CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202155Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2013
See OMB Statement on Page 3.

NDA NUMBER
202155

NAME OF APPLICANT/NDA HOLDER
Bristol-Myers Squibb Company

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ELIQUIS

ACTIVE INGREDIENT(S)	STRENGTH(S)
Apixaban	2.5 mg 5 mg

DOSAGE FORM
Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,967,208 B2	November 22, 2005	February 3, 2023

d. Name of Patent Owner	Address *(of Patent Owner)*	
Bristol-Myers Squibb Company	P.O. Box 4000	
	City/State: Princeton, New Jersey	
	ZIP Code: 08543-4000	FAX Number *(if available)*
	Telephone Number: (609)252-4000	E-Mail Address *(if available)*: patents@bms.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Graphics (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?		
10-12, 34-57, 59, 106-108, 110		☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* The Indications and Usage section of the proposed label includes that ELIQUIS is indicated to reduce the risk of stroke, systemic embolism, (b) (4) in patients with nonvalvular atrial fibrillation, which is covered by the recited claims.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Jing G Sun	Aug. 18, 2011

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Jing G. Sun	
Address To the attention of V.P. and Chief Patent Counsel Route 206 & Provinceline Rd., P. O. Box 4000	City/State Princeton, New Jersey
ZIP Code 08543-4000	Telephone Number
FAX Number *(if available)* (609)252-4526	E-Mail Address *(if available)* patents@bms.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted.** Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

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NDA NUMBER
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NAME OF APPLICANT/NDA HOLDER
Bristol-Myers Squibb Company

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ELIQUIS

ACTIVE INGREDIENT(S)	STRENGTH(S)
Apixaban	2.5 mg 5 mg

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FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,413,980 B1	July 2, 2002	December 22, 2019

d. Name of Patent Owner	Address *(of Patent Owner)*	
Bristol-Myers Squibb Company	P.O. Box 4000	
	City/State: Princeton, New Jersey	
	ZIP Code: 08543-4000	FAX Number *(if available)*
	Telephone Number: (609)252-4000	E-Mail Address *(if available)*: patents@bms.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Jing G. Sun	Aug. 18, 2011

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Jing G. Sun	
Address To the attention of V.P. and Chief Patent Counsel Route 206 & Provinceline Rd., P. O. Box 4000	City/State Princeton, New Jersey
ZIP Code 08543-4000	Telephone Number
FAX Number *(if available)* (609)252-4526	E-Mail Address *(if available)* patents@bms.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

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- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 202155 SUPPL # n/a HFD # 110

Trade Name: ELIQUIS

Generic Name: apixaban

Applicant Name: Bristol-Myers Squibb

Approval Date, If Known: Exact Date Not Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

n/a

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

n/a

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Five

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

n/a

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# n/a

NDA# n/a

NDA# n/a

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# n/a

NDA# n/a

NDA# n/a

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ NO ☐
Explain:

Investigation #2

IND # YES ☐ NO ☐
Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐ NO ☐
Explain: Explain:

Investigation #2

YES ☐ NO ☐
Explain: Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Alison Blaus, RAC
Title: Regulatory Health Project Manager
Date: 26 December 2012

Name of Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Division Director, Cardiovascular & Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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
12/26/2012

NORMAN L STOCKBRIDGE
12/26/2012

Blaus, Alison

From: Greeley, George
Sent: Friday, December 09, 2011 9:40 AM
To: Blaus, Alison
Cc: Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Stockbridge, Norman L
Subject: NDA 202-155 Eliquis

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi Alison,

The email serves as confirmation of the review for Eliquis (Apixaban) product conducted by the PeRC PREA Subcommittee on December 7, 2011.

The Division presented a full waiver in patients for the indication of prevention of stroke or systemic associated with atrial fibrillation because the disease/condition does not exist in children.

The PeRC agreed with the Division to grant a full waiver for this product.

The pediatric record is attached for Eliquis.

1_Pediatric_Record .pdf (64 KB)...

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

NDA 202155

APIXABAN (BMS-562247)

CERTIFICATION: DEBARRED PERSONS

Bristol-Myers Squibb Company and Pfizer hereby certify that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Linda Gambone

10-5-11

Linda Gambone, Ph.D.
Associate Director
Global Regulatory Sciences, U.S. Liaison
Bristol-Myers Squibb Company
P.O Box 4000
Princeton, NJ 08543
linda.gambone@bms.com
(609) 252-3700

Certification Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 202155 BLA # n/a	NDA Supplement # n/a BLA Supplement # n/a	If NDA, Efficacy Supplement Type: n/a
Proprietary Name: ELIQUIS Established/Proper Name: apixaban Dosage Form: 2.5 & 5 mg Tablets		Applicant: Bristol-Myers Squibb Agent for Applicant (if applicable): n/a
RPM: Alison Blaus		Division: Cardiovascular & Renal Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 17 March 2013	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR 22 June 2012

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): NME

☐ Fast Track
☒ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☒ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments: MedGuide is part of labeling, not the REMS

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) CR: 22 June 2012 AP: 28 December 2012
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Included
• Original applicant-proposed labeling	Included
• Example of class labeling, if applicable	n/a

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Included
• Original applicant-proposed labeling	Included
• Example of class labeling, if applicable	n/a
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Included Letter: 22 December 2011 Review: 19 December 2011, 4 April 2012 & 22 October 2012
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA Carton/Container: 22 November 2011 & 26 October 2012 ☒ DMPP/PLT (DRISK) 29 June 2012, 20 December 2012, & 28 December 2012 ☒ ODPD (DDMAC) 28 June 2012 & 10 December 2012 (see also patient labeling reviews) ☐ SEALD ☐ CSS ☒ Other reviews Patient labeling: 31 July 2012 & 7 December 2012
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	Included
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 7 December 2011 If PeRC review not necessary, explain: n/a • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg CR Letter Mtg: 2 August 2012
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 12Aug10 (AVERROES pre-NDA), 24Jan11 (AVERROES Topline), 4May11 (ARISTOTLE pre-NDA), 18Jul11 (ARISTOTLE Topline)
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 2 October 2006
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	n/a
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	n/a
• 48-hour alert or minutes, if available *(do not include transcript)*	n/a
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 22 June 2012 & 28 December 2012
Division Director Summary Review *(indicate date for each review)*	☐ None See CDTL Review (for 1st cycle) & 28 December 2012 (for 2nd cycle)
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 22 June 2012 (1st cycle only)
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ None
• Clinical review(s) *(indicate date for each review)*	2 November 2011, 22 May 2012, 11 June 2012, 22 June 2012, 10 December 2012, 11 December 2012, 17 December 2012, and 21

[6] Filing reviews should be filed with the discipline reviews.

	December 2012
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See 22 May 2012 clinical review n/a
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	3 February 2012 (REMS Request Memo & Letter) ☐ None DRISK REMS Reviews: 29 June 2012 & 20 December 2012 & 28 December 2012
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 18 May 2012
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None Co-signed Stats Review
Statistical Review(s) *(indicate date for each review)*	☐ None 1 May 2012
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None Co-signed Clinical Pharmacology Review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 15 February 2012 and 17 December 2012
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 21 June 2012
• Supervisory Review(s) *(indicate date for each review)*	☐ None Co-signed primary Pharmacology/Toxicology Review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 1 November 2011 (two), 21 February 2012, 13 April 2012, and 16 May 2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 15 February 2012
❖ ECAC/CAC report/memo of meeting	☐ None 1 December 2011 Included in P/T review, page: Yes
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 22 June 2012
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 7 November 2011, 8 November 2011, 7 December 2011, 15 February 2012, 28 February 2012, 18 May 2012, and 22 June 2012
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	15 February 2012
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 27 March 2012 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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
12/28/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

GENERAL ADVICE

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for ELIQUIS (apixaban) Tablets.

We also refer to your February 14, 2012 submission, containing revised carton and container labeling in response to our February 1, 2012 advice letter.

We have reviewed the above referenced material and have the following additional comments:

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 dates are included on all container labels and carton labeling in accordance with 21 CFR 201.17 and 21 CFR 201.18.

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

- 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.

Professional Sample Carton Labeling (5 mg)

- 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 any questions, please call:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

ALISON L BLAUS
10/29/2012

NORMAN L STOCKBRIDGE
10/29/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

ACKNOWLEDGE – CLASS 2 RESPONSE

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

We acknowledge receipt on September 17, 2012, of your September 17, 2012 resubmission of your new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Eliquis (apixaban) tablets.

We also acknowledge receipt of your pre-submissions dated August 22 and 31, 2012.

We consider this a complete, class 2 response to our June 22, 2012, action letter. Therefore, the user fee goal date is March 17, 2013.

If you have any questions, please call:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular & Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

ALISON L BLAUS
09/26/2012

EDWARD J FROMM
09/26/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

MEETING REQUEST GRANTED

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ELIQUIS (apixaban) Tablets.

We also refer to your 27 June 2012, correspondence requesting a meeting to discuss your 22 June 2012 Complete Response letter for this NDA. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: 16 July 2012
Time: 14:00 – 15:30 EST
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

CDER participants:

** Office of New Drugs*

Ellis Unger, M.D.	Director (acting)
Robert Temple, M.D.	Deputy Director (acting)

** Office of New Drugs, Division of Cardiovascular & Renal Products*

Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Martin Rose, M.D, JD	Clinical Reviewer
Nhi Beasley, Pharm.D.	Clinical Reviewer
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff
Alison Blaus	Regulatory Health Project Manager

**Office of Biostatistics, Division of Biometrics I*

James Hung, Ph.D.	Director
Steve Bai, Ph.D.	Statistician

** Office of Scientific Investigations*
Leslie Ball, M.D. Director

** Office of Scientific Investigations, Division of Good Clinical Practices Compliance*
Susan Cummins, M.D. Branch Chief
Sharon Gershon, PharmD Reviewer

Please e-mail me any updates to your attendees to alison.blaus@fda.hhs.gov, by Friday **6 July 2012**. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least **10 business days** prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with my phone number to alert me that you are in the lobby

Submit background information for the meeting (three paper copies or one electronic copy to the application and an electronic copy via email to me) at least **one week** prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by **10 July 2012**, we may cancel or reschedule the meeting.

Please be advised that if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic and the date of submission is on or after October 1, 2012, the application will be subject to "The Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission. Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities. Information on PDUFA V and "The Program" is available at
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

If you have any questions, call me at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Alison Blaus
Regulatory Health Project Manager
Division of Cardiovascular & Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

ALISON L BLAUS
06/27/2012

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 202155 BLA # n/a	NDA Supplement # n/a BLA Supplement # n/a	If NDA, Efficacy Supplement Type: n/a
Proprietary Name: ELIQUIS Established/Proper Name: apixaban Dosage Form: Tablets		Applicant: Bristol-Myers Squibb Agent for Applicant (if applicable): n/a
RPM: Alison Blaus		Division: Cardiovascular & Renal Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 28 June 2012	☐ AP ☐ TA ☒ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): NME - Factor Xa Inhibitor

☐ Fast Track
☒ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☒ MedGuide
☒ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

Version: 1/27/12

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☐ Included
Documentation of consent/non-consent by officers/employees	☐ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) CR on 22June2012
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Copy of Agency's 14 June 2012 and sponsor's 19 June 2012 proposals
• Original applicant-proposed labeling	Included
• Example of class labeling, if applicable	n/a

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	n/a
• Original applicant-proposed labeling	Included
• Example of class labeling, if applicable	n/a
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	22 December 2012 19 December 2011
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEPA ☐ DMPP/PLT (DRISK) ☐ ODPD (DDMAC) ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	29 November 2012 & 22 June 2012 ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 7 December 2011 If PeRC review not necessary, explain: n/a • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 12Aug10 (AVERROES pre-NDA), 24Jan11 (AVERROES Topline), 4May11 (ARISTOTLE pre-NDA), 18Jul11 (ARISTOTLE Topline)
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 2 October 2006
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	n/a
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	n/a
• 48-hour alert or minutes, if available *(do not include transcript)*	n/a
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 22 June 2012
Division Director Summary Review *(indicate date for each review)*	☐ None 22 June 2012
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None (see Division Memo)
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	n/a
• Clinical review(s) *(indicate date for each review)*	2 November 2011, 22 May 2012, 11 June 2012, and 22 June 2012
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	22 May 2012 n/a
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable

[6] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	13 February 2012 3 February 2012 (REMS Request Memo) ☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None Co-signed Stats Review
Statistical Review(s) *(indicate date for each review)*	☐ None 1 May 2012
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None Co-signed Clinical Pharmacology Review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 15 February 2012
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 21 June 2012
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 1 November 2011 (two), 21 February 2012, 13 April 2012, and 16 May 2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 15 February 2012
❖ ECAC/CAC report/memo of meeting	☐ None 1 December 2012 Included in P/T review, pageYes
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 22 June 2012
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 7 November 2011, 8 November 2011, 7 December 2011, 15 February 2012, 28 February 2012, 18 May 2012, and 22 June 2012
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	15 February 2012
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 27 March 2012 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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/s/

ALISON L BLAUS
06/22/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

REVIEW EXTENSION – MAJOR AMENDMENT

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your September 28, 2011, New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for ELIQUIS (apixaban) Tablets.

On January 31, 2012, we received your January 31, 2012 unsolicited major amendment (ARISTOTLE site 1200 data integrity issues) to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is **June 28, 2012**.

In addition, in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012," the timeline for communicating labeling changes and/or postmarketing requirements/commitments, provided in our November 28, 2011, filing communication letter, no longer applies and no new timeline will be provided.

If you have any questions, please call:

Alison Blaus
Regulatory Project Manager
(301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
02/29/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

INFORMATION REQUEST

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eliquis (apixaban) tablets.

The Office of Scientific Investigations (OSI) have the following requests for information:

- Please describe the specific duties and involvement of BMS Senior Clinical Site Manager (b) (6) in the ARISTOTLE study. In addressing our query, please provide
  - a listing of all sites where (b) (6) was involved and the dates of her involvement.
  - her roles and responsibilities with respect to each of the sites through the conduct of the study as well as post-study activities.
  - a description of (b) (6) involvement in oversight of monitoring activities.
- Please describe the specific duties and involvement of CRA Mr. (b) (6) in the ARISTOTLE study. Please provide details of his duties and involvement at Site 1200 and other Chinese sites and non-Chinese sites, including dates.
- Please identify all the sites that were monitored by (b) (6) Please describe the specific duties and involvement of (b) (6) in the ARISTOTLE study.
- Please provide the resumes of (b) (6) (b) (6) and (b) (6)
- Please provide names and dates of employment of the other (BMS) individuals that were fired, as referred to in your Investigation Report (dated January 26, 2012).
- Please explain why (b) (6) did not pass along the full listing of GCP issues identified at Site 1200 to BMS Global Team?
- What was the purpose of the USB drive referred to in the BMS report? What records did it contain? Was it password protected?
- At Site 1200, what sections of the outpatient records contained penciled notations that were later erased? Please describe the contents of the penciled notations that were erased. Please list all other occurrences of source documents or case report forms that appeared to have been altered in a manner meant to evade auditing.

