

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202155Orig1s000

OTHER REVIEW(S)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	ELIQUIS (apixaban) tablets for oral use
Applicant	Bristol-Myers Squibb
Application/Supplement Number	NDA 202155
Type of Application	Original
Indication(s)	To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
Established Pharmacologic Class ¹	factor Xa inhibitor anticoagulant
Office/Division	ODE I/DCRP
Division Project Manager	Alison Blaus
Date FDA Received Application	September 17, 2012
Goal Date	March 17, 2013
Date PI Received by SEALD	December 28, 2012
SEALD Review Date	December 28, 2012
SEALD Labeling Reviewer	Elizabeth Donohoe
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: Under D&A, the second bullet should reference 2.2; in DI the references should be 7.1 under the first bullet and 7.2 under the second bullet.

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI

Selected Requirements of Prescribing Information

• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

- YES** 12. All text must be **bolded**.

Comment:

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Selected Requirements of Prescribing Information

Comment:

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment: Consider adding one space between this statement and the wording of the BW in HL to improve readability.

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: The PI contains the correct format. Note, eLIST (<http://elist/prpllr/public/query/>) and the Xarelto PI states the EPC for rivaroxaban as "factor Xa inhibitor". We recommend that the EPC in the I&U statement in the Highlights for rivaroxaban and apixaban be consistent if appropriate.

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Selected Requirements of Prescribing Information

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *The applicant underlined the www.fda.gov/medwatch website; it should not be underlined.*

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

Selected Requirements of Prescribing Information

- 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
YES Comment:
- 32. All section headings must be **bolded** and in UPPER CASE.
YES Comment:
- 33. All subsection headings must be indented, not bolded, and in title case.
YES Comment:
- 34. When a section or subsection is omitted, the numbering does not change.
YES Comment:
- 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
YES Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
YES Comment:
- 37. All section and subsection headings and numbers must be **bolded**.
YES Comment:
- 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.
YES

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse

Selected Requirements of Prescribing Information

9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see *Warnings and Precautions (5.2)*]”.

Comment: A possible incorrect cross reference was noted in the BW and Section 5.1 W&P: instead of *Dosage and Administration (2.4)* in BW and *Dosage and Administration (2.3)*, we recommend *Dosage and Administration (2.4, 2.5)* for both sections. Recommend also that under *Drug Interactions Studies* subheader in Section 12.3, that the word “also” be removed from the first cross reference.

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- NO** 42. All text is **bolded**.

Comment: The summary text is not bolded.

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

Selected Requirements of Prescribing Information

N/A 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

ERIC R BRODSKY

12/28/2012

Eric Brodsky, signing for Elizabeth Donohoe, SEALD labeling reviewer

LAURIE B BURKE

12/28/2012



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 202155 apixaban (Eliquis) for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

Sponsor: BMS

Review date: 27 December 2012

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 202155

This memo conveys the Division's recommendation to issue an Approval letter for apixaban.

I reference Dr. Grant's CDTL/Divisional Memo of 22 June 2012 for a description of most aspects of the original submission and of issues that led to a Complete Response letter, also dated 22 June 2012. In this memo, I summarize aspects of the clinical review (Beasley and Rose; 22 May 2012) not covered by Dr. Grant, the clinical review in response to the sponsor's resubmission (Beasley and Rose; 10 December 2012), an unsolicited review by Dr. Marciniak (revised 17 December 2012), and a commentary on the Marciniak review (Beasley and Rose; 21 December 2012).

Support for a claim to prevent stroke and systemic embolism in patients with atrial fibrillation comes from two studies, AVERROES and ARISTOTLE.

AVERROES was a randomized, double-blind comparison of apixaban and aspirin in patients with AF, some additional risk factor, and the perceived need to avoid warfarin. The primary analysis was a test of superiority in reducing stroke or systemic embolism. The trial was stopped early (enrollment complete, but before the targeted number of events were observed) for overwhelming benefit, but the sponsor was dissuaded from seeking a claim based on this alone, as warfarin is superior to aspirin in this setting, rationale for avoiding warfarin was questionable in many cases, and ARISTOTLE was soon to complete.

The vast majority of reviewer attention was then on ARISTOTLE, a randomized, double-blind comparison of apixaban (5 mg BID in most subjects) and warfarin (titrated to INR 2-3). Its primary analysis was non-inferiority for prevention of stroke and systemic embolism, using the margin of 1.38 previously accepted by FDA.

The Complete Response letter (22 June 2012) listed 6 issues. Four of these related to difficulty ascertaining who got incorrect study drug dispensed, a problem of both process (no subject-specific kits) and documentation (most importantly, failure to collect bottle labels centrally). The problem of mixing up who received what drug had obvious implications with regard to any non-inferiority analysis, but it also potentially led to worse outcomes among incorrectly dosed warfarin subjects (because of resulting dosing changes introduced to deal with anomalous INR readings, the effects of which would last even after subjects returned to assigned treatment).

As Drs. Beasley and Rose describe, the sponsor provided analyses of labels from a sample of about 1/3 of the 450,000 bottles used, placing a reliable upper bound on the magnitude of the dosing problem. Reasonable analyses show that the impact of this was not enough to account for the superiority of apixaban over warfarin on either stroke or bleeding.

Two unrelated issues were also raised in the CR letter. One had to do with apparent discrepancies between the medication error dataset and underlying case report forms. This issue was resolved by fixing some data entry errors, with no material impact on the resulting analyses. The final issue had to do with multiple entries for the same adverse event in the sponsor's adverse event dataset. While this problem was incompletely resolved, its residual impact is minor.

Key results from AVERROES are summarized in the table below (events per 1000 patient-years; abstracted from pages 110-112 of the original clinical review):

	Apixaban N=2807	Aspirin N=2791	HR (95% CI)
Stroke/SE	16.2	36.3	0.45 (0.32-0.62)
Stroke/SE/MI/Vasc death	42.1	63.5	0.66 (0.53-0.83)
All-cause death	35.5	44.2	0.79 (0.62-1.02)
Vascular	26.5	30.3	
Non-vascular	8.5	13.9	

Although the early study termination seems to have been appropriate, one should expect that early termination will tend to overestimate the treatment effect size.

Key results from ARISTOTLE are shown in the table below:

	Apixaban N=9120	Warfarin N=9081	HR (95% CI)
Stroke/SE ¹	12.7	18.0	0.79 (0.66-0.95)
Stroke	11.9	15.1	
Ischemic	8.4	8.2	
Hemorrhagic	2.4	4.7	
Ischemic→hemorrhagic	0.7	1.2	
Uncertain	0.8	1.3	
Systemic embolism	0.9	1.0	
All-cause death	35.2	39.4	0.89 (0.80-1.00)
Cardiovascular	18.0	20.2	0.89 (0.76-1.04)
Stroke	2.2	3.8	
Heart failure	4.4	5.4	
Sudden	7.4	7.6	
Other ²	4.0	3.4	
Non-cardiovascular	11.4	12.2	0.93 (0.77-1.13)
Respiratory failure	1.1	2.1	
Malignancy	3.5	3.9	
Trauma	0.4	0.8	
Bleeding	0.9	1.0	
Other	1.6	1.5	
Infection	3.9	3.1	
Unknown	5.8	6.9	

Results on the primary analysis establish superiority of apixaban to warfarin (non-inferiority is not an issue).

¹ Subordinate events shown at subjects with events at any time, not necessarily as the first event.

² Systemic embolism, MI, other CV, unobserved

Results on mortality are more difficult to interpret. The nominal p-value according to the pre-specified analysis plan is 0.0465, so “significant”. I address first what ought to be the easier question, whether this represents a treatment effect on mortality, before addressing whether this should be considered superiority over warfarin.

If warfarin had a mortality effect, than one might conclude, even with a p-value for superiority to warfarin >0.05 , that apixaban was superior to placebo. Dr. Marciniak addressed this issue in the 6 studies of warfarin vs. placebo that formed the basis for FDA’s determination of a non-inferiority margin for warfarin. In one of these studies (BAATAF), warfarin reduced mortality by $>50\%$, highly statistically significant, but Dr. Marciniak’s random-effects meta-analysis of all six studies has $p=0.192$ for mortality. However, this result is at odds with a published meta-analysis of the same 6 studies (Hart et al., 1999³), which showed a 26% decrease in the risk of all-cause mortality (95% CI of 3-43%), a difference upon which Dr. Marciniak does not comment.

Whether one might consider apixaban superior to warfarin in reducing all-cause mortality with a $p\approx 0.05$, one could more reliably conclude that even $p\approx 0.05$ is indicative of a benefit of apixaban over placebo. Nor is apixaban the only anticoagulant with at least a favorable lean on mortality compared with warfarin; dabigatran has quite similar data, and Drs. Beasley and Rose suggest that these results might be considered mutually supportive of a mortality effect, much as we used data from losartan and irbesartan to support one another’s effects on diabetic nephropathy.

Credibility to the mortality benefit is aided by the main driver of the benefit, a reduction in mortality attributed to stroke, consistent with the benefit on overall stroke and hemorrhagic stroke⁴. Other contributors to the apparent benefit on stroke are less easy to interpret—reductions in heart failure and respiratory failure.

There is no question that the mortality findings need display in the label. I would favor wording in section 14 that says that various anticoagulants appear to reduce mortality in AF, and that these particular data are not compelling evidence of superiority in this regard to warfarin.

Dr. Marciniak takes a more dichotomous view of the mortality findings, making much of the fact that many quite reasonable sensitivity analyses—count errors, date errors, censoring issues, etc.—yield p-values >0.05 . Were the comparison between apixaban and warfarin the only information available, these issues would be more important than I consider them to be.

Dr. Marciniak raises several other issues warranting response.

He is rightfully concerned about adequacy of follow-up, particularly for vital status, but he counts anyone with data missing for the closeout date the same whether the gap in knowledge is a day or a year. This exaggerates the missing information.

Dr. Marciniak reminds us that prasugrel caused more bleeding than did clopidogrel in TRITON, and was (by Dr. Marciniak’s counts) associated with more cancers reported. In APPRAISE-2 (ACS study), apixaban plus antiplatelet therapy was associated with more bleeding than was the antiplatelet therapy alone, and it was (by Dr. Marciniak’s counts) associated with more reported cancers. In ARISTOTLE, apixaban was associated with less bleeding and fewer cancers. In none of these studies was there an effect on deaths from cancer. It seems most likely to me that bleeding leads to more

³ Hart RG et al. 1999. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Int Med* 131:492-501.

⁴ Beasley and Rose (21 December) note that a similar trend for superiority of apixaban over warfarin for all-cause mortality persists post-treatment. They show that is largely attributable to deaths in the few days after discontinuing for strokes.

vigilance, whether it relates to the affected organ or not, and bleeding thus leads to earlier detection of cancers, an effect that persists for as long as you take these drugs. This sounds like a benefit to me.

The review team and I recommend approval of Eliquis to prevent stroke in patients with non-valvular atrial fibrillation.

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/s/

NORMAN L STOCKBRIDGE
12/27/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion
Division of Consumer Drug Promotion**

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

Memorandum

Date: December 10, 2012

To: Alison Blaus
Regulatory Project Manager
Division of Cardio-Renal Products (DCRP)

From: Emily Baker, PharmD
Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Zarna Patel, PharmD
Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

Subject: **Eliquis (apixaban)**
NDA 202155

OPDP has reviewed the proposed Package Insert (PI) and Medication Guide submitted for consult on October 2, 2012, for Eliquis (apixaban). Our comments are based on the proposed labeling at the following EDR location: [\\CDSESUB1\EVSPROD\NDA202155\0004](#).

DPDP reviewed the proposed PI and our comments are provided directly on the attached proposed PI.

DCDP also reviewed the comments on the proposed Medication Guide from the Division of Medical Policy Programs (DMPP) dated December 7, 2012. We agree with DMPP's comments and have the following additional comments. Our comments on the proposed Medication Guide are provided directly on the version sent to DCRP from DMPP.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the comments for the PI, please contact Emily Baker at 301.796.7524 or emily.baker@fda.hhs.gov.

If you have any questions on the comments for the Medication Guide, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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/s/

EMILY K BAKER
12/10/2012

ZARNA PATEL
12/10/2012

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

PATIENT LABELING REVIEW

Date: December 7, 2012

To: Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products (DCRP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ELIQUIS (apixaban)

Dosage Form and Route: tablets

Application Type/Number: NDA 202-155

Applicant: Bristol-Myers Squibb Co. Pharmaceutical Research Institute

1 INTRODUCTION

On September 17, 2012, Bristol-Myers Squibb Co. Pharmaceutical Research Institute re-submitted for the Agency's review, their Original New Drug Application (NDA) 202-155 for ELIQUIS (apixaban) tablets, in response to a Complete Response Letter issued on June 22, 2012. The proposed indication for ELIQUIS (apixaban) tablets is to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. On October 2, 2012, the Division of Cardiovascular and Renal Products (DCRP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for ELIQUIS (apixaban) tablets.

This review is written in response to a request by DCRP for DMPP to review the Applicant's proposed MG for ELIQUIS (apixaban) tablets.

2 MATERIAL REVIEWED

- Draft ELIQUIS (apixaban) Medication Guide (MG) received on September 17, 2012, and received by DMPP on November 26, 2012.
- Draft ELIQUIS (apixaban) Prescribing Information (PI) received on September 17, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on November 26, 2012.
- Approved XARELTO (rivaroxaban) tablets comparator labeling dated November 2, 2012.
- Approved PRADAXA (dabigatran etexilate mesylate) capsules comparator labeling dated November 2, 2012.

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. In our review of the MG the target reading level is at or below an 8th grade 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 have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- 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 MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SHARON R MILLS
12/07/2012

LASHAWN M GRIFFITHS
12/07/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: October 25, 2012

Reviewer: Kimberly DeFronzo, RPh, MS, MBA
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Drug Name: Eliquis (Apixaban) Tablets
2.5 mg and 5 mg

Application Type/Number: NDA 202155

Applicant: Bristol-Myers Squibb

OSE RCM #: 2012-2310

***** This document contains proprietary and confidential information that should not be released to the public.*****

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1 INTRODUCTION

This review evaluates the revised labels and labeling for Eliquis (Apixaban) Tablets, submitted on February 14, 2012 (see Appendix A). The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the proposed labels and labeling under OSE Review #2011-3740 dated November 18, 2011.

1.1 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the proposed container labels and insert labeling under OSE Review #2011-3740 dated November 18, 2011, and comments were provided to the Applicant in an Advice Letter on February 1, 2012. On February 14, 2012, the Applicant submitted revised labels and labeling in response to our comments, which were not reviewed at that time since the application was likely to receive a complete response. The application received a complete response (CR) on June 22, 2012 for reasons unrelated to the labels and labeling. Subsequently, a resubmission in response to the CR was received by the Agency on September 17, 2012.

2 MATERIALS REVIEWED

DMEPA evaluated the following:

- Revised container labels submitted on February 14, 2012 (Appendix A)
- Revised unit-dose carton labeling submitted on February 14, 2012 (Appendix B)
- Revised hospital unit-dose blister labels submitted on February 14, 2012 (Appendix C)
- Revised professional sample carton labeling submitted on February 14, 2012 (Appendix D)
- Revised professional sample blisters submitted on February 14, 2012 (Appendix E)

Additionally, our recommendations in OSE Review 2011-3740 were reviewed to assess whether the revised labels adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised container labels and carton labeling show that the Applicant has implemented DMEPA's recommendations under OSE Review #2011-3740. However, we have identified additional areas for improvement to ensure the safe use of this product. The following recommendations should be conveyed to the Applicant and implemented prior to approval.

3.1 COMMENTS TO THE APPLICANT

A. Container Label and Unit-Dose Carton Labeling (2.5 mg and 5 mg)

1. We acknowledge that the boxing around the “Rx only” statement on the Principal Display Panel (PDP) was removed, but the prominence of the “Rx only” statement persists with the bold type font. Debold the “Rx only” statement.
2. It is not clear if the lot and expiration date are included. Ensure the lot and expiration date are included on all container labels and carton labeling in accordance with 21 CFR 201.17 and 21 CFR 201.18.

B. Hospital Unit-Dose Blister Card Labels (2.5 mg and 5 mg)

1. The 2.5 mg and 5 mg hospital unit dose labels blister cards still remain too similar in appearance, with the only notable exception in the boxing around the 5 mg strength. There is no distinguishing typography or color that differentiates the two strengths. To avoid selection errors, provide adequate visual difference between the 2.5 mg and 5 mg strengths through additional means such as typography and/or color.

C. Professional Sample Carton Labeling (5 mg)

1. The use of the (b) (4) color block, which matches the font color of your proprietary name, on the left side of the principle display panel, is distracting and should be removed. Additionally, in the future, should you wish to distribute professional samples of the 2.5 mg strength in a similar carton, the extensive use of this color block will minimize the strength differentiation in your professional sample product line.

If you have further questions or need clarifications, please contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

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/s/

KIMBERLY A DE FRONZO
10/25/2012

IRENE Z CHAN
10/26/2012

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

REVIEW DEFERRAL MEMORANDUM

Date: July 30, 2012

To: Norman Stockbridge, MD, PhD
Director
**Division of Cardiovascular and Renal Products
(DCRP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

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

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Medication Guide (MG)

Drug Name (established name): ELIQUIS (apixaban)

Dosage Form and Route: tablets

Application Type/Number: NDA 202-155

Applicant: Bristol-Myers Squibb

1 INTRODUCTION

On September 28, 2011 Bristol-Myers Squibb submitted New Drug Application (NDA) 202155 for ELIQUIS (apixaban) tablets with the proposed indication to reduce the risk of stroke, systemic embolism, ^{(b) (4)} in patients with nonvalvular atrial fibrillation. On October 5, 2011, the Division of Cardiovascular and Renal Products (DCRP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG), for ELIQUIS (apixaban).

This memorandum documents the DMPP review deferral of the Applicant's proposed Medication Guide (MG) for ELIQUIS (apixaban).

