the product's linear barcode to each individual container label in accordance

Table 6. Identified Issues and Recommendations for Bristol Myers Squibb (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		be part of the label and is a requirement per 21 CFR 201.25(c)(2). Also, multiple barcodes may be confusing.	with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text.
Container Label(s) and Carton Labeling Eliquis (apixaban) for oral suspension 0.15 mg			
1.	The statement (b) (4) on the PDP can be improved for clarity.	Unclear instructions can lead to confusion.	We recommend revising the statement to "Open the capsule and mix the contents with liquid."
2.	The 0.15 mg for oral suspension strength is not clearly differentiated due to the similarity between the (b) (4) colors which also overlap with the font colors used for the proprietary name.	Lack of adequate differentiation may contribute to wrong strength errors. Color differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme.	We recommend you choose a different and more contrasting color to differentiate 0.15 mg for oral suspension. In addition, we recommend revising the color scheme of 0.15 mg strength such that the strength and the proprietary name appear in their own unique colors that do not overlap.
Carton Labeling Eliquis (apixaban) for oral suspension 0.15 mg and Eliquis (apixaban) tablets for oral suspension 0.5 mg, 1.5 mg, and 2 mg			
1.	The terminology within the dosage statement (i.e., "usual dosage" and "package insert") is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the dosage statement to read, "Recommended Dosage: see Prescribing Information."
2.	The carton labeling contains redundant information which may contribute to clutter. Specifically, the statement, (b) (4)	We are concerned that this redundant statement may compete with critical drug information on the side panel such as storage and warning statement.	Remove the statement, (b) (4) from the side panel.

Table 6. Identified Issues and Recommendations for Bristol Myers Squibb (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) on the side panel is redundant with the "Recommended Dosage statement."		
3.	We note the carton labeling includes the Medication Guide (MG) Statement "Dispense with Medication Guide". However, the carton labeling does not include how the MG is provided (e.g., accompanied, enclosed, or provided separately).	Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner.	Ensure the Medication Guide statement appears in accordance with 21 CFR 208.24(d).
4.	The side panel on the apixaban for oral suspension contains the statement (b) (4) and the tablet for oral suspension contains the statement (b) (4)	This information may lead to clutter and important information may be overlooked.	We recommend removing the aforementioned statements from the carton labeling.

Table 6. Identified Issues and Recommendations for Bristol Myers Squibb (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling Eliquis (apixaban) for oral suspension 0.15 mg			
1.	The warning statement "Do not swallow the capsule." is expressed as a negative statement.	Post-marketing reports have shown that negative statements (e.g., do not) may have the opposite of the intended meaning because the word "not" can be overlooked and misinterpreted as an affirmative action.	We recommend revising the warning statement to use positive language first followed by negative statement. For example, state "Open the capsule and mix the contents with liquid prior to ingestion." first followed by "Do not swallow the capsule". See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
Carton Labeling Eliquis (apixaban) tablets for oral suspension 0.5 mg, 1.5 mg, and 2 mg			
1.	For the 1.5 mg and 2 mg tablets for oral suspension, the dosage regimen lacks prominence and may be overlooked, such that the strength presentation does not specify that the designated strength (xx mg) is per single unit tablet.	We are aware of product selection and administration errors related to misunderstanding the number of units (i.e., tablets) required for a single dose.	We recommend relocating the total contents statement from the side panel to the principal display panel under "28 (b) (4) (packet)" on the carton labeling to provide further clarity on the total quantity contained within each (b) (4) (packet). Prominently stating the dosage regimen on the carton will convey the number of units required for a single dose. For example, For 1.5 mg tablets for oral suspension state, "Each packet contains 3 x 0.5 mg tablets)." For 2 mg tablets for oral suspension state, "Each packet contains 4 x 0.5 mg tablets."

Table 6. Identified Issues and Recommendations for Bristol Myers Squibb (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The 0.5 mg tablet for oral suspension strength is not clearly differentiated due to the similarity between the (b) (4) colors which also overlap with the font colors used for the proprietary name.	Lack of adequate differentiation may contribute to wrong strength errors. Color differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme.	We recommend you choose a different and more contrasting color to differentiate tablet 0.5 mg for oral suspension. In addition, we recommend revising the color scheme of the 0.5 mg tablet strength such that the strength and the proprietary name appear in their own unique colors that do not overlap.

5 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors, close calls, use difficulties with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use errors. Above, we have provided recommendations in Table 6 for the Applicant. These changes can be implemented without submitting additional HF validation testing data for Agency review.

Additionally, our evaluation of the proposed label(s) and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 5 for the Division. We ask that the Division convey Table 6 in its entirety to the Applicant so that recommendations are implemented for NDA 220073 and NDA 202155/S-40. These changes can be implemented without submitting additional HF validation testing results for Agency review.

APPENDICES:

APPENDIX A. HUMAN FACTORS (HF) VALIDATION STUDY REPORT AND HF-RELATED SUPPORTING DOCUMENTS

- The HF study results report, use-related risk analysis, IFU and background information can be accessed in EDR via: <\\CDSESUB1\EVSPROD\nda220073\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-venous-thromboembolism\5354-other-stud-rep\23036\23036-human-factors-summative-study-report.pdf>

APPENDIX B. INFORMATION REQUESTS (IR) ISSUED DURING THE REVIEW

On 11/8/2024, we issued an IR to provide full intend-to-market samples of the proposed Eliquis 0.15 mg for oral suspension and tablets for oral suspension, including carton and labeling with the USPI and Instructions for Use (IFU) included with the samples.

On 11/19/2024, we issued an IR submit the intend-to-market IFU format for both Eliquis (apixaban) for oral suspension and tablets for oral suspension as the format of the IFU in the Appendix of the HF validation study results report appears different from the IFU contained at the end of the proposed USPI in the submission. On 11/22/2024, the Applicant provided a response to the IR that can be accessed in EDR via:
<\\CDSESUB1\EVSPROD\nda220073\0005\m1\us\2024-11-19-bms562247-resp-fda-hf-ifu-ir.pdf>

APPENDIX C. LABELS AND LABELING,

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^d along with postmarket medication error experiences with similar products, we reviewed the following Eliquis labels and labeling submitted by Bristol Myers Squibb.

- Container label(s) received on 10/17/2024.
- Carton labeling received on 10/17/2024.
- Prescribing Information and Instructions for Use (Image not shown) received on 10/17/2024, available from
<\\CDSESUB1\EVSPROD\nda220073\0001\m1\us\sep2024-pediatric-pas-apixa-pro.pdf>

^d Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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