- Please provide the names of all CROs that monitored the ARISTOTLE study and the locations/regions monitored by each. For China sites, please provide the name of CRO that conducted monitoring; if more than one, provide dates of monitoring coverage.
- Please describe in detail BMS interactions, oversight, and supervision of actions of Senior Clinical Site Managers. Please also describe in detail BMS interactions, oversight, and supervision of actions of all other individuals responsible for monitoring the conduct of ARISTOTLE.
- Please clarify why the GCP violations at site 1200 were not discovered while the trial was being conducted. Please compare and evaluate the site monitoring at this site to other sites in ARISTOTLE.

We respectfully request a formal response to the above request as expeditiously as possible.

If you have any questions, please contact:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Stephen M. Grant, M.D.
Deputy Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

STEPHEN M GRANT
02/15/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

MEETING MINUTES

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ELIQUIS (apixaban) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on February 9, 2012. The purpose of the meeting was to discuss your February 7, 2012 submission, an analysis of the medication errors that occurred in your Phase 3 trial ARISTOTLE. We also discussed the Division's letter dated February 8, 2012 requesting that CRF 800 be collected for each patient in the trial. This meeting was scheduled to discuss your analysis of the medication errors, the Division's letter, and the impact of these errors on the interpretability of ARISTOTLE.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us in writing of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Alison Blaus, Regulatory Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	A
Meeting Category:	Guidance
Meeting Date and Time:	February 9, 2012 at 2pm
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	NDA 202155
Product Name:	apixaban
Indication:	non-valvular atrial fibrillation
Applicant Name:	Bristol-Myers Squibb & Pfizer Inc.
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Meeting Recorder:	Alison Blaus

FDA ATTENDEES

Office of New Drugs, Division of Cardiovascular & Renal Products

Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Martin Rose, M.D, JD	Clinical Reviewer
Nhi Beasley, Pharm.D.	Clinical Reviewer
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff
Alison Blaus	Regulatory Health Project Manager

Office of Biostatistics

James Hung, Ph.D.	Director, Division of Biometrics I
Steve Bai, Ph.D.	Statistician

APPLICANT ATTENDEES

Bristol-Myers Squibb Attendees

Linda Gambone, Ph.D.	Associate Director, Regulatory Affairs
Joseph Lamendola, Ph.D.	VP, Regulatory Affairs
Anthony Waclawski, Ph.D.	VP, Regulatory Affairs
Math Hukklehoven, Ph.D.	Senior VP, Regulatory Affairs
Elora Gupta, Ph.D.	Director, Regulatory Affairs
Victoria Demby, Ph.D.	Manager, Regulatory Affairs
Jack Lawrence, M.D.	VP, Apixaban Development Lead
Michael Hanna, M.D.	Group Medical Director
Fred Fiedorek, M.D.	VP, Global Clinical Research
Robert Wolf, M.D.	VP, Global Clinical Research
Brian Daniels, M.D.	Senior VP, Global Development & Medical Affairs
Elliot Levy, M.D.	Senior VP/Global Pharmacovigilance and Epidemiology
Puneet Mohan, MBBS, M.D., PhD	Executive Director, Medical lead
Lorraine Rossi	Sr. Clinical Operations Lead
Susan Mullin	Associate Director Protocol Management
Kristin Dawson	Associate Director, Biostatistics
Jerry Wang	Director, Biostatistics
Sunil Nepal, Ph.D.	Principal Biostatistician

Pfizer Attendees

Margarida Geraldes Ph.D.	Global Biostatistics, Pfizer
Peter Aprile, RPH	Director, Regulatory Affairs
Susan DeCorte	Regulatory Affairs
Lori Shafner, Ph.D.	Medicine Team Lead
Rogelio Braceras, M.D.	Clinical Lead

1.0 BACKGROUND

Apixaban is an oral factor Xa (FXa) inhibitor developed by Bristol Meyers Squibb (BMS) and Pfizer under (b) (4): IND 68,598 for the prevention of thrombotic events in patients with non-valvular atrial fibrillation (AF); (b) (4)

Two Phase 3 trials were conducted under IND 68,598, ARISTOTLE (CV185030) and AVERROES (CV185048). ARISTOTLE was an active (warfarin) controlled, randomized, double-blind study to evaluate the efficacy and safety of apixaban in preventing stroke and systemic embolism in subjects with non-valvular atrial fibrillation. Unlike ARISTOTLE, AVERROES compared apixaban to ASA in subjects who failed or were considered unsuitable for Vitamin K antagonist treatment.

On September 28, 2011, NDA 202155 was submitted for the following indication based on the data from ARISTOTLE and AVERROES:

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

During review of the clinical trial ARISTOTLE, the Agency review team noted an imbalance (~6:1, apixaban:warfarin) in the number of reported medication errors. While discussing this finding with the applicant, it became apparent that the applicant's summary of treatment errors included subjects who were dispensed active drug for placebo but not subjects who received placebo instead of active drug. After the applicant reanalyzed their data, the number of subjects that received incorrect study treatment nearly doubled, from 773 subjects in the clinical study report to a total of 1503 subjects. After receiving this new analysis on February 7, 2012, the FDA promptly discussed the submission with the applicant and issued an information request letter on February 8, 2012. This letter requested the applicant collect all investigational product (IP) bottle panel stickers, present on CRF 800 (or its equivalent), and compare the container numbers on the stickers to that found in the eCRF and IVRS.

This meeting on February 9, 2012 was scheduled to discuss the applicant's analysis of the medication errors from ARISTOTLE, the Division's information request letter, and the impact these errors have on the integrity of the data from the trial. The slides presented by the applicant appear in Attachment I of these minutes.

2. DISCUSSION

2.1. Process Related Discussion

2.1.1. Investigator Site Staff Role

- The applicant explained that when new investigational product (IP) was needed, the clinical site staff would contact IVRS and receive a new container number. The site staff would record or remember that number and then re-enter that number on the eCRF but the applicant believed that did not always happen immediately. Anywhere between 15 minutes to 24 hours later, IVRS would follow-up with a fax or email confirming the container number provided via phone. This fax/email was kept in the patient's source documentation.
- Once the IP was pulled and dispensed, someone at the site (the investigative staff or pharmacist) would peel off the side panel sticker that included the unblinding sticker, and affix it to CRF 800 (or the site's equivalent of CRF 800). At sites where pharmacists pulled the containers, the container labels may have been kept in the pharmacy and not among the subjects' source documents.
    - *Post Meeting Note*: The applicant confirmed later noted that they could not confirm whether the labels were kept in the pharmacy or the patient's source documentation and that the process varied from site to site.

2.1.2. Clinical Site Monitors Role

- In slide six, the applicant reviewed the site monitor's role in source data verification (SDV). The applicant noted in slide six that all critical fields were 100% source data verified, but later confirmed that the IP related fields were not considered "critical fields" and per the monitoring plan were checked in 1:2 subjects during early site monitoring and later in only 1:5 subjects. The applicant noted that sites that had protocol deviations or significant number of errors detected by data management or monitors would not be able to reduce their level of source data verification to 1:5. The applicant, however, said that there was not a set threshold of errors and that it was determined on a site by site basis.
- In those subjects with 100% SDV (1:2 or 1:5), the monitor was suppose to compare the container number from the IVRS fax/email to the eCRF to the panel sticker removed from the bottle. The Agency was unclear if the monitor verified the labels for those cases when the pharmacist removed the panel sticker and retained it in the pharmacy since it was not part of the subject's source documents. The applicant could not confirm this at meeting.
    - *Post Meeting Note*: The applicant followed up with the CRO that monitored the study (PPD) and all monitors were instructed to review the panel stickers, no matter if it resided in the patient file or the pharmacy.
- The applicant cited 218 instances of incorrect IP being dispensed identified by the site monitoring. Programming, comparing the container number in the eCRF data to the IVRS data, picked up the medication error 1654 times.

2.1.3. Impact of Data Errors

- The Division stated that they did not understand why most of these errors were detected by data management and not by site monitors because the site monitors should have had

access to all three pieces of source documentation. The Division wondered if this fact indicated that the quality of site monitoring was inadequate.

- The Division stated that they believed it likely that the applicant would be able to demonstrate that medication errors alone would not significantly change the apparent outcome of ARISTOTLE. However, it was concerned by a pattern of inadequate trial conduct and oversight (i.e., problems in monitoring at a site in China and the potential unblinding due to differences in sizes of placebo and active apixaban). The Division was uncertain whether it was reasonable to assume that the problems in trial conduct identified by the review team were all or even most of the significant problems.

2.2. Next Steps

- Dr. Stockbridge asked the applicant what they could do to put these errors in perspective. The option of conducting a sensitivity analysis of the data, taking into account the error rate of medication errors already observed was discussed, and how many more errors would have to be observed, assuming the same error rate, to overturn the non-inferiority and the superiority findings.
- The Division also suggested the applicant review the CRF 800s that they have in house (both original and scanned/faxed copies from the site) and compare the container numbers to the IVRS and the eCRF data. It would be helpful to note what errors are found in that subset of CRFs.
- The Division also suggested that the applicant attempt to provide a quantifiable analysis of study monitoring.
- The applicant also agreed to prepare a detailed description of the monitor's responsibilities during the trial, sample monitoring reports prepared during the trial, and the level of oversight that was conducted over the trial as a whole and any corrective action if any that was done to rectify the issue on a study level and not just at the site.
- The applicant agreed to provide a number of analyses and data to the Agency via Gateway on or before February 21, 2012.
- The Division indicated that the submission of new analyses may require a 3 month extension of the PDUFA deadline but that no decision had been made to do so.

3.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
List of information requested by the Division as a result of the February 7, 2012 submission and the February 9, 2012 meeting.	FDA	Provided to the applicant via email on February 10, 2012. This list appears at Attachment II to these minutes
Applicant to provide a written response to Attachment II	Applicant	To be formally submitted and received no later than February 21, 2012

4.0 ATTACHMENTS AND HANDOUTS

Attachment I are slides presented to the Agency during the February 9, 2012 meeting. Attachment II are a written list of analyses requested by the Division.

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Discussion on Next Steps

1. Please verify that the investigational product that each subjects received was the one assigned by the IVRS number and eCRF number. We suggest that you do the following:

- Scan all CRF800s (or their equivalent) that you have available and submit as one pdf document bookmarked for each USUBJID
- Submit analyses comparing the container numbers on CRF 800 to that in the IVRS data set (KITTASSGN) to that in the eCRF. Please submit the data sets containing the CRF800s, the data set containing the container numbers in the eCRF, your analysis data set, the SAS codes used for your analysis and, if applicable, the SAS code used to create the datasets.)
- Provide a data set of all treated subjects in ARISTOTLE with the following columns
    a. USUBJID
    b. Flag if CRF 800 is available
    c. the number of bottles dispensed per subject
    d. number of labels on CRF800 per subject
    e. Number of label bottle numbers (ie., bottle numbers from labels) not included in IVRS database for same subject
    f. Number of IVRS database bottle numbers not included in label bottle numbers for same subject
    g. Number of IVRS database bottle numbers that do not match eCRF bottle numbers for same subject
    h. Flag for CRF800 available (See note that follows)
    i. Flag for those container numbers obtained from CRF (or its equivalent) vs. those obtained from a scan/fax of CRF 800 (or its equivalent)

- Note: There are subjects with CRF 800 that are not included in your current CRF 800 table. If you can complete in a timely manner, we suggest you include all subjects with CRF800 in the above analyses and requests. This may require scanning each CRF for CRF800.

2. Provide an example of a monitoring report from ARISTOTLE from a site at which at least two patients were identified as receiving incorrect study medication

3. **<u>TTR</u>**

a. Provide TTR calculations: (1) including and (2) excluding time while taking medication from bottles dispensed in error. Exclude the first week on therapy and other types of therapy interruptions.
b. Provide summary statistics for warfarin arm patients who received placebo for warfarin for: (1)change from last INR on active warfarin to first INR on placebo for warfarin; (2) change in warfarin dose after first INR on placebo (3) major bleeding rate in the first 60 days after reinstitution of therapy with active warfarin study drug following the medication error that led to administration of placebo for warfarin. (4) major bleeding rate while on placebo for warfarin as result of medication error

4. Please provide an analysis exploring how many medication errors would likely be needed to make the results of the efficacy and safety analyses no longer significantly better (for efficacy please analyze both superiority and non-inferiority) – assume that the outcomes during the period of that the wrong investigational product administration match those observed (Please include raw, analysis and SAS codes)

5. Provide a detailed description of the monitoring done in ARISTOTLE and particularly regarding review of medication information/medication errors. Include the frequency of monitoring visits, description of any blinded aggregate reports generated during the trial to assess the quality of monitoring/site conduct, and a listing of the sites that per protocol deviations seen were reverted back or kept at 100% SDV.

6. Please submit your analyses datasets and SAS codes for the tables in the main section of your Response to the Medication Errors (submission 36, dated February 7, 2012).

7. All of the analyses in the Response to Medication Errors are presented by randomized treatment group. Please present the event rate data for ISTH major bleed, stroke/se, and all cause death by the treatments the patient was actually receiving at the time of the event, 30 days, 60 days and 90 days after the incorrect treatment was received. Please submit these data sets and the SAS codes used for the analyses.

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/s/

ALISON L BLAUS
02/17/2012

NORMAN L STOCKBRIDGE
02/17/2012

Blaus, Alison

From: Blaus, Alison
Sent: Wednesday, February 08, 2012 12:47 PM
To: 'Gambone, Linda'
Subject: RE: NDA 202155 - Jan2012 DMEPA Advice Letter-follow up

Hi Linda-

I would like to confirm that the comments received in the 1Feb12 advice letter also apply to the carton/container labels for the samples of Eliquis. The rationale for this change is the same, to result in optimized readability.

Please retain this email as documentation.
Thank you for raising the question.
Kind regards,
Alison

From: Gambone, Linda [mailto:Linda.Gambone@bms.com]
Sent: Monday, February 06, 2012 4:02 PM
To: Blaus, Alison
Subject: FW: NDA 202155 - Jan2012 DMEPA Advice Letter-follow up

Hi Alison,
Just checking in if you have some insight on this DMEPA clarification-below.
The team is moving forward with adjusting all comments for the patient packaging as described in the letter.