2 CONCLUSIONS

Due to outstanding clinical study deficiencies, DCRP issued a Complete Response (CR) letter on June 22, 2012. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SHARON R MILLS
07/30/2012

BARBARA A FULLER
07/30/2012

LASHAWN M GRIFFITHS
07/31/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion
Division of Consumer Drug Promotion

Memorandum

Date: June 28, 2012

To: Alison Blaus, Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Emily Baker, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Zarna Patel, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 202155 Eliquis (apixaban)
OPDP Labeling Consult Response

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

We acknowledge receipt of your September 30, 2011, consult request for the proposed Package Insert and Medication Guide for Eliquis (apixaban), NDA 202155. OPDP notes that DCRP determined that labeling would not be finalized during the current review cycle and that a Complete Response letter was issued on June 22, 2012. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DCRP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any question on the Package Insert, please contact Emily Baker at 301.796.7524 or Emily.Baker@fda.hhs.gov.

If you have any questions concerning the Medication Guide, please contact Zarna Patel at 301.796.3822 or Zarna.Patel@fda.hhs.gov.

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/s/

EMILY K BAKER
06/28/2012

ZARNA PATEL
06/28/2012



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Review

NDA: 202155
Drug: ELIQUIS (apixaban) 2.5 and 5 mg Tablets
Class: Factor Xa Inhibitor
Applicant: Bristol-Myers Squibb & Pfizer Inc.

Proposed Indication: “ELIQUIS® (apixaban) is indicated to reduce the risk of stroke, systemic embolism, (b) (4) in patients with nonvalvular atrial fibrillation (b) (4)
[REDACTED]

Date of submission: 28 September 2011
Major Amendment: 29 February 2012
Complete Response date: 22 June 2012
PDUFA date: 28 June 2012 (original was 28 March 2012)

❖ REVIEW TEAM

- Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
 - Cross Discipline Team Leader (CDTL)
 - Stephen M. Grant, M.D.
 - Medical Reviewers
 - Nhi Beasley, PharmD (Safety)
 - Martin Rose, M.D., JD (Efficacy)
 - Pharmacology & Toxicology
 - Pat Harlow, Ph.D.
 - Regulatory Health Project Manager
 - Alison Blaus
- Office of New Drug Quality Assessment (ONDQA), Branch I
 - Charles Jewell, Ph.D. (Drug Substance)
 - William “Mike” Adams, Ph.D. (Drug Product)
 - Yong Wang (NIR methods)
- Office of Clinical Pharmacology
 - Ju-Ping Lai, Ph.D.
 - Divya Menon-Andersen, Ph.D.
 - Tzu-Yun McDowell, Ph.D.
- Office of Biostatistics, Division of Biometrics I
 - Steve Bai, Ph.D.
- Office of Surveillance and Epidemiology
 - Forrest “Ray” Ford (DMEPA)
 - Danielle Smith (Risk Evaluation and Mitigation Strategy - REMS)

- Office of Medical Policy
 - Division of Drug Marketing, Advertising and Communications (DDMAC)
 - Emily Baker – Full Product Labeling
 - Zarna Patel – Patient Labeling
 - Patient Labeling Team
 - Sharon Mills (Medication Guide)
- Office of Scientific Investigations (OSI)
 - Sharon Gershon, PharmD (Clinical Studies)

❖ **BACKGROUND**

Apixaban is an unapproved oral factor Xa (FXa) inhibitor being developed by Bristol-Myers Squibb (BMS) and Pfizer under (b) (4)

- IND 68598 for the prevention of thrombotic events in patients with nonvalvular atrial fibrillation (AF)

(b) (4)

Two Phase 3 trials were conducted under IND 68598, ARISTOTLE (CV185030) and AVERROES (CV185048):

- **ARISTOTLE** was active (warfarin) controlled, randomized, double-blind study to evaluate the efficacy and safety of apixaban in preventing stroke and systemic embolism in subjects with nonvalvular atrial fibrillation.
- **AVERROES**, unlike ARISTOTLE, compared apixaban to ASA in patients with non-valvular atrial fibrillation who failed or were considered unsuitable for Vitamin K antagonist treatment.

On 24 January 2011 the Agency informed the sponsor that in light of recent approvals made by the Agency, BMS and Pfizer were advised that any apixaban AF NDA (NDA 202155) would not be considered complete until the data from ARISTOTLE and APPRAISE-2 were submitted. On 4 May 2011 the Agency discussed the format and content of NDA 202155 and how the dossier should be organized due to the decision conveyed in January.

On 18 July 2011 the Agency and sponsor met to discuss the top-line data from ARISTOTLE and discuss any additional datasets that would be needed and/or any FDA NDA review processes that would change in light of these data. The minutes from this meeting are dated 9 August 2011. The application was submitted on 28 September 2011.

❖ **REGULATORY TIMELINE and GENERAL APPLICATION POINTS / MAJOR ISSUES**

This section will cover a number of general application milestones as well as glance over some major issues that were uncovered during the review that impacted timelines. The review of this application proceeded relatively smoothly, meeting all major 21st century review timelines, with approximately 60 information requests since 28 September 2011.

- Pre-IND Meeting: 20 September 2004 (minutes dated 19 October 2004)
- Pre-Phase 3 Trial Discussion (Pre-IND): 21 September 2005 (minutes dated 20 October 2005)
- End of Phase 2 Meeting (Pre-IND): 2 October 2006 (minutes dated 7 November 2006)

- IND (AF) received: 9 November 2006
- ARISTOTLE SPA received: 27 October 2006
- ARISTOTLE No-Agreement SPA Letter dated: 11 December 2006
- AVERROES Pre-NDA Meeting: 12 August 2010 (minutes dated 16 September 2010)
- AVERROES Top-Line Meeting: 24 January 2011 (minutes dated 2 February 2011)
- Follow-up AVERROES TopLine Meeting: 1 March 2011 (minutes dated 16 March 2011)
- ARISTOTLE Pre-NDA Meeting: 4 May 2011 (minutes dated 31 May 2011)
- ARISTOTLE Top-Line Meeting: 18 July 2011 (minutes dated 9 August 2011)
- NDA Submission Received: 28 September 2011
- Filing Meeting: 31 October 2011
- Priority Designation Letter: 28 November 2011
- 74-day Issues Letter with Comments: 8 December 2011
- Executive Carcinogenicity Assessment Committee (CAC) Meeting: 29 November 2011
- Mid-cycle Meeting: 23 January 2012
- DMEPA Carton/Container Advice Letter: 1 February 2012
- REMS Notification Letter: 3 February 2012
- CRF 800 Information Request Letter: 8 February 2012
- Medication Errors Meeting w/Applicant: 9 February 2012 (minutes dated 17 February 2012)
- Office of Scientific Investigations (OSI) Information Request: 15 February 2012
- List of Information Requests from 9Feb12 Meeting Received: 21 February 2012
- Major Amendment Letter: 29 February 2012
- Original PDUFA Date: 28 March 2012
- New PDUFA Date: 28 June 2012

User Fee

The user fee for this application was paid in full on 29 September 2010, prior to the submission of the application (ID (b) (4)).

Pediatric Review Committee (PeRC)

The PeRC meeting to discuss this application was held on 7 December 2011. The PeRC and the Division agreed with the applicant that nonvalvular atrial fibrillation (AF) is reported to be rare in the pediatric population. The prevalence of AF increases with age and, according to the literature, is rarely seen in young populations (Fuster et al., 2006¹). There are also differences in underlying conditions between adult and pediatric populations. Based on this, the strategy of management of AF is different. Surgical cardiac procedures for congenital heart malformations are much more common in children and the procedures may contribute to the resolution of this arrhythmia (Radford et al., 1977²) in children, whereas in adult populations the complete resolution of AF is not achievable for most patients (Olgin and Zipes, 2005³). Therefore, a full pediatric waiver was granted for this application.

Advisory Committee

It was decided at the filing meeting and through internal discussions with various individuals within the Agency that an Advisory Committee (ADCOM) would not be needed for this application. Although this was a new molecular entity (NME), apixaban was the (b) (4) drug submitted for this

¹ Fuster, V., Ryden L. E., Cannom, D. S., Crijns, H. J., Curtis, A. B., Ellenbogen, K. A., Halperin, J. L., LE, Heuzey, J. Y., Kay, G. N., Lowe, J. E., Olsson, S. B., Prystowsky, E. N., Tamargo, J. L. & Wann, S. (2006) ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). Eur Heart J, 27,1979-2030.

² Radford DJ, Izukawa T. Atrial fibrillation in children. Pediatrics 1977;59:250-256.

³ OLGIN, J. E. & ZIPES, D. P. (2005) *Specific Arrhythmias Diagnosis and Treatment*, Philadelphia, PA, USA, Elsevier Saunders

indication (b) (4) in class) and the Division believed at the time (and the Office/Center concurred) that there were no major issues (safety or efficacy) that needed input from the Committee.

The topic of having an ADCOM arose again in light of the trial conduct issues uncovered in December 2011 (BMS' pre-audit findings at site 1200 in China) and in January 2012 (the "medication error" issue). Please see the Major Amendment and Medication Error sections below for more details regarding these issues. After a lengthy discussion that included both the Division and the Office, it was decided that although these issues were concerning for a non-inferiority study, they were still not issues that would typically necessitate input from the Committee. Thus, scheduling and holding an ADCOM during this review cycle would not be warranted. However, all levels of the Agency did agree that this issue should indeed be aired publically, but instead via a publication and/or letter in the New England Journal of Medicine, for example.

Major Amendment

On 4 January 2012, the Division received a letter via email (not officially submitted until 6 April 2012) from the applicant noting significant pre-audit findings at one of their ARISTOTLE investigator sites in China (site 1200). The applicant conducted this routine audit ahead of the Agency's scheduled inspection in late January. This 4 January 2012 email provided the following details:

- A clinical site monitor employed at one the Clinical Research Organization (CRO) for ARISTOTLE, PPD, alleged that records at the clinical investigator site of Dr. Shiyao Wu in Shanghai, China (site 1200) appeared to have been recently changed apparently in preparation for the upcoming FDA inspection of that site.
- Specifically, a chart which contained records of outpatient visits had been altered.
- Prior to the inspection preparation, the outpatient visits were printed records that contained handwritten comments. During the more recent visit, however, the printed records included in the outpatient charts had no handwritten comments.
- BMS determined that at that point there was enough evidence to treat the allegation as potentially accurate.

The applicant probed the issue further and submitted a more detailed account of the audit in a letter dated 31 January 2012. Upon conclusion of the FDA audit of site 1200, the Office of Scientific Investigations drafted a letter to the applicant requesting additional information that was not obtained in the inspection. In this letter dated 15 February 2012, the Agency asked very pointed questions including, but not limited to, the specific roles of those individuals from the applicant and PPD at site 1200, their professional qualifications, their role (if any) at any other ARISTOTLE sites, and more details regarding the quality of the overall monitoring during the trial in China. The applicant provided a response to this OSI letter on 23 February 2012. Upon reading the applicant's 23 February response as well as the Form 483 from the Agency inspection, the Division decided to declare the 31 January 2012 letter a Major Amendment resulting in the addition of three months to the end of the original PDUFA date. The goal of the extra three months was to allow time to review the findings from both the ORA and applicant's inspection and to come to a determination of the impact of such findings on the trial. The additional time would also allow for adequate time to re-inspect the CRO (PPD) as well as the applicant, Bristol-Myers Squibb. These re-inspections were conducted in March. Details of these re-inspections can be found in the OSI review (a summary of the review is captured below).

Medication Errors in ARISTOTLE

On 23 January 12 the Agency requested a teleconference with Bristol-Myers Squibb regarding a table that appeared on page 88 of the clinical study report (CSR). The table questioned noted a 7.3 %

apixaban vs. 1.2% warfarin medication error rate in ARISTOTLE. When the applicant was asked why there was a 6:1 imbalance, the applicant could not provide a rationale. After discussing the table, the applicant re-ran their evaluable patient population analysis excluding these patients and attested that the medication error rate observed did not affect the overall findings of the trial. At the time of this teleconference, it was discovered that the table in the CSR included only those patients who received active apixaban that should have received active warfarin and vice versa. The table did not include those patients that received placebo instead of active of either apixaban or warfarin (or vice versa), it did not include patients that received 2.5 apixaban instead of 5.0 (or vice versa), and finally it did not include those that got the right drug but still the wrong container number per IVRS. To probe the issue further, the applicant proposed a number of analyses to hopefully fully capture the extent of the issue and the impact that this could have had on the overall trial findings. The Agency agreed with this analysis plan on 1 February 2012 which included:

1. Summaries of study drug dispensation errors and sensitivity analyses for the primary efficacy endpoint, ISTH major bleeding, all-cause death, myocardial infarction (MI) and transient ischemic attack (TIA).
2. An statistical and clinical assessment of the impact of these medication errors
3. Details regarding at what point these errors were discovered (as they happened, at the end, after a set amount, etc).
4. A rationale to why was there such a high rate of medication errors and why they were not discovered earlier
5. What corrective action (if any) was done to prevent further medication errors (e.g., Newsletters to the Investigators, increased monitoring visits, re-education of the site staff, etc).

The abovementioned analyses were received on 7 February 2012. Upon receiving the analyses and clinical information, the Agency requested a teleconference for that day to discuss. On that call, it was discovered that the Division did not have the appropriate datasets to recreate the applicant's analyses or to generate our own (e.g., IVRS assignments). On 8 February 2012, the applicant submitted these datasets (KITASSGN.xpt & BMSCONT.xpt). In an email dated 10 February 2012, the applicant added that KITASSGN was not altered in any way and captured what IVRS assigned each patient when a new container was needed at a visit. It is important to note that on 30 March 2012, however, the applicant and the Division learned that this was not the case and that (b) (4) (the CRO that managed the IVRS) did in fact make changes to this dataset.

Although the applicant believed that they came to a number that more accurately captured the total number of medication errors in the trial than the table that appeared in the CSR, the Division did not have confidence that this was the case. As a result, the Division drafted a request that all investigational product (IP) labels be retrieved from the investigator sites (labels affixed to CRF 800) to be absolutely sure what patients actually received during the trial and then to compare those labels to the IVRS and eCRF database. A letter requesting all CRF 800s be collected from the investigator sites was dated 8 February 2012.

Investigational Product Panel Stickers

The IP had a three panel sticker on each container. The site staff/pharmacists were instructed to remove a side panel from the IP prior to distributing it to the patient. This panel sticker contained the container number, batch number, a barcode (decoding to the container number), the manufacturing date as well as an "unblinding sticker" that could be scratched off in the event a patient needed to be unblinded for an emergency medical issue. Upon removing the panel sticker, the site staff were instructed to place this sticker on the CRF 800 for that patient. Upon close out of a patient and/or the site, CRF 800 was to be photocopied (photocopy retained at the site) and

the original sent to BMS. In December 2009, a decision was made by Bristol-Myers Squibb to not collect these CRFs and instead the sites were instructed to retain them at the investigator sites. This change was communicated to the sites/monitors (via email) at the end of 2009, but was not formally made part of the monitoring plan until the final version dated after database lock on 7 July 2011 (database lock was 10 June 2011).

Monitoring of Investigational Product during ARISTOTLE

As typical with a clinical trial of this size, the applicant and PPD utilized “Reduced Site Data Verification (rSDV)” during ARISTOTLE. The monitoring plan detailed which sections that should be reviewed/QC’ed in 100% of those patients and in the remaining data points/CRFs would be reviewed in 1:5 patients (1:2 for the first 5000 patients and then reduced to 1:5 upon monitor discretion). It is important to note that some sites were never moved to 1:5 patients reviewed and some sites were immediately moved to 1:5 regardless of the number of patients accrued to that point. The sections of the source documentation/eCRFs that were to be 100 SDV was very clear. Per the monitoring plan, the source data regarding IP (eCRF, IVRS fax, CRF 800 labels) was not to be 100% SDV and instead only reviewed under the rSDV guidelines.

Following the applicant’s receipt of the CRF 800 request letter, the Agency and applicant met for a meeting on 9 February 2012 (meeting minutes dated 17 February 2012) to discuss the applicant’s analysis of the medication errors from ARISTOTLE (submitted 7Feb12), the Division’s information request letter (8Feb12), and the impact these errors have on the integrity of the data from the trial. Instead of collecting all of the CRF 800s, the applicant and the Agency agreed to review the 8% the applicant already had in house (these CRFs were sent to BMS before the monitoring plan change and/or inadvertently sent in after the change). A vast majority of these CRFs were from Russia.

After the major amendment was issued, the applicant inspected, and upon review of a number of additional analyses, neither the Agency nor the applicant was confident of the true number and type of medication errors that occurred during ARISTOTLE. For this reason, the Agency decided to issue a CR for NDA 202155. Please see the Clinical and Division Director review for a complete account of the analyses completed, unanswered questions, and some possible ways the applicant can assuage the Agency’s outstanding concerns.

Trade name

ELIQUIS was deemed tentatively acceptable on 22 December 2011 and fully acceptable for use on 4 April 2012.

Review Status

At the pre-NDA meeting for AVERROES, it was initially agreed that NDA 202155 would have a rolling submission. However, due to the discussion at the AVERROES top-line results meeting, the Division explained that the application would only be deemed complete with the data from ARISTOTLE and APPRAISE-2. Therefore, the rolling submission was stopped and the final submission (clinical module with ARISTOTLE and APPRAISE-2) was submitted on 29 September 2011.

The applicant requested and was granted a priority review based on the results from ARISTOTLE.

❖ **LABELING REVIEW**

Labeling discussions began in March 2012 with Chemistry and Non-clinical. Both disciplines made edits to their respective sections and these were sent to the applicant in April. The Agency and the

applicant came to the below agreements before the action date. Labeling negotiations for all other sections were deferred until the next review cycle:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus. Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in rats, rabbits, and mice at maternal exposures that were 4, 1, and 19 times, respectively, the human exposure of unbound drug, based on AUC comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

8.2 Labor and Delivery

Safety and effectiveness of apixaban during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using apixaban in this setting [see *Warnings and Precautions (5.2)*].

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring and mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥ 25 mg/kg, a dose corresponding to ≥ 1.3 times the human exposure.

8.3 Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Data in rats indicate significant excretion of apixaban in milk (12% of the maternal dose). Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS therapy, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

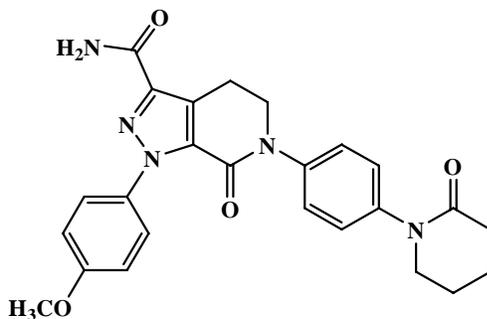
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of apixaban, >69% were 65 and older, while >31% were 75 and older. (b) (4)

11 DESCRIPTION

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 $C_{25}H_{25}N_5O_4$, which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula:



Apixaban is a white to pale-yellow powder. At physiological pH (1.2-6.8), apixaban does not ionize; its aqueous solubility across the physiological pH range is ~0.04 mg/mL. ELIQUIS film-coated tablets are available for oral administration in strengths of 2.5 mg and 5 mg of apixaban with the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. The film coating contains lactose monohydrate, hypromellose, titanium dioxide, triacetin, and yellow iron oxide (2.5 mg tablets) or red iron oxide (5 mg tablets).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Apixaban was not carcinogenic when administered to mice and rats for up to 2 years. The systemic exposures (AUCs) of unbound apixaban in male and female mice at the highest doses tested (1500 and 3000 mg/kg/day) were 9 and 20 times, respectively, the human exposure of unbound drug at the MRHD of 10 mg/day. Systemic exposures of unbound apixaban in male and female rats at the highest dose tested (600 mg/kg/day) were 2 and 4 times, respectively, the human exposure.

Apixaban was not mutagenic in the bacterial reverse mutation (Ames) assay, not clastogenic in Chinese hamster ovary cells *in vitro*, in a 1-month *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes, or in a rat micronucleus study *in vivo*.

Apixaban had no effect on fertility in male or female rats when given at doses up to 600 mg/kg/day, a dose resulting in exposure levels that are 3 and 4 times, respectively, the human exposure.

Apixaban administered to female rats at doses up to 1000 mg/kg/day from implantation through the end of lactation produced no adverse findings in male offspring (F₁ generation) at doses up to 1000 mg/kg/day, a dose resulting in exposure that is 5 times the human exposure. Adverse effects in the F₁-generation female offspring were limited to decreased mating and fertility indices at 1000 mg/kg/day.

Risk Evaluation and Mitigation Strategy (REMS)

Per Section 505-1 of the FDCA, FDA issued a letter, dated 3 February 2012, to the applicant noting the necessity for a REMS for Eliquis. The REMS (communication plan) was to target healthcare professionals to convey information about the increased risk of thrombotic events, including stroke, if Eliquis was discontinued.

The applicant submitted the requested materials, as outlined in the 3 February letter, on 13 February 2012. These materials have not been fully reviewed during this cycle.

❖ **DISCIPLINE REVIEWS**

Below are the conclusions reached by the ELIQUIS team members, organized by role and/or discipline.

Office Memorandum (22 June 2012)

Dr. Temple finalized a memo on 22 June 2012 concurring with the CDTL and Clinical Reviews and recommending a Complete Response.

Divisional Memorandum / Cross-Discipline Team Leader (CDTL) Review (22 June 2012)

Dr. Grant drafted the Divisional/Cross-Discipline Team Leader Review and concurred with the clinical reviewers' recommendation.

Clinical Reviews (dated 2 November 2011, 22 May 2012, 11 June 2012, and 22 June 2012)

Based on Drs Rose and Beasley's review of the clinical data, they recommended a complete response (CR) for NDA 202155. The reviewers explained that they did not have sufficient confidence in the ARISTOTLE study data to approve the application at this time due to a substantial issue involving medication errors. At the time of the action, neither the applicant nor the reviewers were confident of the number and type of errors that occurred, despite considerable effort of both parties. Similarly, neither was ultimately sure of how these errors affected study outcomes.

Furthermore, the applicant had said that they were unaware of the scope of the medication errors during the trial or even when they submitted the NDA in September 2011. The reviewers wrote that they believed the medication errors were due in part to deficiencies in centralized monitoring while data were accruing and less than diligent monitoring at the sites. Notably, there was no evidence that the applicant initiated effective procedural changes to ameliorate the rate of medication errors, such as increasing the intensity of monitoring or the intensity of its centralized data checking procedures.

In summary the uncertainty in the conduct of this study was sufficiently great such that they believed that (1) there was a lack of substantial evidence from adequate and well-controlled clinical investigations that apixaban has the effects its labeling purports it to have (21 CFR Sec. 314.125(b)(5)) and (2) there was insufficient information to determine whether the drug is safe for use as proposed in labeling (Sec. 314.125(b)(4)). In addition, the reviewers believed the proposed labeling is misleading in that it fails to describe and account for the problems in study conduct. (Sec. 314.125(b)(6)).

Biostatistics Review (dated 1 May 2012)

In Dr. Bai's review dated 1 May 2012, he explained that he was making a recommendation on apixaban solely based on the findings of Study CV185030 (ARISTOTLE), which was designed to evaluate the efficacy and safety of apixaban versus warfarin (INR target range 2.0-3.0) in subjects with nonvalvular AF. He explained that the findings of this study were sufficient to conclude that apixaban was superior to warfarin for the prevention of 1) stroke (hemorrhagic or ischemic) and SE, 2) ISTH major bleeding and 3) death due to any cause. However, he added that there were a large number of medication errors uncovered during the final stage of the review process (section 1.4 of his review). Therefore, in light of these significant findings, he could not make a final recommendation until various aspects of the medication errors issue were addressed by the applicant.

Clinical Pharmacology Review (dated 15 February 2012)

The reviewers from the Office of Clinical Pharmacology (OCP/DCP I) determined that this submission was acceptable from a Clinical Pharmacology and Biopharmaceutics point of view provided the applicant agreed with the Agency's labeling recommendations. Labeling negotiations began in June 2012, but final language was not agreed-upon by the action date.

Pharmacometrics Review

Please see the Clinical Pharmacology review dated 15 February 2012 for the pharmacometrics reviewer's findings and final recommendation.

Pharmacogenomics Review

Please see the Clinical Pharmacology review dated 15 February 2012 for the pharmacogenomics reviewer's findings and final recommendation.

Pharmacology & Toxicology Reviews (dated 1 November 2011 (two), 21 February 2012, 13 April 2012, and 16 May 2012)

Dr. Harlow determined that apixaban was approvable from a pharmacology and toxicology perspective for the prevention of stroke and systemic embolism in patients with Nonvalvular atrial fibrillation. Most of the toxicities she identified in the non-clinical studies were either attributable to the pharmacodynamic effect of apixaban or that satisfactory safety margins had been demonstrated relative to human therapeutic exposures. Although no animal deaths occurred during parturition in the pre/postnatal development study, the label was drafted to warn women of child-bearing potential of the high risks for bleeding during labor and deliver. The applicant agreed with Dr. Harlow's assessment and labeling language for this section.

The Division met with the Executive Carcinogenicity Assessment Committee (Exec CAC) on 29 November 2011 to discuss the applicant's 2-year rat and mouse carcinogenicity studies. The committee concurred with the Division that the study was adequate (also noting prior Exec CAC concurrence with the protocol) and that there were no clear drug-related neoplasms in either study.

Office of New Drug Quality Assessment (ONDQA), Branch I, Reviews (dated 7 November 2011, 8 November 2011, 7 December 2011, 15 February 2012, 28 February 2012, 18 May 2012, and 22 June 2012)

Drs Jewell, Adams, and Wang came to a final decision on 18 May 2012 that this application was acceptable from a CMC perspective. The final decision was hinging a final decision from the Office of Compliance on GMP inspection results of the establishments involved in the manufacturing process of apixaban drug substance and drug product. Just prior to the final review, OC confirmed that overall these sites were acceptable.

❖ CONSULT REVIEWS

Office of Scientific Investigations (OSI) Summary Review (26 March 2012 (two), 25 April 2012, 18 May 2012 (three))

Eight clinical investigator sites were inspected in support of this application (seven foreign and one domestic). In addition, an applicant (BMS) inspection, an applicant (BMS) re-inspection, and a CRO (PPD) inspection were conducted.

Dr. Gershon noted that the inspectional findings found during inspections at one U.S. site (Site #796), and five non-U.S. sites (Sites 701, 1301, 1742, 1606, 0019) were minor, and OSI did not believe them likely to influence data integrity, study outcome or subject safety. However, OSI recommended that the data from Site 1200 (Shiyao Wu, China) and Site 1178 (Shulin Wu, China) not be used in the final analysis. Although there were no significant inspectional findings at Site 1178, the possibility of fraud cannot be excluded. In addition, OSI recommended that data from the Chinese sites where either (b) (6) or Mr. (b) (6) worked be excluded from the study analysis. These are Sites 1168, 1178, 1180, 1182, 1198, 1199, 1200, 1206, 1207, 1221, 1223, 1244, 1246, 1247, 1266, 1287, 1547, 1548, 1549, 1550, 1552, 1555, 1556, and 1558. This is because of the allegations of fraud documented to occur at Site 1200 and the potential for misconduct at other sites

within China where Ms. (b) (6) and or Mr. (b) (6) had monitoring oversight or conducted monitoring activities on site.

Overall, OSI believed the study appeared to have been conducted and monitored adequately, based on OSI inspectional findings. Although fraud at Site 1200 in China was well documented, there was no evidence that fraudulent activity occurred elsewhere. OSI recommended that data from 24 sites in China be excluded because they could not provide inspectional evidence to support data integrity and subject safety, given that the Ms. (b) (6) and Mr. (b) (6) worked at these sites. The remaining inspections of clinical investigators, CRO, and applicant did not reveal systemic evidence of inadequate monitoring or data integrity issues. No regulatory violations were identified during the PPD inspection; and minor regulatory violations found during the applicant inspections. OSI recommended that the data submitted by Bristol Myers Squibb may be used in support of the respective indication.

❖ **CONCLUSION**

After taking into consideration all of the primary reviews, consults, and the applicant's additional analyses, the Agency chose to send a Complete Response (CR) for NDA 202155. There are a number of items that can be submitted to assuage the Agency's outstanding concerns, all of which are clearly outlined in the CR letter. The applicant will be provided the opportunity to speak with the Agency, shortly after the CR letter is signed, to lay out what they plan to submit to the NDA in response to the CR. The CR letter was drafted for Dr. Robert Temple's signature and dated 22 June 2012.

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

/s/

ALISON L BLAUS
06/22/2012

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: May 18, 2012

TO: Alison Blaus, Regulatory Health Project Manager
Martin Rose, M.D., J.D., Clinical Medical Officer
Nhi Beasley, PharmD, Safety Medical Officer
Division of Cardiovascular and Renal Drug Products

FROM: Sharon Gershon, Pharm.D
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Acting Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Lauren Iacono-Connors, Ph.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 202155 (IND 68,598)

APPLICANT: Bristol Myers Squibb Company
Princeton, New Jersey

DRUG: Eliquis[®] (apixiban) tablets

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Prevention of stroke, systemic embolism, (b) (4) in patients with non-valvular atrial fibrillation (AF)

RELEVANT ACTION(s)	DATE
Clinical Site/Sponsor Audit Request	November 17, 2011
Inspection Summary Goal Date (Original)	February 28, 2012
Division PDUFA Date (Original)	March 28, 2012
Major Amendment Letter	February 28, 2012
Sponsor/CRO Consult Request (Second)	March 7, 2012
New Action Goal Date	May 15, 2012
New PDUFA Date	June 28, 2012

I. BACKGROUND:

Apixaban, an inhibitor of the coagulation Factor Xa (FXa), is being developed as an antithrombotic/anticoagulant agent for multiple indications. Under NDA 202155, apixaban is proposed for the reduction of stroke and systemic embolism (SE) in subjects with non-valvular atrial fibrillation (AF). The drug is formulated as an oral dosage form (2.5 mg and 5 mg tablets), to be administered twice a day.

AF is a common cardiac arrhythmia, which is present in approximately 2.6 million patients in the United States and is associated with a five-fold increase in the risk of stroke. Current guideline-recommended agents for prevention of stroke in patients with AF include anticoagulants like warfarin or other vitamin K antagonists (VKAs). Other therapies for stroke prevention include aspirin (ASA), and most recently, dabigatran.

Antiplatelet therapy with ASA is recommended in patients with AF at low risk for stroke. ASA is also recommended for some patients at moderate risk for stroke, with a higher estimated risk of bleeding if anticoagulated, or with difficulty accessing high quality anticoagulation monitoring. Whereas warfarin provides effective protection against stroke and systemic embolism, warfarin and other VKAs have a number of limitations: variable pharmacokinetic and pharmacodynamic profiles, numerous drug interactions, need for laboratory monitoring and dosage titrations, and bleeding. All of these factors lead to under use in patients with AF. Warfarin must be carefully dosed and continually monitored by means of International Normalized Ratio (INR) testing. As the INR drops below 2.0, the risk of ischemic stroke rises; as the INR rises above 4.0, the risk of hemorrhagic stroke increases. For patients to be safely anticoagulated with warfarin, the INR should be maintained in a range of between 2.0 and 3.0. In clinical trials, this desirable result is achieved about 65% of the time. To overcome some of the above limitations, newer antithrombotic agents are being developed that are highly selective for specific coagulation factors blocking the synthesis of thrombin.

In early January 2012, BMS notified OSI concerning allegations of suspected GCP misconduct at the clinical investigator site of Dr. Shiyao Wu (Site 1200) in Shanghai, China. A PPD monitor (b) (6) present at the site in preparation for FDA inspection observed (based on her earlier visits to the site) that handwritten comments on subject records were

no longer present. Preinspectional site visits occurred between November 14 and December 7, 2011. In addition, Mr. (b) (6), a second PPD monitor, shared with Ms. (b) (6) that he had changed documents and changed patient data on a USB drive at the direction of Ms. (b) (6), BMS Senior Clinical Site Manager. BMS became aware of these allegations on December 7, 2011. In follow-up, BMS senior management conducted an investigation into these reported allegations and their investigation took place over three weeks between December 20, 2011 - January 12, 2012. The investigation included visits by senior BMS management to China Site 1200, and included a visit to China Site 1178 where a second FDA inspection was to be conducted. As part of their investigation BMS conducted interviews with key study personnel and performed a comprehensive review of study documentation including subject diaries, outpatient visit records, and hospital records. They also performed a comparison between the electronic files for nine subjects on the USB drive to their outpatient visit records. BMS concluded that inappropriate activities had in fact occurred at Site 1200 that involved Ms. (b) (6) Mr. (b) (6), and other BMS staff in China who had knowledge of the GCP deficiencies at Site 1200; that records of subjects on the USB drive had been modified; and that the integrity of the data from Site 1200 had been compromised. The GCP deficiencies identified by BMS included drug accountability issues (missing warfarin bottles), subject diaries that were missing year, month and subject number, informed consent documents signed by different people, four potential unreported SAEs, late reporting of three SAEs, inconsistencies between the SAE report versus eCRF and Chinese versus English versions, possible unreported endpoint events (two bleeds and one stroke), unreported adverse events, source documents missing patient name or number, physical examinations not done at end of treatment visits, ECGs not done at screening, incorrect concomitant medications and stop date.

In their response to an OSI Information Request issued on February 15, 2012, BMS stated that Ms. (b) (6) worked as Site Manager for the BMS ARISTOTLE study and that she visited 18 of the 36 Chinese sites while the study was underway. Her duties included conduct of co-monitoring visits if needed; site recruitment/enrollment; resource needs; and following up on quality issues noted by the Site Monitor. She reviewed site visit reports written by the site monitor. During pre-inspection visits, she reviewed study files and subject medical records and discussed issues with study personnel. The sites in China where Ms. (b) (6) worked were: 1180, 1182, 1199, 1206, 1207, 1221, 1223, 1246, 1247, 1266, 1547, 1548, 1549, 1550, 1552, 1555, 1556, and 1558. She worked on no sites outside China. To prepare for the upcoming FDA inspections, Ms. (b) (6) worked at Sites: 1200 and 1178. PPD employee (b) (6) performed site monitoring responsibilities for the following Sites: 1200, 1198, 1168, 1244, and 1287. Mr. (b) (6) did not work at non-China sites. BMS terminated Ms. (b) (6) and Mr. (b) (6), as well as a third senior BMS management employee who had communicated with Ms. (b) (6) regarding potential GCP violations at the site.

A brief summary of the pivotal protocol and the study results are given below.

STUDY PROTOCOL CV185030: A Phase 3, Active (Warfarin) Controlled, Randomized, Double-Blind, Parallel Arm Study to Evaluate Efficacy and Safety of Apixaban in Preventing Stroke and Systemic Embolism in Subjects with Non-valvular Atrial Fibrillation

(**ARISTOTLE: Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation**)

In this current Phase 3 study, subjects with AF and at least one additional risk factor for stroke were evaluated for study eligibility. Eligible subjects were randomized in a 1:1 ratio to either apixaban or warfarin titrated to a target INR range of 2.0 to 3.0. Subjects who were on warfarin or another VKA prior to randomization had their VKA discontinued prior to randomization. The Intended Treatment Period started on the day of randomization and ended at the efficacy cut-off date. The efficacy cut-off date was the date on which it was expected that the target number of primary efficacy events (448) would have occurred. The date was set (arbitrarily) as January 30, 2011. Primary efficacy events were defined as all suspected efficacy events as adjudicated by the Adjudication Committee (also referred as Clinical Event Committee [CEC]); these included death, stroke, SE, and MI, as defined by the Adjudication Committee charter.

The primary efficacy endpoint was the number of days from randomization to first occurrence of confirmed stroke (hemorrhagic, ischemic or unspecified type) or SE during the Intended Treatment Period.