We just wanted to make sure the comments did/or did not also apply to the one component, which is our 5 mg sample carton container? As this was not addressed in the letter. (This will have impact on promotional pieces, so we want to make sure everything is clear).

Thanks,
Linda

> **From:** Gambone, Linda
> **Sent:** Friday, February 03, 2012 3:22 PM
> **To:** 'Blaus, Alison'
> **Subject:** RE: NDA 202155 - Jan2012 DMEPA Advice Letter
>
> Hi Alison,
> We had one clarification: the letter only addressed our carton/container labels for bottles and blisters for patient dispensing which we will address.
> But there was no feedback on our proposal for sample packaging, which does include ELIQUIS all caps and graphic of additional reduced prominence.
>
> Would we assume that our previous proposal for sample packaging is ok? (i.e. we could maintain these elements for sample only)?
>
> Thanks,
> Linda

From: Blaus, Alison [mailto:Alison.Blaus@fda.hhs.gov]
Sent: Wednesday, February 01, 2012 9:07 AM
To: Gambone, Linda
Subject: NDA 202155 - Jan2012 DMEPA Advice Letter

Hi Linda -

Please find attached DMEPA's comments regarding your 15Dec11 carton/container submission. Please review the letter and amend your labeling accordingly. Please then submit to the Agency. If you could please submit no later then two weeks from now (COB 14Feb12), it would be much appreciated. We are struggling to stay on our timelines.

Thank you in advance!
Alison

Alison Blaus
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Food and Drug Administration
alison.blaus@fda.hhs.gov
p:(301) 796-1138
f:(301) 796-9838

Address for desk and courtesy copies:
Food and Drug Administration
10903 New Hampshire Avenue
White Oak, Building 22, Room 4158
Silver Spring, MD 20993

Address for official submissions to your administrative file:
Division of Cardiovascular and Renal Products
FDA, CDER, HFD-110
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

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/s/

ALISON L BLAUS
02/13/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

INFORMATION REQUEST

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eliquis (apixaban) tablets.

We also refer to your February 7, 2012 submission, containing your analysis and description of the magnitude and impact of the medication errors that occurred during the ARISTOTLE (CV185030) clinical trial. This description also included how and when these medication errors were detected.

In our follow-up teleconference on February 7, 2012, you stated that you cannot verify that the serial number entered on the CRF was the serial number of the drug dispensed to a subject. After the IVRS sent a serial number for the medication to be dispensed to a subject, the investigator was supposed to record contemporaneously the serial number onto the CRF but you cannot verify the time at which the serial number was actually recorded. You also indicated that you believe that on occasion the serial number was entered much later due to problems with electronic data entry. Also within 24 hours the serial number was also transmitted via email or fax and so it was possible that investigators used that email or fax as a source for recording the serial number in the CRF instead of the serial number of the drug actually dispensed. Therefore, we are not confident that all of the medication errors that occurred during ARISTOTLE have been identified, lessening confidence in the accuracy of the conclusions on impact you have provided.

The panel sticker that was removed from each bottle and placed on CRF 800 could provide accurate information. Therefore, we request that all CRF 800s be obtained from the investigative sites for all subjects in order to determine which drug was actually dispensed. The panel stickers should then be scanned, entered into the database, and compared to the bottle numbers that the IVRS transmitted to the site for each patient. This analysis will provide a more accurate picture of the extent of the medication errors.

If upon receipt of this letter you would like to meet and discuss the information requested, the subsequent analysis, or the impact on the timelines, we will make ourselves available.

If you have any questions, please call:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
02/08/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155 **INFORMATION REQUEST**

Bristol-Myers Squibb Company
Attention: Linda Gambone, Ph.D., Associate Director
P.O. Box 4000
Princeton, NJ 08543

Dear Dr. Gambone:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BMS-562247 apixaban tablet.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Confirm that changes to all manufacturing process parameters beyond the ranges provided in the application, will be communicated to the Agency via the appropriate mechanism as outlined in 21 CFR 314.70.

(b) (4)

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If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh K. Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
02/03/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

PRE-APPROVAL REMS NOTIFICATION

Bristol-Myers Squibb Company
Attention: Linda Gambone, Ph.D.
Associate Director, GRS-US Liaison
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your September 28, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Eliquis (apixaban) 2.5 mg and 5 mg tablets.

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Eliquis to ensure the benefits of the drug outweigh the increased risk of thrombotic events, including stroke, if Eliquis is discontinued

Your proposed REMS must include the following:

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Eliquis will support implementation of the elements of your REMS. The communication plan must provide for the dissemination of information about the increased risk of thrombotic events, including stroke, if Eliquis is discontinued. The communication plan will be required for 2 years.

The communication plan must include, at minimum, the following:

- Dear Healthcare Professional letter distributed to appropriate prescribers
- Eliquis REMS website
- Letters to Professional Organizations

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven years after the REMS is initially approved. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the

submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information pertinent to Eliquis (see Appendix A). Additionally, all relevant proposed REMS materials including communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS and the plan for REMS assessments (see Appendix B).

Before we can continue our evaluation of this NDA, you will need to submit the proposed REMS.

For administrative purposes, designate the proposed REMS submission as "**PROPOSED REMS for NDA 202155**" and all subsequent submissions related to the proposed REMS as "**PROPOSED REMS for NDA 202155 -AMENDMENT**." If you do not submit electronically, please send 5 copies of your REMS-related submissions.

We request that you submit your proposed REMS and other REMS-related materials in Word format. Submission in Word format assists in the review of these materials and Word documents can efficiently be made compliant with Section 508 (29 U.S.C. Section 794d) to ensure timely posting of the document on the website upon approval. It is preferable that the entire REMS document and attached materials be in a single Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single Word document.

If you have any questions, please call:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:
REMS Appendices A and B

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/s/

ALISON L BLAUS
02/03/2012

MARY R SOUTHWORTH
02/03/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

GENERAL ADVICE

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ELIQUIS (apixaban) Tablets.

We also refer to your December 15, 2011, submission, containing a response to our November 30, 2011 advice letter that provided comments regarding your proposed carton and container labeling.

Upon review of the above referenced revised labeling, we have the following comments:

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. The literature involving the reading of all CAPITAL letters versus Title case letters supports using title case. "The lower-case printing is much more legible than all-capital printing due to the fact that lower-case letters have more character in terms of variation in shape and the contrasting of ascenders and descenders with short letters…Thus words formed from lower case letters have unique outline pattern, and familiar words can be read as a whole, while all-capital words have no distinct pattern and slow down readers.[1]"

2. We acknowledge that you did reduce the size of the graphic located above the proprietary name; however, it is still overly prominent. Minimize this graphic so it does not compete with the prominence of the proprietary name.

3. We note that you have changed the colors utilized for strength differentiation. However, the differentiation can be improved on the carton labeling by increasing the size of the box highlighting to make the strength more prominent.

Unit Dose Carton Labeling (2.5 mg and 5 mg):

- See comments one through three above

[1] Bloodsworth, J. G. (1993). Legibility of Print. Aiken, SC: Historical Materials (060)—Information Analysis (070), University of South Carolina at Aiken (ERIC Documents Reproduction Service No. ED 355 497)

Please revise your labeling accordingly and submit to the NDA.

If you have any questions, please call Alison Blaus, Regulatory Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
02/01/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000

ATTENTION: Linda Gambone, Ph.D.
Associate Director, GRS-US Liaison

Dear Dr. Gambone:

Please refer to your New Drug Application (NDA) dated September 28, 2011, received September 28, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Apixaban Tablets, 2.5 mg and 5 mg.

We also refer to your October 4, 2011, correspondence, received October 4, 2011, requesting review of your proposed proprietary name, Eliquis. We have completed our review of Eliquis and have concluded that it is acceptable.

Eliquis will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your October 4, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Alison Blaus at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
12/22/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155 **INFORMATION REQUEST**

Bristol-Myers Squibb Company
Attention: Linda Gambone, Ph.D., Associate Director
P.O. Box 4000
Princeton, NJ 08543

Dear Dr. Gambone:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BMS-562247 apixaban tablet.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. For three batches of each strength (pilot or full scale), provide (b) (4) and corresponding HPLC assay values measured on the same tablets. The number of tablets should be sufficient to allow reliable estimation of statistical parameters such as Standard Error of Prediction.
2. Provide plots of (b) (4) of Apixaban tablets 2.5 mg and 5 mg.
3. In the tablets specifications state clearly the number of samples to be tested using large sample size criteria.
4. Your response to Question 25 received on December 09, 2011 did not provide the data needed to set the dissolution acceptance criterion for your proposed product. Provide the following information:

    a. Dissolution profiles (plots) and individual dissolution data for all the clinical, commercial and stability batches produced for apixaban 2.5 and 5 mg tablets.

5. Your response to Question number 26 did not address our request of providing data (b) (4) .

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh K. Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
12/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

REQUEST FOR METHODS VALIDATION MATERIALS

Bristol-Myers Squibb Company
Attention: Porter P. Layne
Group Director, GRS
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Layne:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Apixaban Tablets; 2.5 mg and 5 mg tablets.

We will be performing methods validation studies on Apixaban FCT, 2.5 mg tablets, as described in NDA 202155.

In order to perform the necessary testing, we request the following sample materials and equipments:

SAMPLE AND STANDARDS

(b) (4)

FILTERS FOR SAMPLE ANALYSIS

100
100

(b) (4)

HPLC COLUMNS

(b) (4)

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
12/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

FILING COMMUNICATION

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your New Drug Application (NDA) dated September 30, 2011, received September 28, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for ELIQUIS (apixaban) Tablets.

We also refer to your submissions dated October 4, 7, 13, 14, 19, 28, November 4, 10, 17, 18, 22, December 2 and 7, 2011.

During our filing review of your application, we identified the following potential review issues:

1. We do not understand why you recommend a dose of 2.5 mg BID for patients with any 2 of the 3 following criteria: age ≥ 80 years, body weight ≤ 60 kg and serum creatinine ≥1.5 mg/dL. It does not appear that this recommendation is based on exposure matching. In your response please provide the pharmacokinetic data as well as any exposure-outcome information that supports your proposed dose.
2. Please submit a rationale, with supportive data, for the strategy you recommend for transitioning patients from apixaban to warfarin.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have also identified the following labeling format issues:

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, **CONTRAINDICATION**S, 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.

We request that you resubmit labeling that addresses these issues no later then **December 27, 2011**. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Cardiovascular and Renal Products.

Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please contact:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
12/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

GENERAL ADVICE

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ELIQUIS (apixaban) Tablets.

We also refer to your September 30, 2011 submission, received September 28, 2011, containing your proposed carton and container labels for ELIQUIS (apixaban) Tablets.

Upon review of your abovereferenced carton and container labels, we have the following comments and recommendations:

A. General Comments:

Since all packaging configurations are not unit of use, please 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. Please 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. Please 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. Please 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. Please 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, please revise

the labels to provide more visual differences between the two strengths by using unique colors for each strength.

6. Please 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. Please see comments B 1 through B 5 above.
2. Please also 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):

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, please provide adequate visual difference between the 2.5 mg and 5 mg strengths.

E. Professional Sample Carton Labeling (5 mg):

1. See comments B 1, 2, and 3 above.
2. Please remove or reduce the prominence of the graphic design from the lower one-third of the primary display panel. This distracts from “DISPENSE MEDICTION GUIDE TO EACH PATIENT” statement.

F. Professional Sample Blister Card (5 mg):

Professional samples are dispensed to patients for use at home. The Agency 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.

If you have any questions, please call Alison Blaus, Regulatory Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
11/30/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 202155 BLA# n/a	NDA Supplement #:S- n/a BLA STN # n/a	Efficacy Supplement Type SE- n/a
Proprietary Name: ELIQUIS Established/Proper Name: apixaban Dosage Form: Tablets Strengths: 2.5 & 5 mg		
Applicant: Bristol-Myers Squibb Agent for Applicant (if applicable): n/a		
Date of Application: 28 September 2011 Date of Receipt: 28 September 2011 Date clock started after UN: n/a		
PDUFA Goal Date: 28 March 2012	Action Goal Date (if different): n/a	
Filing Date: 29 November 2011	Date of Filing Meeting: 31 October 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) : 1		
Proposed indication(s)/Proposed change(s): ELIQUIS® (apixaban) is indicated to reduce the risk of stroke, systemic embolism, (b) (4) in patients with nonvalvular atrial fibrillation. (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track ☒ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): n/a

List referenced IND Number(s): 68598

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	**X**			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	**X**			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	**X**			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		**X**		
If yes, explain in comment column.			**X**	
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			**X**	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	**X**			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			**X**	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			**X**	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***			**X**	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			**X**	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		**X**		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			**X**	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: FIVE ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	**X**			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		**X**		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			**X**	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	n/a			
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).		**X**		**Sponsor did not follow ICH E3 numbering**
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	**X**			
Are all establishments and their registration numbers listed on the form/attached to the form?	**X**			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	**X**			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	**X**			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	**X**			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?		**X**		Requested an updated debarment

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				certification with the language verbatim (resubmitted on 5Oct111)
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***		**X**		This is an electronic submission thus the Field Office has access to the EDR.

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	**X**			PeRC has been notified of the NDA and has been given all information in order to schedule a meeting.
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		**X**		Waiver request is inadequate. Sponsor contacted to resubmit.

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

				Resubmitted on 13Oct11.
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			**X**	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	**X**			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		**X**		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	**X**			FDA received trade name request on 4Oct11
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***		**X**		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	**X**			
Is the PI submitted in PLR format?[4]	**X**			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			**X**	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	**X**			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			**X**	No REMS – This will be a MedGuide only.
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	**X**			
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	**X**			DSI consult will be submitted

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? **Date(s):** 2 October 2006 ***If yes, distribute minutes before filing meeting***	**X**			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 12Aug10 (AVERROES pre-NDA), 24Jan11 (AVERROES Topline), 4May11 (ARISTOTLE pre-NDA), 18Jul11 (ARISTOTLE Topline) ***If yes, distribute minutes before filing meeting***	**X**			
Any Special Protocol Assessments (SPAs)? **Date(s):** 11 December 2006 ***If yes, distribute letter and/or relevant minutes before filing meeting***	**X**			

ATTACHMENT

MEMO OF FILING MEETING

DATE: 28 September 2011

BLA/NDA/Supp #: 202155

PROPRIETARY NAME: ELIQUIS

ESTABLISHED/PROPER NAME: apixaban

DOSAGE FORM/STRENGTH: 2.5 & 5 mg Tablets

APPLICANT: Bristol-Myers Squibb

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

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

BACKGROUND:

Apixaban is an oral factor Xa (FXa) inhibitor developed by Bristol Meyers Squibb (BMS) and Pfizer under (b) (4): IND 68,598 for the prevention of thrombotic events in patients with non-valvular atrial fibrillation (AF) (b) (4)

Two Phase 3 trials were conducted under IND 68,598, ARISTOTLE (CV185030) and AVERROES (CV185048). ARISTOTLE was an active (warfarin) controlled, randomized, double-blind study to evaluate the efficacy and safety of apixaban in preventing stroke and systemic embolism in subjects with non-valvular atrial fibrillation. Unlike ARISTOTLE, AVERROES compared apixaban to ASA in patients who failed or were considered unsuitable for Vitamin K antagonist treatment.