The key secondary efficacy endpoints were defined as some composite of stroke, SE or major bleeding and all-cause death during the Intended Treatment Period, as defined by the protocol.

Brief Summary of Results

The sponsor claims that apixaban was superior to warfarin for reduction of stroke (hemorrhagic or ischemic), SE (two-sided $p=0.0114$, $HR=0.79$), and all-cause death (two-sided $p=0.0465$, $HR=0.89$). The incidence of each individual efficacy endpoint including hemorrhagic stroke, ischemic or unspecified stroke, SE, and MI was lower in the apixaban arm than in the warfarin arm.

The non-inferiority (NI) of apixaban versus warfarin for prevention of stroke or SE, using both NI criteria described in the protocol was demonstrated (one-sided p -value < 0.0001). Superiority of apixaban versus warfarin for prevention of stroke or SE was then assessed and also demonstrated (two-sided p -value = 0.0114). The frequency of bleeding-related adverse events (AEs) with onset during the Treatment Period was lower in the apixaban group compared with the warfarin group (25.2% vs. 32.7%, respectively). The most common bleeding-related AEs by System Organ Class (SOC) were respiratory, thoracic, and mediastinal disorders (apixaban 6.9%, warfarin 8.7%), and gastrointestinal disorders (apixaban 5.9%, warfarin 7.6%). The most common bleeding-related AEs (reported for 5% of more subjects in either treatment group) were epistaxis (apixaban 6.2%, warfarin 7.5%), and contusion (apixaban 3.3%, warfarin 5.3%).

Study CV185030 was initiated on December 19, 2006 (first subject visit date) and completed on May 25, 2011 (last subject visit date). The study enrolled 18,201 subjects at 1053 sites in 40 countries. Approximately 40% of the randomized subjects were in Europe,

19% in the US, 6% in Canada, 19% in Latin America, and 16% in Asia/Pacific. The countries with the greatest proportion of randomized subjects ($\geq 5\%$ of the total) were USA (18.8%), Russia (9.9%), Argentina (8.6%), Canada (5.8%), and Ukraine (5.3%). A total of 8,043 (88.2%) subjects in the apixaban group and 7,933 (87.4%) subjects in the warfarin group completed the study.

II. RESULTS (by Site)

For approval of this NDA, an initial OSI Consult (dated November 17, 2011) requested the inspection of seven foreign sites, one domestic site, and the Sponsor (BMS). A second OSI Consult (dated March 7, 2012), requested a re-inspection of the Sponsor (BMS), and an inspection of the CRO PPD who had responsibility for most of site monitoring for ARISTOTLE. The original PDUFA date was March 28, 2012. After the Major Amendment Letter (issued to BMS on February 28, 2012), the PDUFA action date was extended to June 28, 2012. The Major Amendment Letter was issued to give the Review Division more time to review various issues and questions that arose during review of the application. Specifically, these issues related to the following: 1) a large number of medication dispensation errors (disproportionate number of errors in the apixiban versus the placebo arm); 2) potential to unblind by scratching off coverings to IP bottle labels; 3) potential to unblind because of dissimilar appearance between apixiban and matching placebo; 4) concerns of inadequate sponsor monitoring; and 5) implications of potential fraud at Site 1200 and what it meant for acceptability of data from other sites, in China and elsewhere.

Name of Clinical Investigator	No. of Subjects Enrolled	Inspection Dates	Final Classification
Site 701 Janos Takacs Mosonmagyaróvár, Hungary	37	Feb 2 – Feb 8, 2012	VAI
Site 1301 Daniel Raul Vogel Buenos Aires, Argentina	125	Jan 16 – Jan 27, 2012	NAI
Site 1742 Cesar Javier Zaidman BUENOS AIRES, Argentina	73	Jan 30 – Feb 4, 2012	NAI
Site 1606 Sandeep Gupta Lucknow, Uttar Pradesh, India	87	Jan 9 – Jan 19, 2012	VAI
Site 0019 Louis Yao Weston, ON Canada	113	Jan 30 – Feb 9, 2012	Pending (Preliminary Classification VAI)
Site 1200 Shiyao Wu Shanghai, China	35	Jan 30 – Feb 3, 2012	Pending (Preliminary Classification OAI)

Site 1178 Shulin Wu Guangzhou, Guangdong China	44	Feb 6 – Feb 10, 2012	Pending (Preliminary Classification NAI)
Site 796 William Kufs Saratoga, NY 12866	56	Feb 24 – Feb 9, 2012	VAI
Bristol-MyersSquibb Princeton, New Jersey	Sponsor Inspection	Dec 28, 2011 – Jan 27, 2012	Pending (Preliminary ClassificationVAI)
Bristol-Myers Squibb Princeton, New Jersey	Sponsor Re-inspection	Mar 14 – April 5, 2012	Pending (Preliminary ClassificationVAI)
PPD Development Morrisville, NC	CRO/Monitor Inspection	Mar 12 – Mar 16, 2012	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Janos Takacs**Site 701**

Karolina Korhaz-Rendelointezet

Belgy Tipusu Matrix Egyseg-Altalanos Kardio Regi Vamhaz Ter 2-4

Mosonmagyarovar, Hungary 9200

a. What was inspected: The inspection was conducted in accordance with Compliance Program (CP) 7348.811. Dr. Takacs has ^{(b) (4)} IND studies in CDER's COMIS database and no prior inspections. At this site, 41 subjects were screened, and 37 subjects randomized. Three subjects withdrew consent, and one subject did not meet eligibility criteria. There were three deaths (endpoint events) during the study.

An audit of seven subjects' records was conducted. Subject records were reviewed for adverse events, study endpoints, and reported INR values. The data listings were compared to source documentation and to the eCRFs. Drug accountability records were audited, and financial disclosure statements reviewed. Autopsy reports and death certificates were verified for the three deaths (Subjects #7266, #5159, and #18853). These three deaths were the only reported endpoints at the site. The field investigator reviewed the pull-off drug labels attached to the CRF 800 to verify if unblinding had occurred.

b. General observations/commentary: The field investigator reported that Dr. Takacs and his staff were very good about keeping records. The site used electronic charting in this hospital and the entries were locked after the date of entry. The inspection conducted a full audit of seven subject records. No major discrepancies were noted with respect to data listings, source documents, and e-CRFs. There were no discrepancies noted with respect to endpoint events or drug accountability records.

A two-observational Form FDA-483 was issued for the following observations: 1) failure to prepare and maintain accurate case histories with respect to observations and data [21 CFR 312.62(b)]; and 2) an investigation was not conducted according to the investigational plan (21 CFR 312.60).

With respect to Observation 1, minor inconsistencies were noted between source records and corresponding CRFs. For example:

- Medical records document that Subject #3179 began taking metoclopramide on May 19, 2008, whereas the corresponding CRF documents the date as May 15, 2008;
- Progress notes document that Subject #13194 began taking Rantudil on August 11, 2010, whereas the corresponding study worksheet and CRF document a date of August 7, 2012;
- Medical records document eight that units of Actrapid insulin was administered to Patient #5159 on September 17, 2008, whereas the corresponding CRF does not document any concomitant medication.

With respect to Observation 2, the protocol required that a urinalysis be performed at the final treatment visit. For Subject #900, the field investigator noted that according to the laboratory report, no sample was provided for urinalysis at this subject's final treatment visit.

Dr. Takacs provided an adequate response to the FDA-483 inspectional observations in a letter dated February 20, 2012. The letter included a corrective action plan.

c. Assessment of data integrity: Although a few minor regulatory violations were noted during the inspection, they were isolated in nature and unlikely to impact efficacy or subject safety. The study appears to have been conducted adequately at this site, and the data generated by this site may be used in support of the respective indication.

2. Daniel Raul Vogel

Site 1301

Instituto De Investigaciones Clin.as Bahia Corinaldesi,
Av. Colon 305
Bahia Blanca
Buenos Aires, Argentina

B8000FTD

a. What was inspected: The inspection was conducted in accordance with Compliance Program (CP) 7348.811. Dr. Vogel has (b) (4) IND studies in CDER's COMIS database and no prior inspectional history. At this site, 136 subjects were screened, 125 subjects randomized, and 90 subjects completed the study. A total of 35 subjects were discontinued, including 17 deaths (7 in the apixiban arm; 10 in the warfarin arm), and 111 Serious Adverse Events (SAEs) were reported.

An audit of 56 (45% of total number of subjects enrolled) subjects' records was conducted. All study notes were written in Spanish and required English translation by a BMS translator. The field investigator reviewed hand-written source documentation and compared it to entries in the electronic-case report forms. He reviewed inclusion and exclusion criteria for the 56 subjects to ensure eligibility, and he reviewed laboratory assessments, ECGs, vital signs, and physical examinations for accuracy and completeness.

b. General observations/commentary: The field investigator reported that for all study records reviewed, the primary and secondary efficacy endpoint data were supported and corroborated with data listings from the sponsor. There were no discrepancies between source documents, CRFs; and data listings. The field investigator found all subjects were appropriately enrolled, and that test article accountability records were accurately documented. INR data was observed as accurate and complete. He reported that the adverse events were reported in a timely manner, and that clinically significant bleeding events were accurately reported.

There were a few minor deficiencies observed and discussed with Dr. Vogel at the conclusion of the inspection. Subject #08417 was given the wrong study medication bottle number. This error was found the next day by the monitor and reported as a protocol deviation. The subject was contacted immediately, and they returned to the clinic to receive the correct medication. The field investigator also found a few unreported non-serious adverse events for three subjects (fainting sensation for Subject #14192; dizziness for Subject #10440; and hematuria for Subject #9950). The inspection also found that an ECG for Subject #3402 was not performed at the Month 12 Visit, as per the protocol. No FDA-483 was issued.

c. Assessment of data integrity: In general, no significant regulatory violations were noted and no Form FDA-483 was issued. The errors noted are isolated in nature, and not likely to impact data integrity or subject safety. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Cesar Javier Zaidman**Site 1742**

Ciprec Av. Pueyrredon 1746, 2 A
Buenos Aires, Argentina 1119

a. What was inspected: The inspection was conducted in accordance with Compliance Program (CP) 7348.811. Dr. Zaidman has (b) (4) IND studies in CDER's database and no prior inspectional history. At this site, 88 subjects were screened, 73 subjects were randomized, and 65 subjects completed the study. There were eight deaths (3 in the apixiban arm, 5 in the warfarin arm) and 35 reported SAEs.

An audit of 34 subjects' records was conducted. All study notes were written in Spanish and required English translation by a BMS translator. The field investigator reviewed hand-written source documentation and compared them to entries in the electronic-case report forms. The field investigator reviewed inclusion and exclusion criteria, test article accountability records, and primary and secondary endpoint events. He reviewed INR measurements and dosage adjustments; adverse events, clinically significant bleeding events, deaths, laboratory assessments, ECGs, vital signs, and physical examinations.

b. General observations/commentary: The field investigator reported that all subjects reviewed met inclusion and exclusion criteria. He confirmed that clinically significant bleeding events matched those in the sponsor's data listings. The eight deaths were located in source documentation and corroborated with the data listings. The drug accountability records were found to be accurate. The field investigator reported that for all study records reviewed, the primary and secondary efficacy endpoint information and data (within the subject's source records) corroborate the data listings.

With respect to INR management, Dr. Zaidman told the field investigator that he adjusted the warfarin dosage to maintain the INR within the targeted therapeutic range of 2.0 – 3.0. One subject was unblinded during the study. Subject #18531 died due to a cerebral stroke (hemorrhage), and the family wanted to know what medication she was assigned. The site contacted the sponsor, and the sponsor allowed the subject to be unblinded. This incident was documented in the progress notes.

The field investigator found a few minor violations. He found two subjects with unreported adverse events. Subject #11903 had unreported clinically significant laboratory results of low white blood cells (2.9×10^3 gm/dL) and low platelet counts (80,000 platelets per μ l), as per laboratory report dated July 1, 2010. Subject #14333 had an unreported right wrist fracture due to a fall, according to progress notes dated November 12, 2009. No FDA-483 was issued.

c. Assessment of data integrity: In general, no significant regulatory violations were noted and no Form FDA-483 was issued. The study appears to have been conducted adequately at this site, and the data generated by this site appear acceptable in support of the respective indication.

4. Sandeep Gupta Site 1606

Mv Hosp. & Res. Centre
314/30 Mirza Mandi Chowk
Lucknow, Uttar Pradesh, India 226003

a. What was inspected: The inspection was conducted in accordance with Compliance Program (CP) 7348.811. Dr. Sandeep Gupta had [REDACTED]^{(b) (4)} in CDER's COMIS database and no prior inspectional history. At this site, a total of 104 subjects were screened – this represented 99 unique individuals, as five subjects were rescreened (the protocol allowed subjects to be rescreened for certain laboratory abnormalities such as low platelet counts or low hemoglobin). A total of 87 subjects were randomized. There were 12 screen failures. A total of 76 subjects completed the study. Eleven subjects terminated early including 4 subjects who died, 3 subjects who withdrew consent, 3 subjects lost to follow-up, and 1 subject who was terminated from the study following a SAE.

The field investigator conducted a full audit of 30 subject records (~30% of total number of enrolled subjects), including a review of signed and dated informed consent documents (all versions); inclusion and exclusion criteria; subject screening, enrollment and randomization; eCRFs; source documents; treatment/study visit timeframes; documentation of diagnosis and historical treatment of atrial fibrillation and other risk factors for stroke; IVRS confirmation faxes regarding INR values and assignment of investigational product (IP) containers; investigational product accountability logs; prior medication history; concomitant medications; laboratory reports; adverse events (AEs) and SAEs with special attention to bleeding events, stroke and death; documented protocol deviations, and verification of data listings.

The field investigator conducted a 100% verification of the data listings for the 30 audited subjects. He corroborated the source documentation with the CRFs and the data listings for: discontinued subjects, including dates and reasons; deaths and narratives; non-serious AEs and SAEs; bleeding events. The field investigator reported that for all study records reviewed, the primary and secondary efficacy endpoint information and data (as documented in the subject's source records) were supported and corroborated with the data listings from the sponsor; and protocol deviations. In addition, the field investigator randomly selected ten subject records to spot check, focusing on AEs/SAEs, INR values, and IP accountability.

b. General observations/commentary: The field investigator issued a 3-observational Form FDA-483, for the following deficiencies:

Observation 1) Failure to obtain informed consent in accordance with 21 CFR Part 50 prior to conducting study related activities (21 CFR 50.20).

Specifically, the inspection found that subjects did not always sign the newest version of the Informed Consent document at their subsequent visit. This was noted

to be a systemic issue, and occurred specifically with ICD Version 3.0 (at least 15 subjects), Version 3.1 (at least 8 subjects), and Version 4 (at least 32 subjects). The field investigator observed that this observation had been noted by the monitor and documented by the monitoring reports. He also observed that Dr. Gupta had submitted protocol deviation letters to the Ethics Committee (EC) about this issue. After re-training at the site, study subjects were re-consented in a timely manner at their next scheduled visit. At the time the site began screening subjects, IC Version 3, dated July 16, 2008 was in use. There were subsequent updated, translated Version 3's for Hindi and Urdu. There were four subsequent versions to Version 3 used: Version 3.1, Version 4, Version 5 and Version 6. The changes made to Version 3.1 (dated April 29, 2009) were administrative in nature, pertaining to an address change for the site, and a number change for one of the EC members. The changes to Version 4 (dated September 3, 2009) reflected a change in the number of study centers from 800 to 1000 sites and an increase in the number of participants from 15,000 to 18,000. The changes also pertained to compensation for participants. These changes are not likely to impact subject safety. In his February 3, 2012 response letter to the Form FDA-483, Dr. Gupta outlined a corrective action plan to prevent recurrence of this observation.

Observation 2) Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation [21 CFR 312.62(b)].

The following inconsistencies were noted in source documents:

- a) Subject 08624 was seen in the ICU with an SAE of congestive heart failure at the 8 Month Visit on Sept 2, 2009. The source notes documented no (new) AE or SAE. However, this SAE was documented on other source records maintained in the subject's binder and reported via CRF to the Sponsor.
- b) Subject 14891 had an SAE of recurrent vomiting and weakness occurring on September 14, 2009 but the source notes of October 5, 2009 report no AE or SAE. This SAE was documented on other source records within the subject's binder and was reported via CRF to the Sponsor.
- c) Subject 20516 experienced pain in the wrist and joints at the Week 3 Visit occurring on February 8, 2010, although the source record visit notes documented that no AE or SAE was reported at this visit. This AE was documented in other source records within the subject's binder and was reported via a CRF to the Sponsor.
- d) Subject 11688 had two IVRS FAX INR confirmation forms for 2 separate INR values at the 5 month Visit on September 1, 2009 - one taken at 10:46 and another at 14:46. Study records did not explain which value was ultimately accepted by the IVRS Manager.

Observation 3): An investigation was not conducted in accordance with the investigational plan (21 CFR 312.60).

Specifically, the field investigator identified more than 46 subjects who had multiple (at least 3) study visits performed > 7 days outside the protocol-defined window (range was >7 to 25 days out-of-window). Note: The protocol allowed subjects to be seven (7) days outside the window visit.

The field investigator discussed this topic at length during the inspection. Dr. Gupta explained that in India, a patient never goes to the clinic alone, and is always accompanied by a friend, relative or neighbor. Dr. Gupta also explained that the study site is only open during the day, during times that most relatives are at work. The field investigator observed that Dr. Gupta had submitted protocol deviation notification letters to the Ethics Committee to inform them of these out-of-window visits. This action had been recommended by the monitor. The field investigator collected documentation of conversations during the consent process whereby Dr. Gupta told subjects he would send a vehicle for them. The field investigator noted that most of the out-of-window visits occurred towards the middle to end of the study, versus at the beginning.

The inspector noted that the PI knowingly maintained subjects at a low time in therapeutic range (TTR). When subjects in the warfarin arm are insufficiently anticoagulated, it may result in the finding that the study drug (apixiban) is noninferior to placebo since a higher number of events would be expected to occur in the warfarin arm. Dr. Gupta had many discussions with the monitor, and additional training was provided about ways to improve INR control. Dr. Gupta stated that it was his decision to increase or decrease dosages based on patient care and safety. Dr. Gupta explained that if a patient appeared to have no difficulties with the current dosage, he did not like to make adjustments – because, if bleeding occurred by increasing the dose, it might take longer for the subject to get back to the clinic and obtain medical care.

With respect to bleeding events, the field investigator reported that subject records adequately documented if bleeding occurred. If a bleeding event occurred, the study medication would be stopped until a full evaluation was conducted. The field investigator observed that the Sponsor was notified of any bleeding event within 24 hours, and the documentation was then faxed to PPD.

The field investigator also reported that adverse events appeared to be well documented within the source records and on the CRFs. The field investigator did not observe any discrepancies between source documents, data entered on the CRF, and the Sponsor data listings. The field investigator observed that the majority of SAEs were bleeding events, stroke, and death. For the four subjects who died while participating in this study, the cause of death was not known for two (Subjects 8385 and 16832).

The field investigator reported that Dr. Gupta and the site staff were provided additional training on the above issues. The site hired additional staff to respond to the numerous queries and enter information into the eCRFs. This action had been advised by the monitor.

Dr. Gupta provided a response to the Form FDA-483 observational items, in a letter

dated February 3, 2012. In his response letter, he stated that he is committed to conducting clinical research to comply with GCP and all regulatory requirements. He outlined a comprehensive corrective action plan to correct the above deficiencies. OSI considers his response adequate.

c. Assessment of data integrity: Regulatory violations were observed at this site, but these are not considered likely to importantly impact data integrity. In general, the source documents were noted to be in good order and study procedures, adverse events, and other source information were well documented. There were few discrepancies between the source records, the eCRFs, and the background materials. As was previously discussed with the review division, OSI will defer to the review division on the issue of assessment of the potential effect of low TTR on overall study outcome. Otherwise, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

5. Louis Yao
Site 0019
230-1920 Weston Road
Weston, ON
Canada M9N 1W4

a. What was inspected: The inspection was conducted in accordance with Compliance Program (CP) 7348.811. At this site, 122 subjects were screened, 113 randomized, 30 subjects were listed as “early discontinuations: (17 were deaths), and 83 subjects completed the study. The field investigator completed a data audit of 44 subject records that included: review of inclusion and exclusion criteria; efficacy assessments; corroboration of electronic case report forms (eCRFs) with source documents and data listings; adverse event reporting; drug accountability records, and protocol deviations.

b. General observations/commentary: In discussions with the field investigator, she did not report any evidence of underreporting of AEs and did not provide information about her corroboration of the efficacy endpoint data listings with the source data at the site. If any issues are observed after the review of the EIR, OSI will provide an addendum to this CIS.

The field investigator observed that Dr. Yao co-mingled the patient study records with the patient’s non-study medical records. (b) (6)

(b) (6) helped Dr. Yao with the conduct of this study, including the completion of documents. According to her CV, (b) (6)

(b) (6). She was a Cardiology Research Coordinator in other studies. (b) (6)

She is also listed as study coordinator for several studies.

The field investigator reported that Dr. Yao signed every Informed Consent Document that was reviewed. According to signatures on documents, specific responsibilities were as

follows: (b) (6) signed documents documenting the reporting of SAEs, and (b) (6) faxed the INR values. When directly asked about the roles of (b) (6) in the study, Dr. Yao stated that they pretty much did "secretarial work" and were never directly involved with screening, INR readings, dosage adjustments, or identifying SAEs. He also stated that both (b) (6) completed several BMS online-training modules prior to the beginning of the study. (b) (6) told the field investigator that she has been helping Dr. Yao, as a Study Coordinator, since she left her job working with (b) (6). At the present time, Dr. Yao had only (b) (6) helping him with the ARISTOTLE study.

A 2-observational FDA-483 was issued to Dr. Yao at the end of the inspection for the following deficiencies: 1) an investigation was not conducted in accordance with the investigational plan (21 CFR 312.60); and 2) failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

With respect to Observation 1, the following was noted: on February 7, 2009, Subject 09747 experienced a SAE and Dr. Yao unblinded the treatment for that subject only after the subject's daughter demanded to know what her father was taking. This was contrary to the protocol's requirement which states, in part, that the blind should be broken only for a medical emergency.

OSI Reviewer Comments: While unblinding the treatment for Subject 09747 was a protocol violation, it was an isolated event and should not impact the integrity of data generated by the site.

With respect to Observation 2, the following was noted:

- For Subject 04187, the progress notes for all visits between June 11, 2008 and December 15, 2009 are signed and dated March 6, 2010;
- For Subject 00259, progress notes for visits between June 22, 2007 and August 1, 2007 are signed and dated October 11, 2007;
- For Subject 02086, the progress notes for visits between February 13, 2009 and October 13, 2009 are signed and dated March 6, 2010.

OSI Reviewer Comments: Reportedly, Dr. Yao did not review and sign all entries to progress notes for all visits contemporaneously - he would often go back months later to sign them.

- ECG printouts for Subject 00199 and 02086 were not signed by Dr. Yao.
- Visit Date fields in the eCRF were not always completed. For example, the Screening Visit date fields for Subjects 16108, 15551, and 09747 were not completed.
- Electronic signatures in the eCRF were post-dated, between one month to over one year from the visit date for some subjects. Based on this finding, it appears that the PI did not electronically sign off on eCRFs until much later than the subject visit date.

c. Assessment of data integrity: This site had very high enrollment. In general, the regulatory violations noted are isolated in nature based on available information and would

not be expected to impact data integrity. The data generated by this site may be used in support of the respective indication.

PLEASE NOTE: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the field investigator, and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

6. Shiyao Wu

Site 1200

Shanghai 9th Peoples Hosp. Affiliated To Kan Chen M.D.

S. J.T. U. S. M.

No. 639, Zhi Zao Ju Road

Shanghai, China 200011

a. What was inspected: The inspection was conducted in accordance with Compliance Program (CP) 7348.811. Dr. Shiyao Wu has (b) (4) IND studies in CDER's COMIS database, and no prior inspections. For this study, a total of 37 subjects were screened at the site and 35 subjects enrolled. There were two screen failures; five deaths, two withdrawals, and one subject lost to follow-up. Two field investigators were assigned to cover this inspection - they divided their time between covering the routine Compliance Program and addressing the "for cause" addendum to the assignment issued January 20, 2012.

b. General observations/commentary: A multi-part, one item FDA-483 was issued during the inspection for the following:

The study was not conducted in accordance with the study protocol (21 CFR 312.60). Specifically,

- The principal investigator as team leader failed to properly supervise the sub-investigators. The principal investigator failed to ensure prompt reporting of study progress in the CRF as reported by the study monitors.
- User accounts to gain access to computers were shared between two sub-investigators (Dr. (b) (4)), which was prohibited by Protocol Section 9.1.3, which states "user accounts are not to be shared or reassigned to other individuals." Further, the principal investigator allowed Dr. (b) (4) to use his username to enter data into the e-CRF.
- The principal investigator failed to ensure an adequate number of qualified staff and adequate facilities for the duration of a trial to conduct the trial properly. The internet connection at the study site was too slow to allow staff to enter data expeditiously, and some staff took data home on an unsecure drive to complete the task. One sub-investigator stated that it took him at least three hours to completely enter the data for one screening visit.

Additional Information on BMS Findings at Site 1200:

A for-cause inspection assignment addendum was issued in order to confirm allegations of suspected misconduct including alteration of subject records during a pre-inspection audit at Site 1200 (Shiyao Wu) in China. (Please see Background for further details.) The observations of alleged misconduct came from a PPD monitor ((b) (6)) who was at Site 1200 helping to prepare the site for the upcoming FDA inspection. Specifically, Ms. (b) (6) noted that while reviewing a chart which contained records of outpatient visits, she recalled that during an earlier monitoring visit, these same outpatient records contained handwritten comments. During the pre-audit visit, Ms. (b) (6) noted that the printed records had no handwritten comments. In addition, a PPD employee ((b) (6)) told her that he had altered data containing subject records on a USB drive at the direction of Ms. (b) (6) BMS site manager. The records were altered in order to cover-up GCP violations which had occurred at the site.

In their response to an February 15, 2012 OSI Information Request (IR) BMS provided information stating that Ms. (b) (6) worked as Site Manager for the BMS ARISTOTLE study and that she visited 18 of the 36 Chinese sites while the study was underway. Her duties included conduct of co-monitoring visits if needed; site recruitment/enrollment; resource needs; and following up on quality issues noted by the Site Monitor. She reviewed site visit reports written by the site monitor. During pre-inspection visits, she reviewed study files and subject medical records and discussed issues with study personnel. The sites in China where Ms. (b) (6) worked were: 1180, 1182, 1199, 1206, 1207, 1221, 1223, 1246, 1247, 1266, 1547, 1548, 1549, 1550, 1552, 1555, 1556, and 1558. She worked on no sites outside China. To prepare for the upcoming FDA inspections, Ms. (b) (6) worked at Sites: 1200 and 1178. PPD employee (b) (6) performed site monitoring responsibilities for the following Sites: 1200, 1198, 1168, 1244, and 1287. He worked at no non-China sites.

OSI Reviewer Comment: FDA inspection at this clinical revealed that multiple individuals at this site were using the principal investigator's PIN number to access an electronic data system at the site used for eCRF entry. In addition, the principal investigator allowed one of the subinvestigators to use his username to enter data in eCRFs. The PI rarely evaluated subjects personally. These violations represent serious compliance violations, since anyone who entered data under another's identification is committing a fraudulent act. The integrity of the study records are compromised, as is the data contained in those records.

In addition to the FDA inspectional findings, BMS submitted evidence based on their own investigation that fraudulent activity occurred at this site. The BMS Site Manager (b) (6) assigned to this site to prepare for the FDA inspection altered subject records and directed a PPD employee Mr. (b) (6) to alter subject data on a USB drive. These fraudulent activities were reported to occur in an effort to conceal GCP violations at Site 1200. BMS was queried as to the duties of these two individuals during the conduct of the trial as well as which sites they worked at during ARISTOTLE. As detailed above, these two

individuals worked at 23 of the 36 ARISTOTLE sites located in China and one additional site (1178) in preparation for the FDA inspection.

c. Assessment of data integrity: The inspection at this site found that Dr. Wu failed to maintain adequate oversight of the study. This was evidenced by sub-investigators using Dr. Wu's PIN to make entries to records (shared user accounts were prohibited by the protocol). Dr. ^{(b) (4)}, a sub-investigator, continued using Dr. Wu's username and password even after he had his own account. In addition, due to slow internet speed, study coordinators **frequently took records home on an unsecured USB drive to complete entering data into CRFs.** These activities (shared user accounts and unsecure USB drive) could potentially compromise the integrity of the data generated by this site. Dr. Wu admitted that he did not regularly see study subjects – only if there was a special case. In addition to these serious inspectional observations, BMS informed that employees of BMS and PPD had manipulated study records at this site. The extent of data manipulation at this site remains unclear. For these reasons, OSI finds that the reliability of data from this site could not be verified. OSI recommends that data generated by this site be considered unreliable and not be used in support of the NDA.

PLEASE NOTE: A final review of the EIR was not completed at the time this CIS was written. The observations noted are based on preliminary review of the EIR, and communications with the field investigator, and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

7. Shulin Wu

Site #1178

Guangdong General Hosp.
No. 1, The 2nd Zhongshan Road
Guangzhou, Guangdong
China 510080

a. What was inspected: The inspection was conducted in accordance with Compliance Program (CP) 7348.811. At this site, there were 54 subjects screened and 44 subjects enrolled. A total of 31 subjects completed the study. The field investigator completed a review of Informed Consent Documents for all 44 subjects. Comparison of source documents from study visits was made with the eCRFs for seven subjects selected from the beginning, middle and end of the study. This included a review of all the inclusion and exclusion criteria, efficacy assessments, corroborating the source documentations with eCRFs and data listings, drug accountability records, and adverse event reporting. The CRFs were reviewed for completeness and accuracy. Five (5) additional subjects who had been hospitalized during the study were reviewed for serious adverse event reporting and concomitant medication documentation.

b. General observations/commentary: All study records were well organized. There was adequate documentation to ensure all subjects were alive and available for the duration of their stated study participation. Hospital inpatient records were available electronically. A

study nurse had been designated for this trial and was responsible for all electronic data entry. Sub-investigators reviewed and signed (approved) the entries. Data was usually entered the same day or within 24 hours. Safety reports were entered immediately. A few minor discrepancies were noted:

- Subject 10957 was taking Digoxin 0.125 mg QD as noted in the source documents but this medication was not included in the screening medication log on the eCRF.
- Subject 14672 was hospitalized July 6, 2009 – July 21, 2009, for cerebral infarction. During this time, the subject was administered one dose of clopidogrel, which is a restricted but not a prohibited medication per the protocol.

No other problems were noted and no unreported serious adverse events were observed.

c. Assessment of data integrity: Although minor discrepancies were observed, no FDA-483 was issued. However, because of the alleged misconduct and other inappropriate activities that occurred at Site 1200, and that this site (1178) was visited by BMS Senior Clinical Site Manager (b) (6) who reportedly inappropriately influenced the study records at Site 1200 in China, OSI recommends that the data from Site 1178 (as well as all sites in China who were conducting the ARISTOTLE study where either (b) (6) or (b) (6) worked) be excluded from the primary efficacy and safety analysis.

PLEASE NOTE: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the field investigator, An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

8. William Kufs

Site 796

Saratoga Cardio. Assoc., PC
6 Care Lane
Saratoga, NY 12866

a. What was inspected: This domestic site inspection was conducted in accordance with Compliance Program (CP) 7348.811. Dr. William Kufs has (b) (4) listed in CDER's database, and no prior inspectional history. At this site, 65 subjects were screened, 56 subjects were randomized, and 44 subjects completed the study. There were five deaths and seven subject discontinuations. Most discontinuation occurred because of subject request. One subject was discontinued due to poor compliance.

An audit of 25 subjects' records was conducted during the inspection. The field investigator reported that he reviewed subject clinic records and subject files as part of source documentation. There were no paper CRFs, so the field investigator corroborated data entered directly onto the eCRF with the source documentation and the sponsor's data listings.

The following items were audited: adherence to inclusion and exclusion criteria; validation of adverse events; bleeding events; visit schedules and INR testing; protocol violations; investigational product (IP) labeling; drug accountability for eight subjects; potential unblinding (as per assignment request); validation of primary and secondary endpoints, discontinuations; deaths; and informed consent documents for all randomized subjects.

b. General observations/commentary:

The following items were cited in the FDA Form-483:

1) Investigation not conducted according to the investigational plan (21 CFR 312.60). Specifically, two subjects who were enrolled should have been excluded according to the protocol specified exclusion criteria. Subject 04331 was taking 325 mg aspirin/day (protocol specifies exclusion if the subject is taking more than 165 mg aspirin per day); and Subject 15718 was not screened for platelet count (protocol excluded subjects with platelet count $>100,000/\text{mm}^3$)

OSI Reviewer Comment: The CI's response letter dated February 29, 2012 states that aspirin was stopped at study entry for Subject 04331; therefore, this citation appears to be inaccurate. With respect to Subject 15718, the CI's response letter states that Subject 15718 had 'platelet clumping' and therefore, the core laboratory elected not to report a platelet count, and not to report it as abnormal. This was an oversight by the CI. The protocol prohibited subjects with a platelet count $< 100,000 \mu\text{L}$ (later amended to $< 90,000 \mu\text{L}$) due to a higher risk of bleeding. This was an isolated finding, and unlikely to affect data integrity.

2) Investigational drug disposition records were not adequate with respect to quantity [21 CFR 312.62(a)]. The field investigator reviewed drug accountability records of returned medication for eight subjects, and found discrepancies for five of those subjects. For example, for Subject 00104, and Bottle #424040, the drug accountability log documents 52 tablets were returned on September 25, 2009 whereas the subject's personal record documents that 58 tablets were returned. For Subject 00104 and Bottle #103585, the drug accountability log documents 87 tablets returned, whereas the subject's personal records documents 0 tablets returned.

OSI Reviewer Comment: The field investigator found five of eight subjects with a discrepancy between the amount of study drug returned during one of the subject's scheduled visits (discrepancies were between the 'Record of Study Medication – Warfarin/Placebo record' and the 'Individual Subject Clinical Supplies Inventory Warfarin' record). In his response letter, Dr. Kufs commented that at the beginning of the study, subject diaries were encouraged but not required. These errors appear to be discrepancies between the Subject diaries and the drug accountability log, but not discrepancies between the drug accountability log and the number of pills documented in the eCRF. This finding is not likely to importantly impact study drug compliance and data integrity.

3) Failure to report to the sponsor adverse events that may be regarded as caused by the investigational drug [21 CFR 312.64(b)].

Specifically, the field investigator found 12 of 36 serious adverse events (SAEs) that were reported to the Sponsor later than the 24-hour timeframe required by the protocol. For example, Subject 131 experienced a myocardial infarction and was hospitalized on (b) (6). This event was not reported to the sponsor until (b) (6) (4 days later). Subject 167 was hospitalized with anemia on (b) (6). This event was not reported to the sponsor until (b) (6) (10 weeks later). Subject 557 had gastroenteritis on August 19, 2009 and was hospitalized on (b) (6). This SAE was not reported to the sponsor until (b) (6) (3 weeks later).

OSI Reviewer Comments: In his response letter dated February 29, 2012, Dr. Kufs stated that he failed to file some SAEs within 24 hours because he was not notified of the SAE (in some cases) until the subject returned to the clinic for a scheduled visit. For other cases, the subjects had hospital admissions for the event, and the hospital physicians would not notify him until the subject was discharged. Dr. Kufs stated that he would then report the SAE within 24 hours of being notified. The hard copy SAE reports that Dr. Kufs submitted with his response letter substantiates that although the onset date was earlier, Dr. Kufs did in fact report the events within 24-hours of being notified. OSI considers his response acceptable.

c. Assessment of data integrity: Minor regulatory violations were found during the inspection at Dr. Kufs' site. These violations were isolated and adequately addressed by Dr. Kuf in his response letter. The study at Site #796 appears to have been conducted adequately, and the data may be used in support of the respective indication.