On 24 January 2011 (minutes dated 2 February 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.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alison Blaus	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Stephen Grant		Y
Clinical	Reviewer:	Martin Rose Nhi Beasley	Y N
	TL:	Shari Targum Thomas Marciniak	Y Y
Social Scientist Review (*for OTC products*)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OTC Labeling Review (*for OTC products*)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Clinical Pharmacology & Pharmacometrics	Reviewer:	Divya Menon-Andersen Ju-Ping Lai Dhananjay Marathe Tzu-Yun McDowell	Y Y Y Y
	TL:	Raj Madabushi Pravin Jadhav	Y Y
Biostatistics	Reviewer:	Steve Bai	Y
	TL:	James Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Patricia Harlow	Y
	TL:	Thomas Papoian	Y
Statistics (carcinogenicity)	Reviewer:	Matthew Jackson	N
	TL:	Karl Lin	N
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	n/a	n/a
	TL:	n/a	n/a

Product Quality (CMC)	Reviewer:	William "Mike" Adams (DP) Charles Jewell (DS)	Y Y
	TL:	Kasturi Srinivasachar	Y
Quality Microbiology *(for sterile products)*	Reviewer:	n/a	n/a
	TL:	n/a	n/a
CMC Labeling Review	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Facility Review/Inspection	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OSE/DMEPA (proprietary name)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OSE/DRISK (REMS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OC/OSI/DSC/PMSB (REMS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Bioresearch Monitoring (DSI)	Reviewer:	Sharon Gershon	Y
	TL:	Tejashri Purohit-Sheth	N
Controlled Substance Staff (CSS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Other reviewers	Robert Temple (Officer Review); Norman Stockbridge (Division Memo);		Y, Y
Other attendees	Marcus Yap (Risk-Benefit Pilot)		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: CSRs for ARISTOTLE, AVERROES and APPRAISE-2 are not per ICH E3	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: Although a NME, there have been priors in this class and no issues so far that need input from Advisory Committee Members.
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: Issues/Information Request already provided to the sponsor and will be submitted to the NDA on 14 and 28 November.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: Format files for efficacy data sets to be requested from the sponsor prior to the 74day letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: Information requested as part of the walk-through meeting on 13October2011	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments: An information request letter will be issued to the sponsor from ONDQA (Don Henry – ONDQA PM will draft and send the letter to the sponsor prior to filing)	☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Robert Temple (ODE I) **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter

☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Alison Blaus

Regulatory Project Manager Date

Edward Fromm

Chief, Project Management Staff Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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
11/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

PRIORITY REVIEW DESIGNATION

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your New Drug Application (NDA) dated September 30, 2011, received September 28, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for ELIQUIS (apixaban) Tablets.

We also refer to your submissions dated October 4, 7, 13, 14, 19, 28, November 4, 10, 17, 18, and 22, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is March 28, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 28, 2012.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before December 13, 2011.

If you have any questions, please call Alison Blaus, Regulatory Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Stephen M. Grant, M.D.
Deputy Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

STEPHEN M GRANT
11/28/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155 **INFORMATION REQUEST**

Bristol-Myers Squibb Company
Attention: Linda Gambone, Ph.D., Associate Director
P.O. Box 4000
Princeton, NJ 08543

Dear Dr. Gambone:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BMS-562247 apixaban tablet.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance:

Drug Product:

5. Provide a detailed description of the proposed commercial scale drug product manufacturing process or a copy of the master product record which includes this information. This information is not provided in NDA sections 3.2.P.3.3, 3.2.P.3.4, and 3.2.R.1. The description should address the following:

(b) (4)

The Agency recognizes that changes to non-critical process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. However, notification of all changes including changes to process parameters should be provided in accordance with 21CFR 314.70.

(b) (4)

9. 1 Page the proposed HPLC methods:
   h ab Describe how the method validation studies address the potential variations in formulations based on the proposed (b) (4).
   b. Describe how the method validation studies for (b) (4) justify the proposed system suitability criteria. Include the study test results and copies of relevant chromatograms.
   c. Describe the preparation, concentration, maximum storage time, and acceptable storage condition for the stock reference standard solution in methods 95011189 and 95011300.
   d. Identify the acceptable (b) (4) used for sample preparation in methods 95011145 and 95011189 and revise the method validation study to include qualification of the proposed (b) (4).
   e. For the Impurity Precision-Repeatability study in method 95011189, specify the concentration of each impurity.
   f. For the validation study of method 95011300, provide the conclusions from the solution stability study regarding storage conditions and maximum hold time for reference standard, stock reference standard, and test samples of each tablet strength. Revise the method description to include these conclusions.

10. The proposed ranges for the validated operating ranges (VOR) for the HPLC methods are not adequately supported by the data provided in your submission. Provide the following information to support your proposed VOR:
    a. Provide scientific justification (e.g. DOE studies) to support the proposed VOR for the HPLC based methods.
    b. Discuss how the proposed validated operating ranges for the HPLC methods satisfy the ICH Q2(R1) expectation that "The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage."
    c. Describe how you (b) (4) is accommodated by the VOR for your methods.
    d. Describe how the method validation studies justify the proposed VOR. Include the study test results, copies of relevant chromatograms, and dissolution profiles across the proposed range.

11. Regarding the submitted stability information:
    a. Since the application proposes (b) (4) for tablet manufacture, compare the formulation, manufacturing equipment and process parameters used to manufacture the long term stability study (LTSS) and development/stability study batches with those proposed for the proposed commercial drug product.
    b. Either revise the propose (b) (4)

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(b) (4)

Biopharmaceutics:

25. The following information is needed to support your proposed dissolution method and acceptance criterion:
    a. Provide complete dissolution profile data (raw data and mean values) from the bio-batches (PK and clinical) and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e. specification-sampling time point and specification value) of the proposed product.
    b. Submit the dissolution profile data (raw data and mean values) and summary graphs for the drug product batches used in the PK studies CV185019 and CV185024.
    c. Submit the individual Cmax and AUC values from PK studies CV185019 and CV185024 as SAS Transport files.
    d. Under Biopharmaceutical Properties and Clinical Pharmacokinetics of Apixaban (23p2-pharm dev section), it is mentioned that the 5-mg dose (2 x 2.5-mg tablet) with various percentages dissolved (from (b) (4) dissolved in 30 minutes), showed comparable exposure to those obtained following administration of the oral solution. (b) (4)

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh K. Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
11/17/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

NDA ACKNOWLEDGMENT

Bristol-Myers Squibb Company
Attention: Linda Gambone, Ph.D.
Associate Director, Regulatory Sciences, U.S. Liaison
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

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

Date of Application: September 30, 2011

Date of Receipt: September 28, 2011

Our Reference Number: NDA 202155

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 27, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, please contact:

Ms. Alison Blaus
Regulatory Health Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
10/06/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 68598

MEETING MINUTES

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for apixaban (BMS-562247).

We also refer to the meeting between representatives of your firm and the FDA on July 18, 2011. The purpose of the meeting was to discuss the topline results from the ARISTOTLE trial, the upcoming content of the dossier, and a number of process related topics such as a possibly priority review.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	C
Meeting Category:	Guidance – Top-line ARISTOTLE Data
Meeting Date and Time:	18 July 2011 from 13:30 – 15:00
Meeting Location:	FDA White Oak 10903 New Hampshire Ave. Bldg #22, Room 1315 Silver Spring, MD 20993
Application Number:	68598
Product Name:	apixaban (BMS-562247)
Indication:	prevention of stroke and systemic embolism in atrial fibrillation (AF)
Sponsors:	Bristol-Myers Squibb & Pfizer Inc.
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Alison Blaus

FDA ATTENDEES

** Office of New Drugs, Office of Drug Evaluation I*

Robert Temple, M.D.	Director
Ellis Unger, M.D.	Deputy Director

** Office of Drug Evaluation I, Division of Cardiovascular and Renal Products*

Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Thomas Marciniak, M.D.	Clinical Team Leader
Aliza Thompson, M.D.	Clinical Team Leader
Nhi Beasley, PharmD	Clinical Reviewer
Martin Rose, M.D., JD	Clinical Reviewer
Preston Dunnmon, M.D.	Clinical Reviewer
Khin U, M.D.	Clinical Reviewer
Edward Fromm	Chief, Regulatory Health Project Manager
Alison Blaus	Regulatory Health Project Manager

** Office of Clinical Pharmacology*

Divya Menon-Andersen, Ph.D	Team Leader
Ju-Ping Lai, M.D.	Reviewer

** Office of New Drug Quality Assessment*

Charles Jewell, Ph.D.	Reviewer

* *Office of Biostatistics, Division of Biometrics I*

James Hung, Ph.D.	Director
Steve Bai, Ph.D.	Statistician

SPONSOR ATTENDEES

* *Bristol Myers-Squibb Participants*

Clinical Research	
John Lawrence, M.D.	VP, Development Lead, Clinical Research
Michael Hanna, M.D.	Group Medical Director
Puneet Mohan, M.D., PhD	Executive Director
Robert Wolf, MD	Vice President
Biostatistics	
Margarida Geraldes, PhD	Director
Dominic Labriola, PhD	Vice President
Global Regulatory Science	
Linda Gambone, PhD	Associate Director
Elora Gupta, PhD	Director
Joeseph Lamendola, PhD	Vice President
Mathias Hukkelhoven, PhD	Sr. Vice President
Global Pharmacovigilance and Epidemiology	
Danshi Li, M.D., PhD	Associate Medical Director

* *Pfizer Participants*

Clinical Research	
Hubert Pouleur, M.D.	Executive Director
Rogelio Braceras, M.D.	Senior Director
Worldwide Regulatory Strategy	
Elizabeth DaSilva, PhD	Director
Susan DeCorte, PhD	Director
Lori Shafner	Vice President

* *Duke University Participants*

Christopher B. Granger, M.D.	Professor of Medicine
John H. Alexandar, M.D.	Associate Professor of Medicine

1.0 BACKGROUND

Apixaban is an oral factor Xa (FXa) inhibitor being developed by Bristol Meyers Squibb (BMS) and Pfizer under (b) (4) IND 68,598 for the prevention of thrombotic events in patients with non-valvular atrial fibrillation (AF); (b) (4)

(b) (4)

Two Phase 3 trials were conducted under IND 68,598, ARISTOTLE (CV185030) and AVERROES (CV185048). ARISTOTLE was an active (warfarin) controlled, randomized, double-blind study to evaluate the efficacy and safety of apixaban in preventing stroke and systemic embolism in subjects with non-valvular atrial fibrillation. An interim analysis for this trial was performed on 8 July 2010. Unlike ARISTOTLE, AVERROES compared apixaban to ASA in patients who failed or were considered unsuitable for Vitamin K antagonist treatment.

On 24 January 2011 (minutes dated 2 February 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.

This meeting on 18 July 2011 was scheduled for the sponsor to present the top-line data from ARISTOTLE to the Agency and discuss any additional datasets that would be needed and/or any FDA NDA review processes that would change in light of these data.

2. DISCUSSION

2.1. Labeling

Question 1: Does the FDA have any comments on the proposal described for the indication, including the Agency's thoughts on describing the 2 populations and critical endpoints or any other considerations related to appropriately communicating a meaningful indication to prescribing physicians? The indication would therefore read:

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

Discussion during Meeting:
The Agency stated that the proposed indication appeared reasonable based on the reported results of ARISTOTLE, but noted that the eventual indication will be based on review of the data. The Division suggested that the phrase "for the prevention" be replaced by "to reduce the risk" to align this label with other labels.

Question 2: Does FDA agree with the efficacy presentations for proposed labeling (as it appears in the briefing book)?

Discussion during Meeting:
Regarding Table 1 in the Background Document, the Office opined that the (b) (4) outcome is not likely to be listed in a table of efficacy outcomes because the finding was not part of the primary composite endpoint, was not nominally significant, and because the analysis was not part of the sequential testing strategy. Dr. Temple thought it likely that a written description of the data from AVERROES in Table 2 would suffice.

Question 3: Does FDA agree with the safety presentations for proposed labeling (as it appears in the briefing book)?

Discussion during Meeting:
Regarding safety Tables 3 and 4, the Office similarly felt the safety data from AVERROES would not warrant a table in the label.

2.2. Regulatory

Question 4: Based on the outcomes of the ARISTOTLE and AVERROES studies, would the Division consider a Priority Review Designation for the apixaban NDA 202155?

Discussion during Meeting:
Based on the reported results of ARISTOTLE indicating that apixaban significantly reduces mortality and bleeding compared with warfarin, the Agency indicated that a priority review was likely. The decision about priority review will be made by 60 days after the final module submission.

Question 5: Does FDA agree with the proposal for Safety Update?

Discussion during Meeting:
Yes, a 90-day safety update report is acceptable to submit in lieu of the 120-day report.

Question 6: Given the sponsors intention to submit the final sequence of NDA 202155, would the Division consider initiating review of the NDA sequences already provided?

Discussion during Meeting:
The complete modules that have been submitted to FDA (CMC and Non-clinical) are being reviewed by the Agency. The Division suggested that the sponsor submit the AVERROES data ahead of the ARISTOTLE data to determine whether it is in an agreeable structure and format.

Post Meeting Note:
During the week of August 8th, the sponsor agreed to submit the following AVERROES data:

- AVERROES CSR (in ICH format) with all CRFs, adjudication packages and steering committee/DSMB meeting minutes
- AVERROES SDTM and analysis datasets, and associated define files

- Additional requested analyses (from the 12 August 2010 AVERROES preNDA meeting) in the form of a report linked to related datasets (separate folder under module 5 AVERROES study)
- AVERROES eDISH data

2.3. Other

Question 7: Can the Division provide any guidance on safety data collection for these studies?

Discussion during Meeting:
In future studies in valvular AF and secondary stroke prevention, Dr. Stockbridge indicated that the Agency would be amenable to limiting safety data collection to SUSARs and discontinuations for adverse events (AEs). He further noted that the Division has routinely exempted sponsors from expedited reporting of AEs that are efficacy or safety endpoints, as called for in the new Safety Reporting rule.

Question 8: 02-May-2011 voluntary recall of one commercial lot of COUMADIN® Tablets, used in the ARISTOTLE trial.

Discussion during Meeting:
No further discussion.

2.4. Additional Topics Discussed during the Meeting

- Efficacy endpoints and their associated International Normalized Ratio (INR) value - The sponsor explained that they would be conducting analyses of events at differing levels of INR and time within the therapeutic range. Dr. Temple asked the sponsor to also analyze events based on the time above and below therapeutic range.
- Apixaban Acute Coronary Syndrome (ACS) Program - Dr. Grant asked that the DSMB and Steering Committee Meeting Minutes from the apixaban ACS trial be included in the Stroke Prevention in Atrial Fibrillation (SPAF) NDA submission. The sponsor agreed.
- Labeling - The Agency requested that the proposed labeling include recommendations for actions to be taken when patients bleed.
- Primary Efficacy Results and Time in Therapeutic Range (TTR) – After presentation of slide 9 (slides attached as an appendix to these minutes), the Division asked the sponsor to include separate analyses for embolic and hemorrhagic strokes by TTR and to analyze the correlation between INR and efficacy and safety endpoints.
- Liver toxicity Data – The preliminary liver toxicity data was presented on slide 17. The sponsor said that they planned to include unblinded HEAC packets and to provide the eDISH datasets as detailed in the 4 May 2011 ARISTOTLE preNDA meeting.
- Warfarin Transitioning - When drafting the label for the SPAF indication, the Division suggested that data-based instructions (from ARISTOTLE) be provided to the prescriber on how to safely transition to/from warfarin from/to apixaban. When asked how patients were transitioned at study closeout, the sponsor explained that there was an algorithm detailing that if the patient was randomized to apixaban 4 additional doses of apixaban were to be administered while concomitantly giving warfarin; if the patient was randomized to warfarin,

the patient would continue to be given warfarin. Although sham INRs were provided to the investigators for patients assigned to apixaban, the sponsor was blinded to the highest sham INR value. The highest sham value, 4.1, was devised by a (b) (4)

- Dose – The Agency emphasized to the sponsor that they should include all data used to choose the dose administered in ARISTOTLE in the NDA dossier. BMS explained that the data were from the VTE prevention program and have already been submitted to the NDA. The sponsor also agreed to provide the population PK data from ARISTOTLE in the final submission.
- INR and Apixaban – The sponsor said that INR values were obtained in various studies during the AF development program. They did not correlate well with the dose of apixaban. Subjects administered apixaban typically have had INRs of 1.0 to 1.4; even at the higher doses (20 mg QD) INRs were approximately 1.4 to 1.5. The sponsor agreed to provide an analysis of bleeding risk relative to INR in subjects administered apixaban in the NDA.

3.0 OTHER IMPORTANT INFORMATION

3.1. PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

3.2. DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

3.3. MANUFACTURING FACILITIES

To facilitate our inspectional process, the Division of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The sponsor plans to submit the AVERROES data ahead of ARISTOTLE to ensure that it is in an agreeable format and layout – see Section 2.2, Question 6	Sponsor	Week of August 8, 2011

5.0 ATTACHMENTS AND HANDOUTS

The sponsor's slides presented at this meeting are attached, following the minutes

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/s/

ALISON L BLAUS
08/09/2011

ROBERT TEMPLE
08/09/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 68598

MEETING MINUTES

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for apixaban (BMS-562247).

We also refer to the meeting between representatives of your firm and the FDA on May 4, 2011. The purpose of the meeting was to discuss the format and content of your upcoming dossier.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	4 May 2011 from 10 – 11:30am
Meeting Location:	FDA White Oak 10903 New Hampshire Ave. Bldg #22, Room 1311 Silver Spring, MD 20993
Application Number:	68598
Product Name:	apixaban (BMS-562247)
Indication:	prevention of stroke and systemic embolism in atrial fibrillation (AF)
Sponsors:	Bristol-Myers Squibb & Pfizer Inc.
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Meeting Recorder:	Alison Blaus

FDA ATTENDEES

** Office of Drug Evaluation I, Division of Cardiovascular and Renal Products*

Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Mary Ross Southworth, PharmD	Safety Deputy Director
Aliza Thompson, M.D.	Clinical Team Leader
Khin U, M.D.	Clinical Reviewer
Thomas Papioan, Ph.D.	Team Leader, Pharmacology/Toxicology
Edward Fromm	Chief, Regulatory Health Project Manager
Alison Blaus	Regulatory Health Project Manager

** Office of Clinical Pharmacology*

Rajnikanth Madabushi, Ph.D	Team Leader
Ju-Ping Lai, M.D.	Reviewer

** Office of New Drug Quality Assessment*

Charles Jewell, Ph.D.	Reviewer

** Division of Scientific Investigation*

Sharon Gershon, PharmD	Reviewer

** Office of Biostatistics, Division of Biometrics I*

Steve Bai, Ph.D.	Statistician

SPONSOR ATTENDEES

Bristol-Myers Squibb

** Clinical Research*

Michael Hanna, M.D.	Group Medical Director
John Lawrence, M.D.	Vice President, Development Lead
Puneet Mohan, M.D., Ph.D.	Executive Director
Charles Frost, Ph.D.	Director

* *Biostatistics*	
Margarida Geraldes, Ph.D.	Director
David Henry, Ph.D.	Executive Director
* *Global Regulatory Science*	
Linda Gambone, Ph.D.	Associate Director
Elora Gupta, Ph.D.	Director
Joeseph Lamendola, Ph.D.	Vice President
* *Global Pharmacovigilance and Epidemiology*	
Danshi Li, M.D., Ph.D.	Associate Medical Director
* *Regulatory CMC*	
Ambarish Singh, Ph.D.	Associate Director
* *Global Dossier Management*	
Jennifer Carlino	Senior Regulatory Associate
* *Global Regulatory Documentation*	
Diptee Gajjar, PhD	Director

Pfizer Inc.

* *Clinical Research*	
Hubert Pouleur, M.D.	Executive Director
Rogelio Braceras, M.D.	Senior Director
* *Worldwide Regulatory Strategy*	
Elizabeth DiSilva, Ph.D.	Director

1.0 BACKGROUND

Apixaban is an oral factor Xa (FXa) inhibitor being developed by Bristol Meyers Squibb (BMS) and Pfizer under (b) (4) IND 68,598 for the prevention of thrombotic events in patients with non-valvular atrial fibrillation (AF); (b) (4)

(b) (4)

Two Phase 3 trials are being or were conducted under IND 68,598, ARISTOTLE (CV185030) and AVERROES (CV185048). ARISTOLE is an ongoing active (warfarin) controlled, randomized, double-blind study to evaluate the efficacy and safety of apixaban in preventing stroke and systemic embolism in subjects with non-valvular atrial fibrillation. An interim analysis for this trial was performed on 8 July 2010. Unlike ARISTOTLE, AVERROES compared apixaban to ASA in patients who failed or were considered unsuitable for Vitamin K antagonist treatment.

On 24 January 2011 (minutes dated 2 February 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.

This meeting on 4 May 2011 was scheduled to discuss the format and content of NDA 202155 and how the dossier should be organized due to the decision conveyed in January.

2. DISCUSSION

2.1. Questions Posed by the Sponsor

1. Does the Division concur with the above mentioned plan for summarizing data from the AF studies in the SCE and SCS (see Section 2 of the Briefing Book for the detailed plan)?

   Preliminary Response
   Your SAP for your Summary of Clinical Efficacy and Integrated Summary of Efficacy (included in the briefing package and dated May 19, 2010) indicates that efficacy analysis results will be presented for ARISTOTLE, AVERROES and the Japanese Phase 2 study in patients with atrial fibrillation; this is acceptable.

   Your SAP for your Summary of Clinical Safety and Integrated Summary of Safety (also included in the briefing package and dated May 19, 2010) indicates that bleeding will be categorized only using the ISTH scale. Please also categorize bleeding using the TIMI and GUSTO scales. It also indicates that APPRAISE-2 will not be included because the trial "will be ongoing at the time of the submission." The trial was terminated prematurely and should be included in the Summary of Clinical Safety and Integrated Summary of Safety.

   Discussion
   Slide 2 was presented to the Division and the Division agreed that the sponsor's approach was acceptable.

2. Does the Division concur with the above mentioned plan for summarizing data from other non-AF studies (see Section 2 of the Briefing Book for the detailed plan)?

   Preliminary Response
   Yes; see also response to question 1.

   Discussion
   See Discussion under question 1.

3. Does the Division agree with this narrative proposal (as outlined in Section 2 of the Briefing Book)?

   Preliminary Response
   At the August 12, 2010 AVERROES Pre-NDA Meeting, we agreed with your proposal to submit narratives for AVERROES for events meeting the criteria shown in Table 2.1B. However, based on the sample narrative provided in your current briefing document, it is unlikely that the narratives generated using your automated tool will facilitate review. We recognize the difficulty of generating the large number of narrative that would meet the criteria outlined in the table (you report that the number would be upwards of 18,000). In your briefing package, you propose to provide additional information (e.g., via narrative writing/review by physicians or other medical personnel) for a subset of events. Another option would be to submit higher quality narratives but to provide them for a more limited number of events (and not submit any narratives using the automated tool). For example, we are uncertain of the value of submitting SAEs for bleeding. We will discuss this issue with you at our meeting.

Please note that your sample narrative (Appendix 4) both states that the drug was withdrawn BEFORE the patient allegedly experienced the AEs and also that "following the AEs the drug was withdrawn..."

Discussion

The sponsor proposed to provide the highlighted narratives on slide 3. The Division advised the sponsor to provide narratives for "Discontinuations due to an adverse event" and "Neurological AEs/SAEs". The Division added that "Discontinuations due to an adverse event" should also include those patients who withdrew their consent due to an adverse event. Narratives for discontinuations due to an endpoint event did not need to be provided as these events would have adjudication packages. The Divison advised the sponsor that they should be prepared to furnish to the FDA other narratives upon request during review of the NDA.

The sponsor also committed to providing narratives, in eDISH format, for all liver related events. The sponsor was referred to the AVERROES pre-NDA meeting minutes, dated 16 September 2010, for what constitutes an adequate narrative (for all narratives, not only eDISH) and the criteria for classifying an event as an eDISH liver narrative. The sponsor also agreed to provide datasets in eDISH format. The specifications for eDISH datasets and narratives were provided via email to Linda Gambone on 11 May 2011 and an updated version on 31 May 2011.

4. Does the Division concur with the above mentioned proposal for the CRFs, adjudication information, and datasets for the ARISTOTLE study?

Preliminary Response

Please provide CRFs for all discontinuations/withdrawals regardless of investigator assessment of relation to AEs.

Regarding adjudication information, please provide the following:

(i) The number of events sent from sites to the sponsor and subsequently submitted to the adjudication committee; and the number NOT submitted with the reasons
(ii) How events were triaged from the sites to the adjudication committee
(iii) How blinding was maintained in the preparation and submission of adjudication information to the adjudication committee
(iv) Outcome of adjudication of "sequence events" – i.e., > 1 endpoints occurring during the same day.

Please do not split any raw or analysis datasets. Although the guidance notes that datasets over 400MB should be split, we request that the datasets be kept intact and submitted via hard drive. SDTM datasets should be split only if the dataset is over the 4GB limit. If needed, we have a define.XML file that provides an example of how to represent a split domain.

Discussion

The sponsor outlined the CRFs that they planned to submit in the dossier on slide 4. The Division agreed with their proposal but added that CRFs for SAEs would not be needed for any study, but the sponsor should be prepared to furnish to the FDA other CRFs upon request during review of the NDA.

5. Based on the feedback received from the FDA at the 01-Mar-2011 meeting, we understand that additional analyses will be requested for the ARISTOTLE study. Can the Division provide these additional analyses requests for the ARISTOTLE study at your earliest convenience?

Preliminary Response
Please see the additional analyses/datasets section at the end of the preliminary comments. Please submit the requested datasets with Module 5.

Discussion
See discussion around the additional analyses/datasets below.

6. Does the Division concur with the above mentioned proposal for the narratives, CRFs, and datasets for the APPRAISE-2 study (see Section 2.1 of the Briefing Book for the full proposal)?

Preliminary Response
Yes.

Discussion
No further discussion.

7. Does the FDA agree with the CRF submission proposal as was agreed in the context of AVERROES only NDA submission (see Section 2.2 of the Briefing Book for the detailed plan)?

Preliminary Response
Yes. We prefer to have the safety data linked to the CRF page. Please also provide a blank text searchable CRF showing the hypertext links.

Discussion
The sponsor presented slide 8. The Division agreed that their approach was acceptable.

8. Does the FDA agree with the dataset format proposal as was agreed in the context of AVERROES only NDA submission (see Section 2.2 of the Briefing Book for the detailed proposal)?

Preliminary Response
Yes.

Discussion
No further discussion.

9. BMS is proposing not to submit the AE, laboratory, demographic, and exposure SDTM v1.1 datasets for ongoing and concluded studies? Of note, the FDA agreed with this proposal for the blinded studies in the context of AVERROES only NDA submission.

Preliminary Response
We agree that you do not need to submit these datasets for on ongoing studies or for completed studies in non-AF indications.

Discussion
The Agency clarified the above preliminary response applied to APPRAISE-2 and that they did not expect datasets for this study.

10. Does the Division have any questions regarding the updates to the CMC section of the dossier?

Preliminary Response
We have no questions at this time. The described updates can be made up to the time of official filing.

Discussion
No further discussion.

11. We do not see the need to provide a new NDA application for AF, and prefer to retain the current rolling NDA 202155 which will be completed with the last submission sequence 0002. To facilitate FDA review, we also plan to provide a detailed Reviewer's Guide in the Module 1 of NDA 202155. Does the Division agree with this approach?

Preliminary Response
Yes.

Discussion
No further discussion.

12. Does the Agency agree that an FDA-approved (b) (4) (b) (4)

Preliminary Response
No, see below.

Discussion
No further discussion.

13. If not, does the Agency agree that a Medication Guide-as part of the US product labeling but outside of a REMS - is adequate to inform patients of the bleeding risks of apixaban as an anticoagulant?