9. Bristol Myers Squibb Research & Development

P.O. Box 4000 (Mail Stop: D22-05)
Princeton, NJ 08543-4000

Sponsor Inspection – (December 28, 2011 – January 27, 2012)

a. What was inspected: This was a high priority inspection in accordance with Compliance Program 7348.810. Two field investigators were assigned to cover this inspection. They reviewed monitoring reports for the eight clinical investigator sites and documented systemic issues at the sites; they identified sites that had poor INR control and how improvements were being made; they looked at the adjudication process and commented on how well communication was conducted between the site, PPD, and the sponsor; they verified how well adverse events, especially bleeding events, were reported to the sponsor; they also verified how and if endpoint events were reported to the sponsor.

The field investigators asked the sponsor for information about the change in their decision to not collect the CRF 800's from the site. They asked the sponsor questions about the potential for the site to break the blind by scratching off the label covering that contained the product name. This was the portion of the label affixed to the CRF 800 page.

b. General observations/commentary: At the end of the inspection, a 2-observational Form FDA-483 was issued for: 1) failure to ensure proper monitoring of the study and ensure the study is conducted in accordance with the investigational plan (21 CFR 312.50); and
2) an investigator who did not comply with the general investigational plan was not promptly brought into compliance [21 CFR 312.56(b)]

With respect to Observational Item #1, the field investigators reported inadequate monitoring at Site 1200 (China) and Site 1606 (India), as evidenced by review of site monitoring reports (MVR).

As reported, Site 1200 had 4 different monitors, and there was considerable variation in the quality of the MVRs from the various monitors. Since PPD did not have a presence in China at the time of the study, BMS hired contractors paid by PPD but who were managed by BMS in China to conduct monitoring at Site 1200. The monitors used BMS forms for completing monitoring visits. The monitoring reports revealed that Site 1200 did not complete documents (CRFs and query resolutions) in a timely manner. For 18 of 25 monitoring visits, the field investigators found that the monitors failed to complete those sections of the MVR that indicated the names of individuals from BMS or PPD at the site during the monitoring visits. For 4 of 18 visits, the field investigators reported that the Source Data Verification Documentation section which verified if source data corroborated with the CRF entries was not completed.

While reviewing monitoring reports for Site 1606, the field investigators observed documentation that Site 1606 consistently had difficulty with entering data from source records onto the eCRF in a timely manner. The field investigators also observed the following: Site 1606 did not respond to data queries in a timely manner; Site 1606 did not always inform the IRB of SAEs in a timely manner; Site 1606 had numerous out of window visits; Site 1606 showed problems with providing the correct versions of the ICD for the patient to sign; Site 1606 had numerous investigational products (IPs) issues, including bottles not returned by the subjects and bottles lost by the site. The field investigators observed that despite the apparent multitude of IP issues described by the MVR, that the monitor only documented one time (in an MVR towards the end of the study) that there were many IP bottles not returned by the subjects. Despite these problems, the site was approved by the sponsor for an increase in enrollment and was granted two extra study coordinators. The sponsor also provided more staff at the site to help keep up with data entry. The field investigators reported that because Site #1606 had so much difficulty maintaining subjects within the targeted therapeutic range, that BMS provided refresher training on the importance of INR control at the site.

With respect to their decision to maintain CRF 800's on site, BMS explained to field investigators during the inspection, and in their written response, dated February 17, 2012, that in July 2009 a decision was made by BMS to stop the process of collecting CRF pages with labels affixed and forwarding them for processing. Instead, those pages were to be kept with other study documents and made available for monitoring.

They did this in order to retire the process of collecting CRF label pages for new studies. BMS stated that regardless of where the labels resided the monitoring of key aspects of the study, including drug accountability, and verification of protection of the blind, did not change. BMS reported that all monitors were instructed to review the panel stickers on the CRF 800 and identify and report if any unblinding occurred.

The field investigators also reported that monitors from 2 of the 8 sites reviewed failed to ensure that sites recorded the amount of IP returned and final IP disposition. At Site 1200, the field investigators reported that 43 kits (11 apixaban kits and 32 warfarin kits) were documented as lost by subjects. This amounts to 17 of 35 subjects enrolled losing at least one kit during the course of the study. The loss of these kits was rarely documented in the MVR. At Site 1606, the field investigators noted illegible and missing records of the final disposition of IP.

With respect to Observation 2, at Site 1606, the field investigators found that the PI was consistently late in entering data into the eCRF, was late in answering data queries, and was late in reviewing and approving eCRF data. The sponsor provided the site with extra study coordinators to assist the site with efforts of increased enrollment.

c. Assessment of data integrity: Although regulatory violations were noted during the inspection specific to several problematic sites, overall the study appears to have been conducted adequately by the sponsor, and the data may be used in support of this NDA.

PLEASE NOTE: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the field investigator, and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

Sponsor Re-Inspection (March 14 – April 5, 2012):

During the period of March 14 – April 5, 2012, FDA field investigators re-inspected the sponsor at the BMS facility in Lawrenceville, N.J. On March 14 and 15, the investigators were accompanied by Martin Rose, Medical Officer and Alison Blaus, Senior Regulatory Project Manager in the Division of Cardiovascular and Renal Drug Products. BMS responded to the Form FDA-483 observations in a letter dated April 26, 2012.

a. What was inspected: The sponsor re-inspection was conducted to more fully address the adequacy of sponsor oversight and monitoring during the conduct of the ARISTOTLE trial. The adequacy of oversight and monitoring was questioned based

on the findings of alleged fraud at Site 1200, as well as the information noted by the review division that some subjects received the wrong drug (medication dispensation errors), based on mismatches between container codes entered in the eCRF at the site and the IVRS assignment. The sponsor re-inspection was also conducted to address questions about potential unblinding and the high rate of medication dispensation errors noted by the review division. The field investigators were asked to review monitoring reports for the following five sites selected randomly (high enrollment), and summarize ongoing issues found at those sites:

- Site #310 (Kharman, Germany, 192 subjects)
- Site #1438 (Horacek, Germany, 130 subjects)
- Site #872 (Chzhov, Russia, 110 subjects)
- Site #903 (Nierop, Netherlands, 98 subjects)
- Site #463 (Hong, South Korea, 105 subjects)

b. General observations/commentary:

A 2-observational FDA-483 was issued at the conclusion of the inspection for the following:

Observation 1: An investigator who did not comply with the general investigational plan and regulatory requirements was not promptly brought into compliance. Specifically, the Sponsor failed to ensure compliance of study conduct in two out of five sites reviewed through clinical site monitoring when the sites were continually found to conduct the study inadequately (according to the protocol, applicable regulatory requirements and applicable laws of the country in which the research was conducted). For example:

1. The Principal Investigator for Site #903 failed to (a) ensure IP compliance and accountability for at least one time point in 38 out of 67 subjects; (b) perform all protocol required procedures; (c) sign the medication prescriptions as required by Dutch law; (d) obtain informed consent forms prior to the required procedures; (e) delegate and approve a sub-investigator prior to study participation; (e) ensure the required protocol visits were performed within the allowed window; and (f) store the PI under appropriate conditions.
2. The PI for Site #463 failed to: (a) ensure IP compliance in 33 of 72 subjects; (b) perform all protocol required procedures; (c) delegate and approve a Study Coordinator to participate in the study; (d) obtain updated versions of the ICD; and (e) ensure the required protocol visits were performed within the allowed window.

BMS Response: In their response letter, dated April 26, 2012, BMS states that despite efforts to monitor, there were areas where site performance was not as expected, but they do not believe these issues affected the validity of the data in this trial. BMS audited Site #903 during the trial when 35 of 65 subjects had been randomized. Improvement in site performance was noted following the BMS audit. Concerning the finding of instances where an ECG or laboratory test was not performed as required (Site #463), BMS states these

missed procedures were sporadic across subjects and visits. There were no adverse events temporally associated with the missed procedures.

OSI Reviewer Comment: OSI considers the BMS response acceptable.

Observation 2a: failure to ensure proper monitoring of the study. Specifically, the field investigator observed that the Site Monitoring Plan (SMP) for this study was approved January 3, 2008. However site initiation visits (SIV) and interim monitoring visits occurred prior to the approval date for the SMP. Examples are as follows:

- Site initiation visits (SIV) occurred on July 26, 2007 (for Site #310), August 10, 2007 (for Site #463), and September 11, 2007 (for Site #872). These monitoring visits occurred before approval of the SMP (January 3, 2008)
- Six interim monitoring visits occurred between September 20, 2007 and December 25, 2007 for Site #310 and Site #872, respectively. These monitoring visits occurred before approval of the SMP (January 3, 2008).

BMS Response: In their response letter, BMS states that these site visits to the above sites were made using a working draft of the SMP (Version 6, dated July 11, 2007). The working draft included all information necessary to conduct quality SIVs and interim site monitoring visits. In addition, BMS explained that the SOP for developing the SMP allowed for the SMP to be developed in four stages to accommodate the study progress milestones.

OSI Reviewer Comment: OSI considers the BMS response acceptable.

Observation 2b: According to the IP Storage Accountability and Reconciliation section of the SMP, the Clinical Research Associate (CRA) should confirm that the accountability log and the inventory agree. The site personnel did not count the study drug during each scheduled visit, and monitors (a/k/a CRAs) at the site failed to review the drug accountability logs during their monitoring visits to ensure the number of pills documented as returned corroborated with the number of pills on hand at the site.

BMS Response: In their response, BMS acknowledged a systematic issue at one site (#903), where pill counts were performed at 81% of visits. However, at Site #463, drug accountability was performed at 98% of visits, and instances where it was not performed were isolated and sporadic. The frequency of missed pill counts was noted to improve throughout the study, as noted by compliance checks documented in monitoring visit reports.

OSI Reviewer Comment: OSI considers the BMS response acceptable.

Observation 2c: According to the SMP, the IP labels which were affixed to CRF 800 pages should be kept at the clinical sites effective as of July 2009. This was not followed. For example, approximately 72 out of 1,034 sites returned the IP label CRF 800 pages to the Sponsor between August 14, 2009 to September 19, 2011.

BMS Response: In their response letter, BMS states that there was a change regarding the CRF label pages while the study was ongoing, and confusion existed as to whether these pages were to be returned or not.

OSI Reviewer Comment: OSI agrees that there was a communication problem and confusion arose on how to handle the CRF 800 pages (containing the affixed labels for unblinding) throughout the conduct of the study. When the CRF 800 pages were maintained at the site, either in the pharmacy or elsewhere, the labels could theoretically be scratched off and unblinded. However, according to the field investigators, the site monitors did not identify unblinding as an issue during monitoring. **OSI considers the sponsor's response adequate.**

In addition to the above observational items listed on the FDA-483, several relevant verbal observations were presented to the sponsor at the end of the inspection. In brief, they were the following:

One item pertained to medication dispensation errors. In late January 2012, the review division raised questions about the description in Section 4.3 of the ARISTOTLE Clinical Study Report that 7.3% of apixaban subjects and 1.2% of warfarin subjects had received, at some point in the study, a study medication container of the incorrect type. It was possible that these medication dispensation errors, especially when a subject receives either double active or double placebo can lead to safety events. The review division asked the sponsor in an Information Request (IR) to describe, if any, the impact of these errors (whereby subjects received the wrong medication) on the integrity of data.

During a February 2012 meeting, the review division asked the sponsor for a further quantification of medication errors to assess whether the proportion of previously reported medication errors could have been under-estimated (0.38%), and to assess the impact of medication errors on the interpretability of the study results. BMS had examined all container numbers entered into the web-based eCRF, and calculated that 0.38% of all labels did not match the labels assigned in the IVRS. In their response letter dated April 26, 2012, BMS stated that upon further evaluation of these types of errors the rate of study medication treatment errors in this trial was low ($\leq 0.1\%$ of study medication dispensing) and balanced across treatment arms. The true proportion of errors in medication dispensations was likely even lower than the 0.38% that was derived earlier, so that the containers dispensed to the subjects very closely matched what was intended by IVRS. Further, BMS states that the actual impact on patient safety does not appear to have been significant. Only four primary efficacy or safety outcome events occurred during or within 90 days after a period of treatment with double active or double placebo. Further, the low rate of study medication treatment errors and their random nature along with the results of sensitivity analyses suggest that the study conclusions are robust.

A second item pertained to reevaluating the monitoring report template to ensure that enough information was captured. The template used by PPD was very detailed, whereas the template used by BMS used a Yes/No question format. BMS stated that critical GCP principles were captured within the BMS monitoring report, but that they would undertake a

re-evaluation of the content of the report as part of ongoing improvements. It is noted that the PPD (detailed) template was used for the majority of sites in the ARISTOTLE trial.

c. Assessment of Data Integrity: Through review of monitoring reports, the field investigators observed ongoing issues relating to IP compliance and accountability at two of five sites. For the study as a whole, pill counts were performed at 92% of all study visits, and subject compliance was noted to be equally as high. These IP issues are unlikely to directly impact data integrity. Though other minor regulatory violations were found during the reinspection at the Sponsor site, the issues were adequately addressed by the BMS response letter. OSI considers the data acceptable in support of the respective indication.

PLEASE NOTE: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the field investigator, and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

10. PPD Development

3900 Paramount Pkwy
Morrisville, North Carolina 27560

a. What was Inspected: This was a high priority inspection in accordance with Compliance Program 7348.810. There were 1053 clinical investigator sites in 40 countries for the ARISTOTLE trial. The inspection focused on PPD monitoring activities at the eight clinical investigator sites referenced in the original assignment. BMS had responsibility for managing two of the eight sites selected to review. This included the two China sites, Site #1178 and Site #1200. During the inspection, the field investigator reviewed selected monitoring reports from six of the eight sites referenced in the assignment.

b. General observations/commentary: The field investigator reported that the monitoring reports appeared to be thorough and completed in accordance with the monitoring plan. Throughout the trial, weekly, biweekly, bimonthly, and quarterly meetings were held among team members to discuss the progress and issues regarding the study. The Core team consisted of PPD, BMS, IVRS, Lab and other individuals.

The field investigator reported that in China, BMS contracted with PPD to provide temporary site monitor staff to supplement BMS-China site monitor employees. PPD provided BMS with monitors at Site 1178 and Site 1200 in China, and these monitors reported directly to BMS management. According to BMS procedures, PPD was contracted to perform clinical monitoring, project management, data management, pharmacovigilance, and medical monitoring for BMS during the ARITOTLE trial. An electronic filing system called ESF was used to upload all trial related documents directly to BMS, and all official records were stored at the BMS offices. The inspection collected copies of documents that contained operational and site information used by PPD during the conduct of the ARISTOTLE study. In addition, they collected the following documents relevant to the site inspections:

- List of significant deviations for the eight inspected sites, including issues with informed consent and reporting SAEs on time.
- Summary of issues at Site 1606 (Gupta, India), such as delays in data entry, delays in responding to queries, and not reconsenting subjects in a timely manner; and a timeline for how PPD handled the listed issues.
- List of all Investigational Product issues noted during the monitoring visits. A description of these issues included things such as a wrong warfarin container given to the subject, or incorrect container number dispensed. At some sites, appropriate training was performed to site staff, and the investigators were instructed to contact the patient and ask the subject to stop taking IP from the wrongly assigned bottle and to return to the site to be given a new correct IP bottle. AEs were appropriately assessed.

OSI Reviewer Comment: For ARISTOTLE, study monitoring was provided by PPD in all countries except Russia, Ukraine and Israel. In China, BMS contracted with PPD to provide temporary site monitor staff to supplement BMS China Site Monitor employees. The monitors performed their study-related job responsibilities under the direction of BMS-China Site Managers. In China, the Senior Clinical Site Manager also provided support to the Clinical Site Managers to oversee the activities of the site monitors (PPD employees). In China, Ms. (b) (6) (as Site Manager) was the primary BMS contact with the site. She communicated with team members regarding study-related issues. Ms. (b) (6) reviewed site visit reports across all 36 sites in China between November 2008 and July 2011. Because she was a BMS employee, there was potential conflict of interest in her role as Site Manager in China.

c. Assessment of Data Integrity: No Form FDA-483 was issued during the inspection. In general, it appears that clinical monitoring was adequate for the ARISTOTLE trial overall. Records appeared complete and organized; the SOPs were adequate to ensure quality assurance throughout the trial. The data for this study may be considered acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Eight clinical investigator sites were inspected in support of this application (seven foreign and one domestic). In addition, a sponsor (BMS) inspection, a sponsor (BMS) re-inspection and a CRO (PPD) inspection were conducted.

Site 1301 (Vogel) and at Site 1742 (Zaidman) in South America, the inspections found that in general, they adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. A few instances were identified of failing to report non-serious AEs at the both sites, but the events were not significant, and not likely to impact overall safety efficacy.

Site 701 (Takacs) in Hungary had minor recordkeeping inaccuracies, and was classified as VAI, but in general the data was acceptable in support of the NDA.

The inspection at Site #796 (Kufs) in New York identified minor regulatory violations including enrollment of two subjects who did not meet inclusion criteria; and minor inconsistencies in IP accountability records. The inspection also cited Dr. Kufs for failing to report SAEs in a timely manner. However, in most cases, it appears that the subjects were hospitalized for their events, and Dr. Kufs was not directly notified. Once informed of the event, Dr. Kufs reported the event on that date. These findings are not likely to importantly impact data integrity.

OSI was notified by BMS on January 27, 2012, concerning allegations of suspected misconduct at Dr. Shiyao Wu's Site 1200 in Shanghai, China. Specifically, a PPD monitor (b) (6) alleged that documents may have been altered (under the direction of a BMS site manager (b) (6) in preparation for the upcoming FDA inspection at that site. It was also alleged that this BMS site manager (b) (6) intentionally withheld information of findings in order to influence the outcome of the inspection. In their Allegations of Suspected Misconduct Investigations Report (January 26, 2012), BMS states that the misconduct at Site 1200 was an isolated site-specific event which resulted in compromise of the data from Site 1200. BMS stated that appropriate disciplinary action was taken including termination of employment of three employees. Lastly, BMS would provide revised statistical analysis of the ARISTOTLE study to exclude data from Site 1200.