Preliminary Response
Yes, a Medication Guide should be included as part of product labeling.

Discussion
No further discussion.

14. We would appreciate the Agency's perspective regarding the need for additional risk management strategies for a new anticoagulant such as apixaban.

Preliminary Response
The need for additional risk management strategies will be determined during the course of the review. At this time, nothing additional is required.

Discussion
No further discussion.

2.2. Additional Comments

1. The SCE SAP and the ARISTOTLE SAP both indicate that for analyses of key efficacy endpoints, the efficacy "cutoff date" will be determined and documented prior to study unblinding. Knowledge of the exact date a trial will end is not needed for defining the time windows for key efficacy analyses; an algorithm can still be specified without knowledge of the exact trial end date and should be specified. This needs to be discussed at the upcoming meeting.

   Discussion
   The Division requested that a sensitivity analysis be conducted with a cut-off date of 2, 7 and 30 days post-treatment and stated that the Division will likely perform sensitivity analyses using additional cut-off dates.

   The Division asked how the sponsor transitioned patients from apixaban to warfarin after they completed the trial. The sponsor explained that they had a well defined algorithm in the protocol and required extensive monitoring by the sites. The sponsor noted that they captured to what medication each patient was transitioned, but did not collect INR measurements after the last visit.

2. Under Section 2.3 of the briefing document (Clinical Pharmacology) you propose to access blinded data after the last patient's last visit but before database lock, "with the appropriate firewall in place" in order to "facilitate the exposure-response assessment and report preparation." We strongly advise that you postpone these analyses until AFTER the database lock and do NOT break the blind prior to database lock.

   Discussion
   The sponsor confirmed that they will comply with the above and not access unblinded data to facilitate their exposure-response analysis preparations.

   Dr. Madabushi asked BMS how often PD samples were obtained in ARISTOTLE. The sponsor confirmed that 1-2 samples were taken post-dose on all patients.

3. Attached as an appendix to the preliminary responses from the AVERROES preNDA (dated August 9, 2010) were two documents provided by the Division of Scientific Investigations. The first document had data requests that were to be addressed in your initial submission. Referenced under number three of this document is the "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" guidance. That guidance can also be found as an appendix to those preliminary comments. Please apply these requests to ARISTOTLE and not AVERROES in your dossier.

   Discussion
   The sponsor agreed to provide the DSI datasets, but asked a clarifying question in slide 11. Sharon Gershon agreed to review the question with her management and to follow-up with the sponsor at a later date.

   Post-Meeting Note
   DSI responds as follows to the sponsor's request for clarification. Please note that DSI is not asking for datasets (.xpt files) for these items (safety labs and concomitant medications) but rather a pdf document with listings by site. If the sponsor still has concerns that inclusion of the listings of concomitant medications and safety labs would

result in a pdf document that is too large to make creation of the document feasible, then we would agree that the site specific listing pdf may be submitted without the safety labs and concomitant medication listings. In this event, the sponsor should be aware that post-submission an additional information request will be issued for safety labs and concomitant medications listings for a subset of sites chosen by the review team and we request that you turn around the site specific information for safety labs and concomitant medications within 5 business days of our request. In regard to these two listings we request the following information be included: 1) listing of concomitant medications together with dates of administration; and 2) for safety laboratory monitoring, LFT values are sufficient, for serum alanine aminotransferae, serum aspartate aminotranferase and total bilirubin.

2.3. Additional Analyses & Data Sets.

2.3.1. *Datasets for Efficacy Analyses*

2.3.1.1. Include a dataset containing multiple records per subject randomized to warfarin in ARISTOTLE and the following information: the unique subject id, center id, date of INR measurement, value of INR, indicator of whether or not the subject was on warfarin at the time of INR measurement, indicator for whether a subsequent dose adjustment was made (increased, decreased, no change).

Discussion

The sponsor presented slide 6 and explained that the warfarin dose was not captured on the CRF and hence could not be provided in the above dataset.

In addition to the INR data for warfarin subjects, the Division also requested that all INR data for apixaban subjects be submitted. The sponsor said that they did not believe that INR levels correlated well with apixaban, and that Factor Xa assays (currently 510k cleared) correlated better. The Division acknowledged the sponsor's statement, but still wanted the data. The sponsor agreed to provide the INR data for apixaban treated subjects in the dossier. The sponsor also agreed to provide the data relating to apixaban and Factor Xa assays.

2.3.1.2. Include a dataset containing one record per subject randomized to warfarin in ARISTOTLE and the following information: unique subject id, center id, baseline use of warfarin (yes or no), duration of time in study (days), duration of time in study (days) that subject was on study medication (excludes periods of medication interruptions), number of INR measurements made during/as part of study, maximum number of days between two consecutive INR measurements while subject was on study medication, start date for that period (i.e., date of INR measurement beginning that period), end date for that period (i.e., date of INR measurement ending that period).

Discussion

No further discussion beyond that discussed under 2.3.1.1.

2.3.1.3. Include a dataset containing multiple records per subject randomized to warfarin in ARISTOTLE and the following information: unique subject id, site/center number, country of site, region of site, and the % time in range, % time below range, and %

time above range for the following INR ranges: 2-3 and 1.5-4. The percentage of time in, above and below a given range should be calculated for the following study time periods for each subject: <1 month, ≤ 3 months, ≤ 6 months, ≤12 months and overall.

The time in these ranges should be calculated in two ways as specified below:

- Time in therapeutic range excluding warfarin treatment interruptions (TTRE): The evaluation of a patient's compliance to warfarin during treatment period should be assessed by the % of days when the INR is in the required range. A linear interpolation using the Rosendaal method should be performed. A linear equation should be fitted using the actual measured INR values. After the linear equation is fitted, a value will be substituted for each day when the patient took study medication and did not have an actual INR measurement. For patients who had temporary discontinuation of study warfarin, the time interval between temporary discontinuation and restart of medication should not be counted. If INR is evaluated during the first week of randomization, the INR value should not be used.
- Time in therapeutic range including warfarin treatment interruptions (TTRI): calculation as above, but include periods of temporary discontinuation of study warfarin (i.e., interpolate as if no interruption had occurred).

We also request that you provide the SAS code used to create this dataset along with any intermediate datasets used.

Discussion
No further discussion beyond that discussed under 2.3.1.1.

2.3.1.4. Please include a dataset (subjects who permanently discontinued study medication only) containing one record per subject and information on whether or not the subject was treated with an anticoagulant following study medication discontinuation, and if so, what anticoagulant was used. If this information is contained in another dataset in the specified format, a separate dataset does not need to be submitted.

Discussion
No further discussion.

2.3.2. *Datasets for Safety Analyses*

2.3.2.1. Please include a dataset containing multiple records per subject and the following information: the unique subject id, treatment arm, randomization date, study termination date, first medication date, last medication date, type of bleed event (example, "major" by protocol definition), bleed event number for each subject, event date, time of event (days from randomization), indicator for an adjudicated major bleed, indicator for investigator reported major bleed, indicators for location of EACH critical organ bleed (example, indicator for GI bleed, indicator for intracranial bleed), indicator for hemoglobin drop of ≥ 2 g/dL, indicator for hemoglobin drop of ≥ 5 g/dL, indicator for ≥ 2 U transfusion, indicator for ≥ 4 U transfusion, indicator for bleeding associated with hypotension requiring intravenous inotropes, indicator for requiring surgical intervention to stop bleeding, indicator for bleeding requiring hospitalization, and indicator for bleeding resulting in death.

Discussion
The sponsor acknowledged the above request, but indicated that some of the requested information was not collected (see slide 7). The Division also agreed to follow-up with the sponsor regarding the safety (bleeding) analysis dataset after the meeting.

Post-Meeting Note
With regard to the bleeding event number, the dataset should indicate if the bleeding event is the first, second, third, etc bleeding event for the subject. It is understood that multiple bleeding events may occur in one day (or over a few days) and that for the purpose of this dataset, these should be given the same bleeding event number.

2.3.2.2. A dataset that contains multiple records per subject and the following information: the unique subject id, treatment arm, randomization date, study termination date, first medication date, last medication date, the following liver test results, ratios, and date of collection: ALT, AST, total bilirubin, and alkaline phosphatase, and an indicator for central or local lab. All liver test results should be in consistent units. Note that there is a date associated with each lab test, e.g., ALT_date, AST_date.

Discussion
The Agency explained that the above request is separate from the eDISH datasets and that they should refer to the eDISH specifications provided via email on 11 May 2011 and to the AVERROES pre-NDA meeting minutes regarding liver narratives.

2.3.2.3. A dataset that contains multiple records per subject and the following information: the unique subject id, treatment arm, the date and results of all laboratory tests done to rule out other causes of drug induced liver injury.

Discussion
The Agency explained that the above request is separate from the eDISH datasets.

2.3.3. *Other Requests*

Discussion
The Agency clarified that all of the below requests were limited to ARISTOTLE, with the exception of 2.3.3.7 (Steering Committee and DSMB meeting minutes) which applied to all three trials (ARISTOTLE, AVERROES, and APPRAISE-2)

2.3.3.1. Please submit all SAS code used and all datasets used. For example, if a SAS code contains a macro, please include the macro code.

Discussion
No further discussion.

2.3.3.2. Please submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the NDA. The table should contain the following:

a. title of the table or figure in NDA
b. a hyperlink to location of table or figure with page number
c. a hyperlink to the name of the SAS code used to create table or figure

Discussion
The sponsor provided a proposal to satisfy the above preliminary request in slide 12. The Division agreed with their proposal.

2.3.3.3. Please submit a SAS dataset that contains the following four columns: study number, unique subject id, indicator for CRFs submitted, and indicator for narrative submitted.

Discussion
No further discussion.

2.3.3.4. An adjudication dataset should be submitted that contains what triggered the event for adjudication, each adjudicators' result and date of adjudication, final adjudication result, the study number, unique subject id, treatment arm, and date of event.

Discussion
The sponsor showed slide 13 and agreed to provide the requested dataset, but would not be able to include each adjudicator's results as that was not captured (only the final adjudication result). The Division requested that the dataset indicate what triggered the request for adjudication (e.g., the site investigator or the Adjudication Committee). The Division asked the sponsor to include reasons for not adjudicating an event initially referred for adjudication and reasons events were re-adjudicated, if any were.

2.3.3.5. Please provide sample clinical trial kits, identical to those used during ARISTOTLE. One kit from the warfarin arm and another from apixaban should be provided to Ms. Blaus' desk address.

Discussion
The sponsor noted that they planned to provide the kits for each treatment arm.

2.3.3.6. Please provide a dataset for time to primary event (both safety and efficacy) censoring patients without an event at the date of last known information about the event of interest (not vital status check at the end of the study). Include whether censoring was determined by a patient visit or by telephone call.

Discussion
On slide 14, the sponsor explained that patients were censored at the time of last known information, but noted that whether that visit was in person or via phone call was not captured. BMS added that there was an amendment during the trial to request that the patient come to the investigational site for the 30-day follow-up visit instead of a phone call, but they did not capture which was done.

2.3.3.7. Please include Steering Committee and DSMB meeting minutes (including any data/slides presented to the Committee) for ARISTOTLE.

Discussion
The above request was expanded to include AVERROES and APPRAISE-2, in addition to ARISTOTLE.

2.3.3.8. In addition to the "subgroups of interest for efficacy assessments" identified in your SCE SAP, efficacy findings should also be provided for the following subgroups: prior VKA use, aspirin use at baseline, clopidogrel use at baseline, type of atrial fibrillation and findings in the U.S. CHADS2 scores should be broken down into the following groupings: 0, 1, 2 and ≥3.

Discussion
In response to the above request, the sponsor proposed to include an analysis for the group of subjects with $CHADS_2$ scores ≤ 1, 2 and ≥ 3. The Division found this proposal acceptable. The Division also requested analysis of the group of subjects with and without a history of stroke/TIA at baseline.

2.3.3.9. A description of the responsibilities of each ARO or CRO. Please redact any financial information.

Discussion
No further discussion.

2.3.3.10. Please provide your clinical trial monitoring plan for ARISTOTLE.

Discussion
No further discussion.

2.3.3.11. Please provide your detailed data management plan for ARISTOTLE, including both manual and programatical data checks used throughout the study.

Discussion
No further discussion.

3.0 OTHER IMPORTANT INFORMATION

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Updated DSI Site Section Tool Guidance and Related Requests	FDA (Alison Blaus)	Provided via email on 11 May 2011 and included as an attachment to these minutes
Updated eDISH specifications	FDA (Alison Blaus)	Provided via email on 11 May 2011 and 31 May 2011

5.0 ATTACHMENTS AND HANDOUTS

The slides presented at this meeting and the DSI site selection criteria are attached, following the minutes.

15 pages have been withheld as b4 (CCI/TS) immediately following this page

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:

    a. Site number
    b. Principal investigator
    c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
    d. Current Location of Principle Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:

    a. Number of subjects screened for each site by site
    b. Number of subjects randomized for each site by site
    c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:

    a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
    b. Name, address and contact information of all CROs used in the conduct of the clinical trials
    c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
    d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

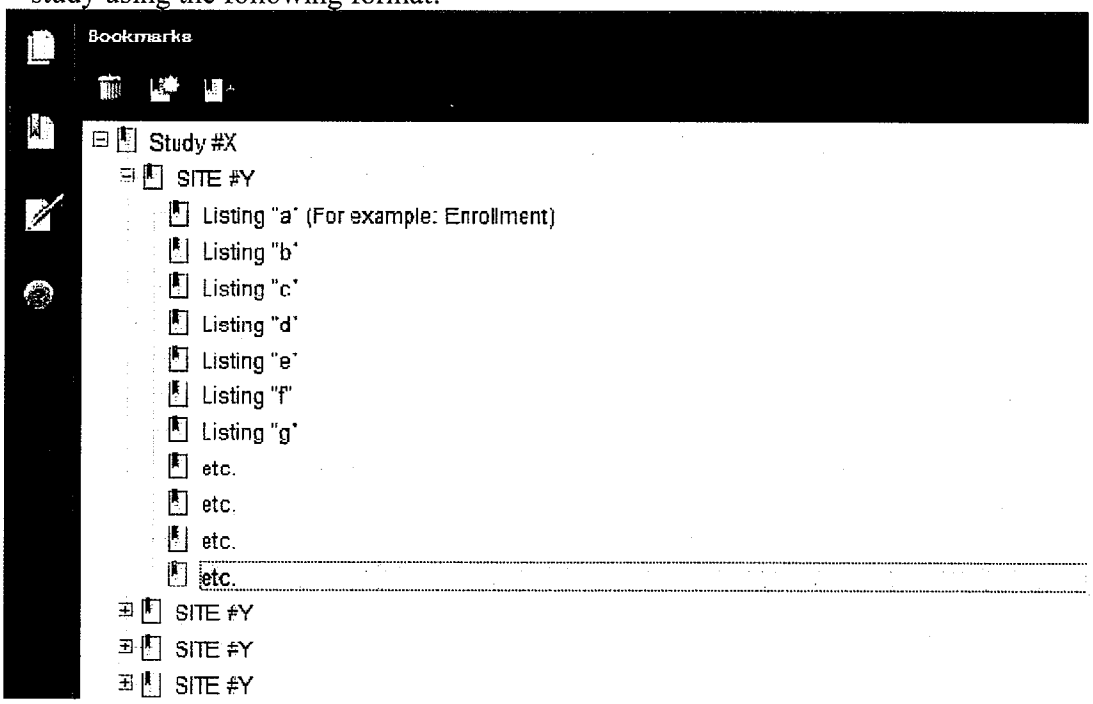
4. For each pivotal trial provide a sample annotated Case Report Form.
5. For each pivotal trial provide original protocol and all amendments.

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:

a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
b. Subject listing for treatment assignment (randomization)
c. Subject listing of drop-outs and subjects that discontinued with date and reason
d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of laboratory tests performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

DSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to the attached document, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, that includes requested data for each pivotal study submitted in your application.

Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

I. INTRODUCTION

The purpose of this electronic submission of a single new clinical site dataset is to facilitate the timely evaluation of data integrity and selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

II. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection and are not intended to support evaluation of efficacy. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Variance (TRTEFFV) – the variance of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Variance (SITEEFFV) – the variance of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in theDefine file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR".

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1.

III. CREATING AND SUBMITTING THE DATA FILE (SUBMISSION TEMPLATE AND STRUCTURE)

A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt). The file may be submitted electronically through the FDA Electronic Submission Gateway (ESG) referencing the active IND number or via secure CD addressed to the Division of Scientific Investigations point of contact.

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFV	Treatment Efficacy Result Variance	Num	Floating Point	Variance of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFV	Site-Specific Efficacy Effect Size Variance	Num	Floating Point	Variance of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFV	SITEEFFE	SITEEFFV	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

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
05/31/2011

NORMAN L STOCKBRIDGE
05/31/2011

DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
CDER, DCRDP (HFD-110)
10903 New Hampshire Ave.,
Silver Spring, MD 20993-0002

FDA
10903 New Hampshire Ave
Silver Spring, MD 20993-00025600

Transmitted via email to:	joseph.lamendola@bms.com
Attention:	Joseph Lamendola
Company Name:	Bristol-Myers Squibb Company
Phone:	(609) 252-4722
Subject:	**IND 68598 – 1Mar11 AVERROES Follow-up TopLine Meeting Minutes**
Date:	16 March 2011
Pages including this sheet:	5
From:	**Alison Blaus**
Phone:	**301-796-1138**
Fax:	**301-796-9838**

*******PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Meeting Minutes

Date:	1 March 2011
Application:	IND 68,598
Drug:	apixaban
Sponsor:	BMS and Pfizer
Meeting Purpose:	Guidance – Follow-up Top Line Results
Meeting Type:	Type C

FDA Participants:

* *Office of Drug Evaluation I*	
Robert Temple, M.D.	Director
Ellis F. Unger, M.D.	Deputy Director
* *Office of Drug Evaluation I, Division of Cardiovascular and Renal Products*	
Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff
Alison Blaus	Regulatory Health Project Manager

Bristol-Myers Squibb Participants:

* *Global Regulatory Science*	
Mathias Hukkelhoven, Ph.D.	Senior Vice President
Joseph Lamendola, Ph.D.	Vice President
Anthony Waclawski, Ph.D.	Vice President
* *Global Clinical Research*	
John Lawrence, M.D.	Vice President, Development Lead

Pfizer, Inc. Participants

Hilary Malone, Ph.D.	Senior Vice President and Head, Worldwide Regulatory Strategy
Lori Shafner, Ph.D.	Vice President, Medicines Team Leader

Background

Apixaban is an oral factor Xa (FXa) inhibitor being developed by Bristol Meyers Squibb (BMS) and Pfizer under (b) (4) IND 68,598 for the prevention of thrombotic events in patients with non-valvular atrial fibrillation ((b) (4)

(b) (4)

Two Phase 3 trials are being or were conducted under IND 68,598, ARISTOTLE (CV185030) and AVERROES (CV185048). ARISTOLE is an ongoing active (warfarin) controlled, randomized, double-blind study to evaluate the efficacy and safety of apixaban in preventing stroke and systemic embolism in subjects with non-valvular atrial fibrillation. An interim analysis for this trial was performed on 8 July 2010.

Unlike ARISTOTLE, AVERROES compared apixaban to ASA in patients who failed or were considered unsuitable for Vitamin K antagonist treatment. On 1 June 2010, the Division was informed that the AVERROES DMC formally recommended to the Steering Committee that AVERROES be terminated for overwhelming efficacy (The DMC's letter to the Steering Committee, dated 31 May 2010, was provided to the Agency). The DMC's decision was based on data from the formal interim analysis conducted on 30 April 2010 and additional data provided to the DMC on 27 May 2010. The Agency met with the sponsor and the

academic research organization (Population Health Research Institute) that conducted the trial on 4 June 2010 to discuss the data reviewed by the DMC and its regulatory implications.

BMS/Pfizer met with the Agency on 12 August 2010 for a pre-NDA meeting to discuss the format and content of this dossier, NDA 202155 (minutes dated 16 September 2010). At that meeting, the Agency agreed to a rolling review of the NDA. The quality module was submitted 29 September 2010.

A follow-up meeting was scheduled on 24 January 2011 (minutes dated 2 February 2011) to review in more detail the final topline data from AVERROES. In light of recent approvals made by the Agency, BMS and Pfizer were advised that Module 5 of NDA 202155 would not be considered complete until the data from ARISTOTLE and APPRAISE-2 were submitted. This meeting on 1 March 2011 was a follow-up to that meeting to discuss in more detail some of the points raised. The backgrounder for this meeting was submitted to the IND on 24 February 2011.

Discussion during the Meeting:

** Content of NDA 202155*

The Division reiterated the comments made at the 24 January 2011 meeting that the results of ARISTOTLE, in which apixaban is compared to warfarin, are needed prior to approval of a NDA to market apixaban for treatment of patients with non-valvular atrial fibrillation. Dr. Temple added that the Division had not concluded that to be approved for this indication that a drug must be superior to warfarin or another approved anticoagulant. However, such a drug certainly would need to establish non-inferiority to one of the approved anticoagulants to be approvable.

** Population enrolled in AVERROES*

The Division agreed that if a drug is demonstrated to benefit a subpopulation for a particular indication, it is not always necessary to characterize the effect in the broader population for that drug to be approvable. The Division, however, re-stated its belief that BMS/PFIZER had not studied a relevant subpopulation in AVERROES, given that dabigatran is now approved for the population that was enrolled in AVERROES.

Should apixaban ultimately be approved for the stroke prevention in atrial fibrillation indication, the Division stated it was likely that the results of AVERROES could be described the Clinical Studies section of the Package Insert (PI). Whether or not the AVERROES results would be included in the indication section of the PI would constitute a review issue.

** Review Designation*

BMS/Pfizer asked the Division about the possibility of a priority review for NDA 202155. Dr. Stockbridge stated a definitive answer could not be provided prior to submission but it would be unlikely if apixaban was not superior to warfarin in ARISTOTLE. He added that if apixiban were non-inferior to warfarin (with a hazard ratio of 1 or less), the time in therapeutic range were as good as or better than that observed in RE-LY, and bleeding in the apixaban subjects were significantly less, then a priority designation could be considered.

Post Meeting Note:

BMS/Pfizer asked that if the Division would be requesting additional analyses, that they provide the request in advance of the submission. These analyses will be provided at the upcoming ARISTOTLE pre-NDA meeting on 4 May 2011.

Meeting recorder: _____
Alison Blaus

Meeting concurrence: _____
Robert Temple, M.D.

Draft: ab 9 March 2011
Final: ab 16March 2011

RD:

Fromm - 9 March 2011
Grant - 9 March 2011
Stockbridge - 9 March 2011
Unger - 10 March 2011
Temple - 15 March 2011

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
03/16/2011

ROBERT TEMPLE
03/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 68598

ADVICE/INFORMATION REQUEST

Bristol-Myers Squibb
ATTENTION: Porter P. Layne, Ph.D., M.B.A.
Group Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Layne:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for apixaban (BMS-562247).

We also refer to your submission dated February 17, 2011, containing a request for clarification of the Agency's minutes from the January 24, 2011 meeting regarding the AVERROES Top-Line data (minutes dated February 2, 2011).

We have the following comments in response to your requests:

1. In the Background section, we agree that, "The quality module was submitted 29 September 2010", should be replaced by:

   "The Nonclinical module was submitted 29 September 2010. The Quality module and the CSRs and datasets for the Clinical Pharmacology/Biopharmaceutics module were submitted 03 November 2010."

2. Regarding the safety data for AVERROES and ARISTOTLE, we agree that the safety data for these two studies should be pooled in the ISS for rare events such as liver function tests.

3. We agree that the second sub-bullet under "*ARISTOTLE Status and Submission Requests*" should read, "The Sponsor anticipates a "RE-LY range" mean time-in-therapeutic range of ~64%".

4. Lastly, we agree that the third sub-bullet under "*ARISTOTLE Status and Submission Requests*" should read, "In AVERROES, the discontinuation rate appears to be lower for those administered apixaban than for those administered aspirin".

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening adverse experiences associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)];

- Reporting any serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk, in writing to this Division and to all investigators within 15 calendar days after initial receipt of this information [21 CFR 312.32(c)(1)]; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

If you have any questions, please contact Alison Blaus, Regulatory Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

NORMAN L STOCKBRIDGE
02/25/2011

Reference ID: 2910396

DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
CDER, DCRDP (HFD-110)
10903 New Hampshire Ave.,
Silver Spring, MD 20993-0002

FDA
10903 New Hampshire Ave
Silver Spring, MD 20993-00025600

Transmitted via email to:	porter.layne@bms.com
Attention:	Porter Layne
Company Name:	Bristol-Myers Squibb Company
Phone:	(609) 252-4722
Subject:	**IND 68598 – 24Jan11 AVERROES Top Line Meeting Minutes**
Date:	2 February 2011
Pages including this sheet:	32
From:	**Alison Blaus**
Phone:	**301-796-1138**
Fax:	**301-796-9838**

*******PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Meeting Minutes

Date:	24 January 2011
Application:	IND 68,598
Drug:	apixaban
Sponsor:	BMS and Pfizer
Meeting Purpose:	Guidance – Top Line Results
Meeting Type:	Type C

FDA Participants:

** Office of Drug Evaluation I*	
Robert Temple, M.D.	Director
Ellis Unger, M.D.	Deputy Director
** Office of Drug Evaluation I, Division of Cardiovascular and Renal Products*	
Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Mary Ross Southworth, PharmD	Safety Deputy Director
Khin U, M.D.	Clinical Reviewer
Martin Rose, M.D.	Clinical Reviewer
Edward Fromm	Chief, Regulatory Health Project Manager
Alison Blaus	Regulatory Health Project Manager
** Office of Clinical Pharmacology*	
Rajnikanth Madabushi, Ph.D	Team Leader
Ju-Ping Lai, M.D.	Reviewer
** Office of New Drug Quality Assessment*	
Charles Jewell, Ph.D.	Reviewer
** Office of Biostatistics*	
James Hung, Ph.D.	Director, Division of Biometrics I
Steve Bai, Ph.D.	Statistician

Bristol-Myers Squibb Participants:

** Clinical Research*	
Michael Hanna, M.D.	Group Medical Director
John Lawrence, M.D.	Vice President, Development Lead
Puneet Mohan, M.D., PhD	Executive Director
David Synhorst, M.D.	Group Director
Robert Wolf, M.D.	Vice President Cardiovascular
** Biostatistics*	
Margarida Geraldes, PhD	Director
** Global Regulatory Science*	
Linda Gambone, PhD	Associate Director
Elora Gupta, PhD	Director
Porter Layne, PhD	Group Director
Anthony Waclawski, PhD	Vice President
** Global Pharmacovigilance and Epidemiology*	
Danshi Li, M.D., PhD	Associate Medical Director
Janice Wherry, M.D.	Group Director

Pfizer, Inc. Participants

* *Clinical Research*	
Hubert Pouleur, M.D.	Executive Director
* *Worldwide Regulatory Strategy*	
Susan DeCorte	Senior Director
Elizabeth DaSilva, PhD	Director
* *Medicines Team Leader*	
Lori Shafner, PhD	Vice President

Background

Apixaban is an oral factor Xa (FXa) inhibitor being developed by Bristol Meyers Squibb (BMS) and Pfizer under (b) (4) IND 68,598 for the prevention of thrombotic events in patients with non-valvular atrial fibrillation (AF); (b) (4) (b) (4)

Two Phase 3 trials are being or were conducted under IND 68,598, ARISTOTLE (CV185030) and AVERROES (CV185048). ARISTOLE is an ongoing active (warfarin) controlled, randomized, double-blind study to evaluate the efficacy and safety of apixaban in preventing stroke and systemic embolism in subjects with non-valvular atrial fibrillation. An interim analysis for this trial was performed on 8 July 2010.

Unlike ARISTOTLE, AVERROES compares apixaban to ASA in patients who failed or are unsuitable for Vitamin K antagonist treatment. On 1 June 2010, the Division was informed that the AVERROES DMC formally recommended to the Steering Committee that AVERROES be terminated for overwhelming efficacy (The DMC's letter to the Steering Committee, dated 31 May 2010, was provided to the Agency). The DMC's decision was based on data from the formal interim analysis conducted on 30 April 2010 and additional data provided to the DMC on 27 May 2010. The Agency met with the sponsor and the academic research organization (Population Health Research Institute) that conducted the trial on 4 June 2010 to discuss the data reviewed by the DMC and its regulatory implications.

The sponsor met with the Agency on 12 August 2010 for a pre-NDA meeting to discuss the format and content of this dossier, NDA 202155 (minutes dated 16 September 2010). At that meeting, the Agency agreed to a rolling review of the NDA. The quality module was submitted 29 September 2010.