The FDA inspection at Site 1200 (Shiyao Wu, China) found that the PI did not exercise adequate control over the conduct of the study. This finding was evidenced by shared user accounts between subinvestigators, which might potentially compromise the integrity of the data. The FDA inspection also found that study coordinators frequently took home unsecured USB drives that contained patient data to enter into eCRFs because of the slow internet speed at the site. OSI considers that these two activities could have potentially compromised the integrity of the data at the site, and recommends the data not be used in the final analysis.

In addition, OSI received information from BMS that Ms. (b) (6) worked as Site Manager for the BMS ARISTOTLE study and she visited 18 of the 36 Chinese sites while the study was underway; that her duties included conduct of co-monitoring visits if needed, site recruitment/enrollment; resource needs, and following up on quality issues noted by the Site Monitor; and she reviewed site visit reports written by the site monitor. During pre-inspection visits, she reviewed study files and subject medical records and discussed issues with study personnel. The sites in China where Ms. (b) (6) worked were: 1180, 1182, 1199, 1206, 1207, 1221, 1223, 1246, 1247, 1266, 1547, 1548, 1549, 1550, 1552, 1555, 1556, and 1558. She worked on no sites outside China. As stated above, to prepare for the upcoming FDA inspections, Ms. (b) (6) worked at Sites 1200 and 1178. In addition, PPD employee (b) (6) (the PPD employee who admitted that he had altered data containing subject records on a USB drive at the direction of Ms. (b) (6) BMS site

manager) performed site monitoring responsibilities for the following Sites: 1200, 1198, 1168, 1244, and 1287.

The inspection of Site 0019 (Dr. Yao, Canada) was classified as VAI. This site had very high enrollment. The field investigators observed that Dr. Yao did not adhere to good GCP practices because he co-mingled his study records with his private practice records, and he post-dated entries in progress notes for some visits, often by several months. This means that Dr. Yao did not always review entries written in progress notes until several months later, and would then sign and date the progress notes on the date he read them. Though this is considered as poor GCP practice, it is not likely to have impacted data integrity. In general, the regulatory violations noted were isolated and not likely to impact data integrity.

The inspection at Site 1606 (Dr. Gupta, India) was classified as VAI. This site had very high enrollment. The main findings at this site were that the site knowingly maintained subjects at a low TTR. Once the sponsor became aware of the issues at this site, they provided additional training to Dr. Gupta and his staff on ways to improve INR management. OSI considers the data acceptable at this site.

The CRO PPD was inspected and no regulatory violations were found. The sponsor (Bristol-Myers Squibb) was inspected twice. The first inspection was a routine sponsor inspection, and minor regulatory violations were found. The second sponsor inspection was conducted to review issues of oversight and monitoring, medication dispensation errors, investigational product issues and potential for unblinding. Minor regulatory violations were found, but these violations did not appear to compromise the overall integrity of the data.

The inspectional findings found during inspections at one U.S. site (Site #796), and five non-U.S. sites (Sites 701, 1301, 1742, 1606, 0019) were minor, and OSI does not believe them likely to influence data integrity, study outcome or subject safety.

However, OSI recommends that the data from Site 1200 (Shiyao Wu, China) and Site 1178 (Shulin Wu, China) not be used in the final analysis. Although there were no significant inspectional findings at Site 1178, the possibility of fraud cannot be excluded. In addition, OSI recommends that data from the Chinese sites where either (b) (6) or Mr. (b) (6) worked be excluded from the study analysis. These are Sites 1168, 1178, 1180, 1182, 1198, 1199, 1200, 1206, 1207, 1221, 1223, 1244, 1246, 1247, 1266, 1287, 1547, 1548, 1549, 1550, 1552, 1555, 1556, and 1558. This is because of the allegations of fraud documented to occur at Site 1200 and the potential for misconduct at other sites within China where Ms. (b) (6) and or Mr. (b) (6) had monitoring oversight or conducted monitoring activities on site.

Overall, the study appears to have been conducted and monitored adequately, based on OSI inspectional findings. Although fraud at Site 1200 in China was well documented, there is no evidence that fraudulent activity occurred elsewhere. OSI has recommended that data from the above 24 sites in China be excluded because we cannot provide inspectional evidence to support data integrity and subject safety, given that the Ms. (b) (6) and Mr. (b) (6) worked at these sites. The remaining inspections of clinical investigators, CRO, and

sponsor did not reveal systemic evidence of inadequate monitoring or data integrity issues.

No regulatory violations were identified during the PPD inspection; and minor regulatory violations found during the Sponsor inspections. OSI recommends that the data submitted by Bristol Myers Squibb may be used in support of the respective indication.

{See appended electronic signature page}

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CONCURRENCE:

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

/s/

SHARON K GERSHON
05/18/2012

SUSAN D THOMPSON
05/18/2012

LAUREN C IACONO-CONNORS
05/18/2012

DSI CONSULT: Request for Clinical Inspections

Date: 5 March 2012

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Susan Thompson
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Martin Rose, M.D., JD, Medical Officer
Nhi Beasley, PharmD, Medical Officer
Stephen Grant, M.D., Cross-Discipline Team Leader
Norman Stockbridge, M.D., Ph.D., Division Director/ Division of
Cardiovascular & Renal Products

From: Alison Blaus, Regulatory Health Project Manager/ Division of
Cardiovascular & Renal Products

Subject: Request for Clinical Site Inspections

I. General Information

Application#: 202155

Applicant: Bristol-Myers Squibb

Applicant contact information:

Linda Gambone, Ph.D.

Associate Director

Global Regulatory Sciences, U.S. Liaison

Bristol Myers Squibb Research & Development

Office Phone: 609.252.3700

Fax: 609.252.6000

Cell phone: 609.213.4922

Email: linda.gambone@bms.com

Drug Proprietary Name: ELIQUIS

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Priority (+ Major Amendment)

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Eliquis is indicated for the prevention of stroke, systemic embolism, (b) (4)
in patients with non-valvular atrial fibrillation (b) (4)

PDUFA: 28 June 2012

Action Goal Date: 28 March 2012

Inspection Summary Goal Date: 28 February 2012

DSI Consult

version: 5/08/2008

II. Protocol/Site Identification

All sites are sites in the ARISTOTLE study in patients with atrial fibrillation, CV185030.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Bristol-Myers Squibb (Sponsor)			
PPD (CRO responsible for the monitoring of ARISTOTLE)			

III. Site Selection/Rationale

The rationale for re-inspecting the sponsor and inspecting the CRO are related. We would like to further understand the medication errors in the trial, ARISTOTLE, and the quality/adequacy of the CRO and sponsor monitoring during the trial. We also want to further assess the impact of these medication errors and whether the apparent lack of adequate medication monitoring indicates inadequate monitoring of other aspects of the trial.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results and safety results pertinent to decision-making: excess deaths, bleeding, or primary efficacy events (strokes and systemic emboli) in the control arm.
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Please see section IV. Related to Data quality issues detailed in the sponsor's 10Feb12 and 21Feb12 submissions.

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify).

IV. Tables of Specific Data to be Verified (if applicable)

Please inspect the following materials regarding the ARISTOTLE study (CV185030):

1. The monitoring plan for ARISTOTLE originally provided for the original tear-off panel from the medication bottle labels to be collected by the monitors and sent to BMS, but the plan was amended in 2009, about midway through the study. (These panels are usually referred to as “labels”.) After the amendment, the original labels were kept at the sites. Please ask why this change was made. Is there any documentation of the rationale for this change?
2. For the original labels that are at BMS, please characterize why only these were obtained from the sites while other original labels pulled from bottles before the change in the monitoring plan in 2009 were retained at the sites.
3. Labels that BMS states are illegible. The sponsor indicates that there are 187 illegible labels (Excel spreadsheet of illegible labels is attached. The file includes the site id and subject ID). Are they illegible? How difficult is it to read the bottle number? The sponsor states that if the label had a handwritten number or if it was torn then it was considered illegible, but the sponsor appears to not provide all reasons for “illegibility”. Can you tell if there are labels deemed illegible that do not fit the sponsor’s definition of illegible? Can you determine when the number was handwritten onto the label- at the manufacturer or at investigative sites (suggesting that an investigator wrote the number on the bottle)? Can you tell what was supposed to be in the bottle (warfarin or apixaban 2.5 mg or apixaban 5 mg or matching placebo - you should not be able to tell active from placebo, but the label might state for example warfarin 2 mg or placebo)?
4. The sponsor’s label data set (LBL030) contains a total of **35,859** legible labels. The sponsor used single data entry to create this data set. Please spot check a handful of the subject’s labels. We suggest that you concentrate on warfarin/placebo bottle labels since the text on these labels are smaller than the apixaban/placebo labels, and thus may be more difficult to read. Note that we can provide you with the entire database or just select subjects.
5. Determine the total number of labels the sponsor has. They do not report this number. BMS reports that they have **35,859** legible labels, but they did not report the total number of labels.
6. Examine the log of study drug shipment to sites. What was the process for maintaining this log? It was during the sponsor’s comparison of the log, to the list of subject transfers between sites and the clinical database that the sponsor asserts transcription errors occurred in the clinical database. That is, the log of study drug shipment to sites indicated that a particular container number was never at the site, even though the clinical database stated that a subject received that container.
7. Attempt to determine when medication errors were detected. Was the sponsor aware of these errors during the time data was being collected? If so, what was the sponsor’s response and why did the sponsor not alter the dispensing or packaging of the treatments? If the medication errors were detected during the time data cleaning and reconciliation, why weren’t the errors detected during the trial? Please provide insight on the adequacy of the monitoring by both the CRO and sponsor.
8. We are concerned that the apparent lack of adequate medication monitoring might also indicate inadequate monitoring of other important aspects of this event driven trial. The BMS investigational report at site 1200 in China indicates that there might have been some unreported important events (4 subjects with SAEs, 2 subjects with bleeds, 1 subject with an MI and 1 subject with a stroke). The report also states that there were some inconsistencies in SAE reports versus eCRF and unreported

Page 4-Request for Clinical Inspections

AEs that were in the inpatient charts.) Please examine the CRO's and sponsor's medical monitoring of SAEs and primary outcome events (stroke, major bleeds, and MI). Did it seem adequate and did they follow their proposed protocol for medical monitoring of ARISTOTLE?

Should you require any additional information or clarification of the above, please contact Alison Blaus at 301-796-1138 or Martin Rose at 301-796-1957.

Concurrence: (as needed)

_____ Cross-Discipline Team Leader
_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

SITEID	SUBJID	DCONTN
26	951	U
26	3856	u
125	137	u
228	1937	u
228	12567	u
231	833	u
231	1247	u
231	2624	u
231	3039	u
231	3039	u
231	4076	u
231	4606	u
237	6725	U
237	9384	U
244	8535	U
245	1961	U
245	2135	U
245	2135	U
245	2549	U
245	12885	U
247	755	U
247	4732	U
247	4735	U
248	651	U
248	3725	U
248	4014	U
248	4014	U
250	1176	U
250	2081	U
250	3950	U
260	2756	U
404	1659	U
404	1659	u
404	1659	u
404	2267	U
404	2267	U
404	2724	u
404	4776	u
404	4776	u
404	6129	u
404	8790	u
404	8790	u
404	10733	u
404	10733	u
404	11343	U
404	11343	u
422	5781	u
462	929	U
462	1371	U

SITEID	SUBJID	DCONTN
462	1635	U
462	2075	U
462	2694	U
560	962	u
565	1518	U
565	8622	U
565	14825	U
579	7271	U
579	7271	U
613	4137	u
616	2942	U
616	3204	U
616	9610	U
667	4526	U
669	781	U
669	844	U
669	1418	U
669	2789	U
698	2056	U
744	6028	U
757	1221	U
757	1928	U
757	2301	U
757	2763	U
757	6439	U
757	6999	U
757	10560	U
757	12886	U
800	4905	u
800	5489	U
852	1359	U
852	4304	U
872	932	U
872	1104	U
872	1504	U
872	1884	U
872	1884	U
872	1921	U
872	2386	U
872	2387	U
872	2387	U
872	2657	U
872	6294	U
872	6295	U
872	6648	U
872	6795	U
872	8856	U
872	13673	U
893	444	U
931	1166	u

SITEID	SUBJID	DCONTN
931	3515	u
931	3728	u
931	6191	U
958	214	u
1092	491	u
1092	622	u
1106	1264	u
1106	1264	u
1204	2861	u
1213	2117	U
1213	2121	U
1213	2229	U
1213	2922	U
1213	3283	U
1213	3495	U
1213	4647	u
1213	4665	U
1214	2867	U
1214	5404	U
1214	10568	U
1214	11232	U
1214	11896	U
1214	15144	U
1215	2322	U
1237	3226	U
1237	3226	U
1237	6535	U
1237	7076	U
1256	8373	U
1256	8373	U
1259	3026	U
1260	6332	U
1261	3560	U
1261	12132	U
1267	2269	U
1267	3554	U
1267	3554	U
1267	10629	U
1270	2366	U
1270	11006	U
1270	11007	U
1270	12303	U
1274	3016	U
1274	3829	U
1274	4299	U
1274	8275	U
1274	8275	U
1274	8281	U
1274	8374	U
1275	2543	U

SITEID	SUBJID	DCONTN
1275	8067	U
1275	11598	U
1295	8454	U
1295	9473	u
1296	6086	U
1296	13439	U
1314	4885	U
1314	9716	U
1318	3469	u
1318	3469	u
1318	5450	u
1318	5450	u
1318	13310	U
1351	6792	U
1351	7989	U
1351	12452	U
1351	13186	U
1541	6519	U
1541	7073	U
1542	6662	U
1545	8495	U
1545	10470	U
1545	15426	U
1606	7517	u
1606	7837	u
1606	9106	u
1607	13650	u
1716	16367	U
1746	9554	U
1746	10682	U
1769	11089	U
1769	11917	U
1769	13009	U
1769	13433	U
1769	13625	U
1769	14231	U
1769	15078	U

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/s/

ALISON L BLAUS
03/07/2012

MARTIN ROSE
03/07/2012

STEPHEN M GRANT
03/07/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 202155

Name of Drug: ELIQUIS (apixaban) Tablets

Applicant: Bristol-Myers Squibb

Labeling Reviewed

Submission Date: 20 September 2011

Receipt Date: 28 September 2011

Background and Summary Description

NDA 202155 provides information in support of the following indication:

ELIQUIS® (apixaban) is indicated to reduce the risk of stroke, systemic embolism, (b) (4) in patients with nonvalvular atrial fibrillation (u) (4)

Please see the previous pages of the RPM Filing Review for relevant regulatory history and information regarding the pivotal Phase 3 trial, ARISTOTLE.

REVIEW

The submitted labeling referenced above was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review (Attachment 1). No labeling deficiencies were identified.

The following “non-SRPI” labeling issues were identified, however. These issues were identified by OSE (DMEPA – Forest Ford), ONDQA (Charles Jewell) and myself. These issues were communicated to the applicant as part of the 74-day letter (dated 8 Dec 2011):

1. To improve readability, in **HIGHLIGHTS** under **DOSAGE AND ADMINISTRATION**, please bullet each dose and its corresponding information.
2. For clarity, please define all abbreviations and acronyms upon its first appearance in the Full Prescribing Information (FPI).
3. When writing numbers with symbols or units, insert a space between the number, symbol, or unit for better readability. For example revise “2.7%” to read “2.7 %” and “81mg” to “81 mg”. In addition, provide each unit of measure with each number.

4. Please consider stating numbers greater or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100”.
5. Please delete the registered trademark symbol, “®”, that appears after every “ELIQUIS” throughout the FPI. The registered trademark symbol is acceptable only once in FPI and it already appears in Section 1.
6. In the **DOSAGE AND ADMINISTRATION** subsection 2.1, Recommended Dose does not state that Eliquis (apixaban) is scored or is intended to be divided or split in half. Since the tablets are not scored, revise to statement “Eliquis (apixaban) 5 mg tablets and Eliquis (apixaban) 2.5 mg tablets are to be swallowed whole and not crushed or chewed. Dosage will be individualized based on individual patient medical needs.”
7. Please delete subsection 2.7, Pediatric and Adolescent. Since there is no recommendation to provide for this patient population, please only note this in Section 8, **SPECIFIC POPULATIONS**.
8. In Section 4, **CONTRAINDICATIONS**, please list only known hazards and not theoretical possibilities (i.e., (b) (4) If the contraindication is not theoretical, describe the type and nature of the adverse reaction. Also, if there is a listed Contraindication, there must be an analogous subsection in **WARNINGS AND PRECAUTIONS** (Section 5). Therefore, if you believe that this is not a theoretical concern, please add a new warning.
9. Per 21 CFR 201.57, if there have been no studies in the pediatric patient population, subsection 8.4 should read as follows verbatim:

“Safety and effectiveness in pediatric patients have not been established”
10. In Section 16, **HOW SUPPLIED/STORAGE AND HANDLING**, please list all packaging options, including DNC numbers. For example, please also list the Hospital Unit Dose labels for blister packs.

CONCLUSIONS/RECOMMENDATIONS

No SRPI deficiencies were identified in the review of this labeling. All other issues identified above were conveyed to the applicant in the 74-day letter. The applicant was asked to resubmit labeling that addresses all identified labeling deficiencies by 27 December 2011. The resubmitted labeling will be used for further labeling discussions.

Alison Blaus

Regulatory Project Manager

Date

Edward Fromm

Chief, Project Management Staff

Date

Attached: Selected Requirements for Prescribing Information (SRPI)

Attachment 1: Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)

<ul style="list-style-type: none">• Patient Counseling Information Statement (required statement)
<ul style="list-style-type: none">• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**
 - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) ~ 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) -- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
[http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.h
tm.](http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm)

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., (b) (4)). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**
 - A horizontal line must separate the TOC and FPI.
 - The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
 - The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).
- **Boxed Warning**
 - Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for

the text.

- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

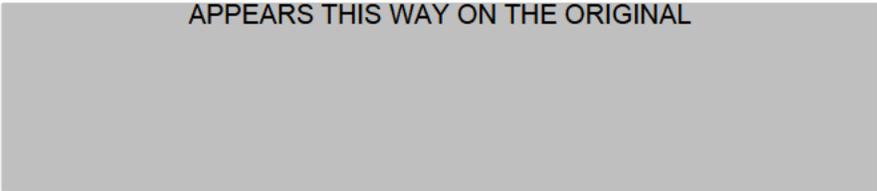
- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

ALISON L BLAUS
12/08/2011

Executive CAC

Date of Meeting: November 29, 2011

Committee: David Jacobson-Kram, Ph.D., OND-IO, Chair
Abigail Jacobs, Ph.D., OND-IO, Member
Paul Brown, Ph.D., OND-IO, Member
Dan Mellon, Ph.D., DAAAP, Alternate Member
Thomas Papoian, Ph.D., DCRP, Supervisor
Patricia Harlow, Ph.D., DCRP, Reviewer

Presenting Reviewer: Patricia Harlow, Ph.D.

Author of Draft: Patricia Harlow, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA: 202-155

Drug Name: Apixaban (BMS 562247)

Sponsor: Bristol Myers Squibb Company and Pfizer

Background:

Apixaban is a direct Factor Xa inhibitor. In the Phase 3 trial for prevention of stroke in patients with non-valvular atrial fibrillation, the daily apixaban dose was 10 mg (5 mg BID). Although the cancer bioassays used multiple apixaban lots that differed in particle size distribution and process used for synthesis, the apixaban in all these lots was (b) (4) form of apixaban.

Rat Carcinogenicity Study:

Sprague Dawley rats (60/sex/group) received daily oral doses of 0, 50, 200, and 600 mg/kg/day of apixaban administered through the diet to males for 104 weeks and to females for 97-100 weeks. The total exposures to apixaban in the high dose males and females were 5.4 and 9.4 fold, respectively, the mean total exposure in patients receiving the recommended human dose (RHD) of 5 mg BID. However, the exposures to unbound apixaban in male and female rats were 1.6 and 3.4 fold the exposure to unbound drug in patients receiving the RHD.

No significant treatment-related effects were observed on mortality, bodyweight gain, and food consumption. However, the mean body weight and body weight gain decreased up to 10% and 15%, respectively, in the high dose male group compared to the control group from Weeks 60 to 104. Some statistically significant non-neoplastic findings, such as increased extramedullary hematopoiesis, increased pigment, and decreased thrombosis are consistent with the pharmacodynamic effect of apixaban as a Factor Xa inhibitor.

The incidences of malignant lymphoma, a common tumor, displayed a tendency to increase with dosage in both male and female rats. However, in neither sex was either the trend or the pairwise comparison between the concurrent control and the high dose animals found to be statistically significant by CDER criteria.

Mouse Carcinogenicity Study:

CD-1 mice (60/sex/group) received daily oral doses of 0, 10, 20, and 60 mg/kg/day of apixaban administered through the diet for 104 weeks. The total exposures to apixaban in the high dose males and females were 2.4 and 5.4 fold, respectively, the mean total exposure in patients receiving the RHD. However, the exposures to unbound apixaban were 8.8 and 20.1 fold the mean exposure to unbound drug in patients receiving the RHD.

No significant treatment-related effects was observed on mortality, bodyweight gain or food consumption. However, the high dose female group gained approximately 10% less bodyweight than the control group from Week 6 through 76. Although the incidences of convulsions, reported as being similar to the laboratory historical incidence, were not related to apixaban treatment, the high incidence in untreated control mice, particularly in males, was considered unusual in this study. The non-neoplastic findings of extramedullary hematopoiesis in the liver in male mice and hemorrhage in the thymus of female mice are consistent with the pharmacodynamic effect of apixaban as a factor Xa inhibitor.

The incidences of a few tumors increased in the higher dose groups compared to those in the control groups. The incidence of Schwannoma (nerve sheath tumor) was numerically increased in the mandibular salivary gland of high dose males; however, the p value (0.027) for this tumor in the trend test did not attain the significance level of $p_t < 0.025$ required for a rare tumor to be considered positive. The incidence of the combination of hemangiomas and hemangiosarcomas ($p_t = 0.0487$), uterine/cervical glandular polyps alone ($p_t = 0.0230$), and the combination of uterine/cervical glandular polyps and adenocarcinomas ($p_t = 0.0081$) were numerically increased in high-dose females. However, none of these tumors had a p-value that attained the significance level of $p < 0.005$ required for a common tumor to be considered positive according to CDER statistical criteria. Therefore, no statistically significant neoplastic finding was related to apixaban treatment under the conditions of this study.

Executive CAC Recommendations and Conclusions:

Rat:

The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the protocol.

The Committee concurred that there were no clearly drug-related neoplasms.

Mouse:

The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the protocol.

The Committee concurred that there were no clearly drug-related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

/Division File, DCRP
/T. Papoian, Supervisor, DCRP
/P. Harlow, Reviewer, DCRP
/A. Blaus, CSO/PM, DCRP
/A.Seifried, OND-IO

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/s/

ADELE S SEIFRIED
12/01/2011

DAVID JACOBSON KRAM
12/01/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: November 18, 2011

Reviewer(s): Ray Ford, RPh, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader Lubna Merchant, PharmD, MS, Team Leader
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh, Division Director
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength: Eliquis (Apixaban) Tablets 2.5 mg and 5 mg

Application Type/Number: NDA 202155

Applicant/sponsor: Bristol-Myers Squibb

OSE RCM #: 2011-3740

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This review evaluates the proposed container labels, carton labeling, and insert labeling for Eliquis (apixaban) 2.5 mg and 5 mg tablets (NDA 202155). This review is in response to a request from the Division of Cardiovascular and Renal Products (DCRP).

1.1 BACKGROUND OR REGULATORY HISTORY

Eliquis (apixaban) 2.5 mg and 5mg tablets are a New Molecular Entity (NME). The applicant and the Food and Drug Administration (FDA) agreed on August 12, 2010 to the proposal for a “rolling submission” of reviewable units for Eliquis (apixaban) 2.5 mg and 5 mg tablets (NDA 202155). The proposed proprietary name, Eliquis was found acceptable in OSE review 2010-654 (IND-066106). The proprietary name is being re-evaluated as an NDA in OSE review 2011-3740.

1.2 PRODUCT INFORMATION

Eliquis (apixaban) is a factor Xa inhibitor (anticoagulant) indicated to reduce the risk of stroke, systemic embolism, (b) (4) in patients with nonvalvular atrial fibrillation. Eliquis (apixaban) is supplied as 2.5 mg and 5 mg tablets. The recommended dose of Eliquis (apixaban) is 5 mg taken orally twice daily. In patients with at least 2 of the following characteristics: age greater than or equal to 80 years, body weight less than or equal to 60 kg, or serum creatinine greater than or equal to 1.5 mg/dL (133 µmol/L), the recommend dose of Eliquis (apixaban) is 2.5 mg orally twice daily. Eliquis (apixaban) does not require monitoring. There is no antidote for Eliquis (apixaban). A medication guide is required when a patient receive a prescription for Eliquis (apixaban) under the Risk Evaluation and Mitigation Strategies (REMS) program.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted September 28, 2011
- Carton Labeling submitted September 28, 2011
- Professional Sample Carton and Blister unit labeling submitted September 28, 2011
- Insert Labeling submitted September 28, 2011

3. CONCLUSIONS AND RECOMMENDATIONS

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

The proposed label and labeling introduce vulnerability that can lead to medication errors. The established name, strength, and medication guide statement are not prominent. In addition, error-prone abbreviations, symbols, acronyms are used throughout the labeling. We advise that the following recommendations be implemented prior to approval:

A. General Comments:

Since all packaging configurations are not unit of use, ensure that enough medication guides are provided such that the dispenser can be provide one medication guide with each new or refilled prescription in accordance with 21 CFR 208.24(b) (1).

B. Container Label for 2.5 mg and 5 mg (60 count and 180 count)

1. Revise the presentation of the proprietary name from all upper case letters (ELIQUIS) to title case (Eliquis) to improve readability.
2. The graphic design above the proprietary name is too prominent and distracting. Decrease the prominence of the graphic design to optimize readability.
3. We note that the established name is half the size of the proprietary name. However, the established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors including typography, layout, contrast and other printing factors in accordance with 21 CFR 201.10(g) (2).
4. Revise the presentation of the dosage form so that it is commensurate with the prominence of the active ingredient (established name).
5. The 2.5 mg and 5 mg strengths are not well differentiated from each other. The (b) (4) colors are prominent on each label minimizing the strength differentiation.. For example the color used for the established name is (b) (4) which appears on both the 2.5 mg and 5 mg label. The same (b) (4) color is used to differentiate the 2.5 mg strength. Similarly, the color used for the proprietary name of the 5 mg is identical to the color used for the strength presentation and the same (b) (4) color is used on the 2.5 mg label. This minimizes the contrast between the 2.5 mg and 5 mg strength. To avoid selection errors, revise the labels to provide more visual differences between the two strengths by using unique colors for each strength.
6. Decrease the prominence of “Rx only” and remove boxing around “Rx only” on the Primary Display Panel (PDP).

C. Unit Dose Carton Labeling (2.5 mg and 5 mg)

1. See comment in B 1 through B 5 above.
2. Ensure the lot and expiration date are included on the carton label in accordance with 21 CFR 201.17 and 21 CFR 201.18

D. Hospital Unit-Dose Blister Card labels (2.5 mg and 5 mg)

1. The 2.5 mg and 5 mg hospital unit dose labels blister cards are identical in appearance. There is no distinguishing typography or color that differentiates the two strengths. In a hospital setting the unit dose blisters do not always remain in the unit dose carton provided. To avoid selection errors, provide adequate visual difference between the 2.5 mg and 5 mg strengths.

E. Professional Sample Carton Labeling (5 mg)

1. See comment B (1), (2), and (3) above.
2. Remove or reduce the prominence of the graphic design from the lower one-third of the primary display panel. This distracts from “DISPENSE MEDICATION GUIDE TO EACH PATIENT” statement.

F. Professional Sample Blister Card (5 mg)

1. Professional samples are dispensed to patients for use at home. DMEPA recommends using containers compliant with the Poison Prevention Protection Act (PPPA) designed with Child Resistant Closures (CRC). This may help mitigate exposure of children to this medication when used in the home setting.

G. Insert Labeling

1. General Comments:

The applicant has used throughout the HIGHLIGHTS OF PRESCRIBING INFORMATION, and FULL PRESCRIBING INFORMATION error prone abbreviations. The symbols $<$, \leq , $>$, \geq were utilized in the insert labeling to represent “less than,” “less than or equal to,” “greater than,” or “greater than or equal to,” respectively. These symbols can be misinterpreted as the opposite of the intended symbol or mistakenly used as the incorrect symbol. In particular, a “ < 10 ” can be misread as “40.” As part of a national campaign to decrease the use of dangerous symbols², the FDA agreed not to use such error-prone symbols in the approved labeling of products because these abbreviations can be carried over to prescribing. Therefore, DMEPA recommends that $<$ be replaced with “less than,” \leq be replaced with “less than or equal to,” $>$ be replaced with “greater than,” and \geq be replaced with “greater than or equal to.”

2. Define all abbreviations and acronyms for clarity.
3. When writing numbers with symbols or units, insert a space between the number, symbol, or unit for better readability. For example revise “2.7%” to read “2.7 %” and “81mg” to “81 mg”. In addition, provide each unit of measure with each number.

² Institute for Safe Medication Practices (ISMP). ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP: 2010

4. Consider stating numbers greater or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100”.
5. In the DOSAGE AND ADMINISTRATION section 2.1 Recommended Dose does not state that Eliquis (apixaban) is scored or is intended to be divided or split in half. Since the tablets are not scored, revise to state “Eliquis (apixaban) 5 mg tablets and Eliquis (apixaban) 2.5 mg tablets are to be swallowed whole and not crushed or chewed. Dosage will be individualized based on individual patient medical needs.”

If you have further questions or need clarifications, please contact OSE Regulatory Project manager, Phuong Nina Ton, at 301-796-1648.

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

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/s/

FOREST R FORD
11/18/2011

LUBNA A MERCHANT
11/21/2011

CAROL A HOLQUIST
11/22/2011

DSI CONSULT: Request for Clinical Inspections

Date: 14 November 2011

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Susan Thompson
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Martin Rose, M.D., JD, Medical Officer
Nhi Beasley, PharmD, Medical Officer
Stephen Grant, M.D., Cross-Discipline Team Leader
Norman Stockbridge, M.D., Ph.D., Division Director/ Division of
Cardiovascular & Renal Products

From: Alison Blaus, Regulatory Health Project Manager/ Division of
Cardiovascular & Renal Products

Subject: Request for Clinical Site Inspections

I. General Information

Application#: 202155

Applicant: Bristol-Myers Squibb

Applicant contact information:

Linda Gambone, Ph.D.

Associate Director

Global Regulatory Sciences, U.S. Liaison

Bristol Myers Squibb Research & Development

Office Phone: 609.252.3700

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Drug Proprietary Name: ELIQUIS

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Eliquis is indicated for the prevention of stroke, systemic embolism, (b) (4)
in patients with non-valvular atrial fibrillation. (b) (4)

PDUFA: 28 March 2012

Action Goal Date: 28 March 2012

Inspection Summary Goal Date: 28 February 2012

DSI Consult

version: 5/08/2008

II. Protocol/Site Identification

All sites are sites in the ARISTOTLE study in patients with atrial fibrillation, CV185030.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
<p>#0701 Janos Takacs, MD Orszagos Gyogyszereszeti Intezet Zrinyi U. 3. Budapest 1051 Hungary</p> <p>P: 3696574742 F: 3696575762 E: [REDACTED] (b) (6)</p>			
<p>#1301 Daniel Raul Vogel, MD Instituto De Investigaciones Clin.as Bahia Blanca (Office) Av. Colon 305 Bahia Blanca, Buenos Aires B8000FTD</p> <p>P: 5492914076594 F: 542914545379 E: DVOGEL@INFOVIA.COM.AR Argentina</p>			
<p>#1742 Cesar Javier Zaidman, MD Ciprec (Office) Av. Pueyrredon 1746, 2 A Buenos Aires, Buenos Aires 1119 Argentina</p> <p>P: 5491144074402 F: 541148229891 E: cjz@ciprec.org</p>			

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
<p>#1606 Sandeep Kumar Gupta, MD Mv Hosp. & Res. Centre (Office) 314/30 Mirza Mandi Chowk Lucknow 226003 India</p> <p>P: 919336077839 F: 915224016051 E: sandeepkumar.gupta@rediffmail.com</p>			
<p>#0019 Louis C.H. Yao, MD Dr Louis Yao's Office (Office) 230-1920 Weston Road Weston, ON M9N 1W4 Canada</p> <p>P: 4162417119 F: 4162412623 E: [REDACTED] (b) (6)</p>			
<p>#0796 William Kufs, MD Saratoga Cardio. Assoc., Pc (Office) 6 Care Lane Saratoga Springs, NY 12866 United States Of America</p> <p>P: 5186930142 F: 5186930112 E: wkufs@saracard.com</p>			
<p>#1178 Shulin Wu, MD Guangdong General Hosp. (Office) No. 106, The 2nd Zhongshan Road Guangzhou, Guangdong 510080 China</p> <p>P: 862083875453 F: 862083875453 E: [REDACTED] (b) (6)</p>			

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
<p>#1200 Shiyao Wu, MD Shanghai 9th Peoples Hosp. Affiliated To S. J.T. U. S. M. (Office) No.639,Zhi Zao Ju Road Shanghai, Shanghai 200011 China</p> <p>P: 862163088657 F: 862163088657 E: (b) (6)</p>			

III. Site Selection/Rationale

The rationale for selecting individual sites is provided in the table above. The rationale for these sites varied. Some sites were selected because of low site time in warfarin therapeutic range. At these sites, we would like to know whether the site was following the study procedures directed at maintaining INR in the therapeutic range, and if the sponsor attempted to educate the sponsor on how to do that or responded in some way to the site’s poor performance. Some sites were selected because of imbalances favoring apixaban in key study parameters.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results and safety results pertinent to decision-making: excess deaths, bleeding, or primary efficacy events (strokes and systemic emboli) in the control arm.
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): low time in therapeutic range for Warfarin,

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify). Largest enrollment, low TTR, asymmetric occurrence of primary outcome events between study arms, high incidence of major bleeding (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include several foreign sites in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites (delete this if it does not apply):

We have requested these sites for inspection (international and/or domestic) because of the one or more of the following reasons: low time in therapeutic range, high rate of warfarin arm bleeding and/or death, and high rate of warfarin arm primary endpoint events. *state reason(s) and prioritize sites.*

ARISTOTLE had over 18,000 subjects at more than 1000 sites globally. Potential problem sites tended to be outside the US. The eight requested sites will cover a tiny fraction of enrolled subjects. The attached spreadsheet describes the reasons for the selection of each site. We have tried to select sites to make travel efficient by grouping sites in distant regions (i.e., 2 sites in China and 2 in Argentina).

Priority of sites:

- 1. 1606**
- 2. 1301**
- 3. 1178**
- 4. 1742**
- 5. 1200**
- 6. 0796**
- 7. 0019**
- 8. 0701**

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

Please contact Dr. Rose for specific data to be reviewed at the investigational sites.

Should you require any additional information, please contact Alison Blaus at 301-796-1138 or Martin Rose at 301-796-1957.

Concurrence: (as needed)

_____ Cross-Discipline Team Leader
_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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

/s/

ALISON L BLAUS
11/16/2011

MARTIN ROSE
11/16/2011

STEPHEN M GRANT
11/16/2011

NORMAN L STOCKBRIDGE
11/17/2011