This meeting was scheduled to review in more detail the final top line data from AVERROES. The slides presented at this meeting can be found as an appendix to these minutes.

Discussion during the Meeting:

- *Target Population for Apixaban*

Dr. Stockbridge started by stating he was unsure how a label for apixaban might describe the patients who would benefit from apixaban now that an NDA for dabigatran has been approved. The sponsor stated that the patients for whom apixaban would be indicated are (b) (4) (b) (4) Dr. Temple responded that dabigatran 150 mg bid, which was demonstrated superior to warfarin in RE-LY, is now available for the population studied in AVERROES. Warfarin is markedly superior to aspirin for prevention of stroke and other systemic emboli in patients with atrial fibrillation and so, despite a lack of direct comparison between dabigatran and aspirin, it is clear that dabigatran is superior to aspirin for this indication. Further, the effect of apixaban compared to warfarin is unknown at this time. Approving an anticoagulant that has not

demonstrated at least noninferiority to warfarin raises a safety concern, specifically that the use of apixaban in lieu of more effective therapy could result in an increased rate of stroke in this patient population. As noted in the April 1995 document signed by President Bill Clinton and Vice President Gore entitled *Reinventing Regulation of Drugs and Medical Devices* "In certain circumstances…it may be important to consider whether a new product is less effective than available alternative therapies, when less effectiveness could present a danger to the patient or to the public. For example, it is essential for public health protection that a new therapy be as effective as alternatives that are already approved for marketing when…the disease to be treated is life-threatening or capable of causing irreversible morbidity (e.g., stroke or heart attack)…." Given the uncertainty as to whether apixaban is as effective as available alternative therapies, it is the Office's position, therefore, that an NDA for apixaban for treatment of atrial fibrillation, (b) (4) (b) (4) should not be submitted until the final results of ARISTOTLE are available.

The sponsor responded that apixaban might be indicated for (b) (4) (b) (4)

In summary, the Agency indicated that it believes that the primary registration study for apixaban should be ARISTOTLE, and that AVERROES is a supportive study. Like ARISTOTLE, the AVERROES study would be described in the label, but as part of the Clinical Studies section, section 14, and would be unlikely to result in an additional claim.

- *Submission*

The sponsors asked whether they could submit the AVERROES data in the near term, to afford the Division the opportunity to begin their clinical review. The Office requested that all modules of this rolling submission, including clinical, be submitted as complete modules. The Division stated that the ISS in this submission should pool all of the apixaban studies but that the ISE can describe them separately.

- *ARISTOTLE Status and Submission Requests:*
  - Final patient visits are to begin this month, January, 2011.
  - The sponsor anticipates a "RE-LY range" time-in-therapeutic-range of ~67%.
  - The discontinuation rate appears to be lower for those administered apixaban than those administered aspirin
  - The Division stated that although both Intent to Treat (ITT) and On Treatment (OT) populations should be analyzed, OT was the preferred analysis for ARISTOTLE because it was a non-inferiority study. If a superiority analysis is performed, the ITT population should be the primary analysis.

Meeting recorder: _____
Alison Blaus

Meeting concurrence: _____
Robert Temple, M.D.

Draft: ab 26Jan11
Final: ab 2Feb11

RD:

U 28Jan11
Fromm 28Jan11
Southworth 28Jan11
Grant 29Jan11
Stockbridge 2Feb11
Unger 2Feb11
Temple 2Feb11

26 pages have been withheld as b4 (CCI/TS) immediately following this page

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/s/

ALISON L BLAUS
02/02/2011

ROBERT TEMPLE
02/02/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

(b) (4)
NDA 202155

INFORMATION REQUEST

Bristol-Myers Squibb
ATTENTION: Porter P. Layne, Ph.D., M.B.A.
Group Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Layne:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for apixaban (BMS-562247).

We also refer to your amendment, dated November 18, 2010, submitted (b) (4) Reference is also made to the apixaban rolling New Drug Application (NDA) for the prevention of stroke or systemic embolism associated with atrial fibrillation in patients that are not eligible for warfarin, NDA 202155.

We request that the APPRAISE-2 full clinical study report and data be submitted to NDA 202155 as part of the clinical section.

As sponsor of (b) (4), you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include: (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, please contact Alison Blaus, Regulatory Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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
11/24/2010

NORMAN L STOCKBRIDGE
11/29/2010

DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
CDER, DCRDP (HFD-110)
10903 New Hampshire Ave.,
Silver Spring, MD 20993-0002

FDA
10903 New Hampshire Ave
Silver Spring, MD 20993-00025600

Transmitted via email to:	porter.layne@bms.com
Attention:	Porter Layne
Company Name:	Bristol-Myers Squibb Company
Phone:	(609) 252-4722
Subject:	**IND 68598 – 12Aug10 AVERROES Pre-NDA Meeting Minutes**
Date:	16 September 2010
Pages including this sheet:	24
From:	**Alison Blaus**
Phone:	**301-796-1138**
Fax:	**301-796-9838**

*******PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Meeting Minutes

Date:	12 August 2010
Application:	IND 68,598
Drug:	apixaban
Sponsor:	BMS and Pfizer
Meeting Purpose:	Pre-NDA
Meeting Type:	Type A

FDA Participants:

* *Office of Drug Evaluation I*	
Robert Temple, M.D.	Director
* *Office of Drug Evaluation I, Division of Cardiovascular and Renal Products*	
Norman Stockbridge, M.D., Ph.D.	Director
Stephen M. Grant, M.D.	Deputy Director
Mary Ross Southworth, PharmD	Deputy Director for Safety
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical
Robert Fiorentino, M.D., M.P.H.	Medical Officer
Patricia Harlow, Ph.D.	Pharmacologist
Edward Fromm, RPh, RAC	Chief Regulatory Health Project Manager
Alison Blaus	Regulatory Health Project Manager
* *Office of Oncology Drug Products, Division of Hematology Products*	
Jeanne Wang, M.D.	Medical Officer
Marcus Cato	Regulatory Health Project Manager
* *Office of Clinical Pharmacology*	
Rajnikanth Madabushi, Ph.D.	Team Leader
**Office of New Drug Quality Assessment*	
Kasturi Srinivasachar, Ph.D.	Chemistry Pharmaceutical Assessment Lead
* *Office of Biostatistics*	
Ququan Liu, Ph.D.	Statistician
* *Electronic Submissions*	
Jared Lantzy	Electronic Submission Support Staff

Participants:

* *Bristol-Myers Squibb*	
Puneet Mohan, M.D., Ph.D.	Executive Director - Clinical Research
John Lawrence, M.D.	Vice President, Development Lead - Clinical Research
Michael Hanna, M.D.	Group Director - Clinical Research
Margarida Geraldes, Ph.D.	Director - Biostatistics
Charles Frost, Pharm.D.	Director - Clinical Pharmacology
Cynthia Piccirillo	Director, Global Dossier Management eRegulatory Liaison
Diptee Gajjar, Ph.D.	Principal Documentation Director - Global Regulatory Documentation
Porter Layne, Ph.D.	Group Director - Global Regulatory Science
Elora Gupta, Ph.D.	Director - Global Regulatory Science
Anthony Waclawski, Ph.D.	Vice President - Global Regulatory Science
Mathias Hukkelhoven, Ph.D.	Senior Vice President - Global Regulatory Science
* *Pfizer*	
Neville Jackson, M.D.	Vice President - Clinical Research
Enayet Talukder, Ph.D.	Senior Director - Biostatistics

Rebecca Boyd, Ph.D.	Executive Director - Clinical Pharmacology
Susan DeCorte	Senior Director - Worldwide Regulatory Strategy
Robin Evers, Ph.D.	Vice President - Worldwide Regulatory Strategy
Lori Shafner, Ph.D.	Vice President - Medicines Team Leader

Background

Apixaban is an oral factor Xa (FXa) inhibitor that is being developed by Bristol Meyers Squibb (BMS) and Pfizer under (b) (4) IND 68,598 for the prevention of thrombotic events in patients with non-valvular atrial fibrillation (AF): (b) (4)

(b) (4)

Two Phase 3 trials are being conducted under IND 68,598, ARISTOTLE (CV185030) and AVERROES (CV185048). ARISTOLE is an active (warfarin) controlled, randomized, double-blind, parallel arm study to evaluate the efficacy and safety of apixaban in preventing stroke and systemic embolism in subjects with non-valvular atrial fibrillation. An interim analysis for this trial was performed on July 8, 2010.

Unlike ARISTOTLE, AVERROES compares apixaban to ASA in patients who failed or are unsuitable for Vitamin K antagonist treatment. On June 1, 2010, the Division was informed that the AVERROES DMC formally recommended to the Steering Committee that AVERROES be terminated for overwhelming efficacy (The DMC's letter to the Steering Committee, dated May 31, 2010, was provided to the Agency). The DMC's decision was based on data from the formal interim analysis conducted on April 30, 2010 and additional data provided to the DMC on May 27, 2010. The Agency met with the sponsor and the academic research organization (Population Health Research Institute or PHRI) that conducted the trial on June 4, 2010 to discuss the data reviewed by the DMC and its regulatory implications.

The purpose of this meeting was to review the procedural and formatting/content aspects of the planned dossier. A follow-up meeting is planned for 4Q 2010, following the availability of top-line data from the AVERROES study. The slides presented at this meeting can be found as an appendix to these minutes.

Questions for the Division (the questions below appear in their entirety in the pre-NDA briefing book):

1. Does the FDA agree with this proposed Rolling Submission strategy and timeline?

Preliminary Response:
Each module should be complete upon submission, including CMC data on the 5-mg tablets. We will accept complete modules in a rolling submission if no drugs other than warfarin are available at the time of the submission.

Discussion During Meeting:
The Division and the sponsor agreed that all modules would be complete upon submission, with the exception of Module 5. The Agency agreed to take 26 complete clinical pharmacology reports ahead of the summary or AVERROES related data. The AVERROES data would be submitted in its entirety in the 1Q 2011.

The Agency clarified that the degree to which the NDA will be reviewed prior to the last piece of the submission is resource dependent. The availability of other therapy for this indication will also have an impact on our internal timelines.

Post-meeting Note:
To assist the sponsor in their preparation of the clinical pharmacology section, they were provided the Clinical Pharmacology Review Aid via email on August 25, 2010.

2. Does the FDA have any comment on the eCTD sequence numbering being proposed?

Preliminary Response:
The Electronics Submissions group agrees with the proposed sequence numbering, however, sequence 0001 – 0003 should be coded as an amendment relating to "Sequence 0000 (original application). The cover letter and form should indicate when the final portion of the rolling submission has been submitted, as that submission will be used as the clock start date.

Discussion During Meeting:
There was no further discussion.

3. Can the FDA provide guidance on review management of common dossier sections by the 2 Divisions?

Preliminary Response:
The management of the review will depend on the timing of the submissions to the two Divisions.

Discussion During Meeting:
The Agency reiterated that the review would depend on the timing of the submissions, but added that the manner in which it is reviewed will be an internal decision.

4. Does the FDA agree with the CRF submission proposal?

Preliminary Response:
The Division does not agree with some aspects of your proposed plan. All CRFs for subjects with a serious adverse event, death or discontinuation of study drug due to an AE should contain all *solicited and unsolicited* documents received from investigational sites. In addition, the FDA requests that CRFs for all neurologic and cardiovascular non-serious AEs (e.g., a SOC of NEURO or CV, including bleeds) be submitted with the NDA, as well as any supplemental CRFs generated for such AEs (as described in Section 7.3 of the protocol).

Discussion During Meeting:
The sponsor agreed to comply with the above request regarding CRFs, but suggested the criteria for neurological events as appears on Slide 11 of the appendix. The Division agreed to their new plan for submitting neurological CRFs. The sponsor also agreed to have all nonserious adverse event CRFs available quickly upon request and to include all information reviewed by the Adjudication Committee.

5. Does the FDA agree with the dataset format proposal?

Preliminary Response:
Please do not split large datasets. If the analysis datasets are derived from CRF-based datasets, and not the submitted SDTM datasets, the CRF-based datasets should be submitted as well. Please also provide the analysis programs that are used for primary and secondary endpoints analyses.

Discussion During Meeting:
The sponsor agreed to provide both the CRF-based datasets as well as the derived datasets from which the analyses were generated.

6. Are there any other specific requests (e.g., datasets, listings, summaries, MedDRA version considerations, requirements from other Divisions including the Division of Scientific Investigation) that we need to be aware of?

Preliminary Response:
From an electronic submissions standpoint, only the summaries should be placed in module 2 (2.7.3 and 2.7.4) but the actual ISE and ISS should be placed in Module 5.3.5.3. Please also refer to the Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document.

Please submit all final monitoring and data management plans (not summaries) utilized during AVERROES. Please also include an index of any Standard Operating Procedure (SOPs) referenced by any entity involved in the conduct of the trial.

Attached as an appendix to these preliminary responses are two documents provided by the Division of Scientific Investigations. The first document has data requests that should be included in your initial submission. Referenced under number three of this document is the "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" Guidance. This guidance can be found as the second appendix. (These documents were appendices to the preliminary comments dated 9Aug10)

Discussion During Meeting:
The sponsor agreed to provide the data as specified in the preliminary comments as well as the complete and final data management and monitoring plans in the dossier. The adequacy of the data management and monitoring plans will be evaluated by DSI upon submission.

Post-meeting Note:
Please include in the dossier the contract agreement between the CRO and the sponsor, with the financial information redacted.

7. BMS is proposing not to submit the blinded AE, laboratory, demographic, and exposure SDTM v1.1 datasets for the ongoing studies; does the FDA agree with this proposal?

Preliminary Response:
Yes.

Discussion During Meeting:
No further discussion regarding this question.

8. Does the FDA have any further questions concerning this monitoring plan

Preliminary Response:
Please see the preliminary comment under question 6.

Discussion During Meeting:
No further discussion.

9. After the database is unblinded at the patient level to the project team (PHRI, BMS, and Pfizer), BMS will receive a database transfer from PHRI in form of SAS datasets. These datasets will be used by BMS to develop the analysis datasets. The analysis datasets will be the basis for the analyses that will be

reported in the CSR. BMS will be responsible for processing the datasets received from PHRI to ensure that the datasets are CDISC compliant before submitting it to the FDA. Does the FDA agree with this proposal? Specifically, are there recommendations or specific requirements from the FDA so they can be addressed early in the dossier preparation process?

Preliminary Response:
FDA notes that "BMS does not have ongoing access to the database; and therefore has not participated in the process of assessing or issuing queries for this study." As the applicant, you are responsible for the accuracy and integrity of the data submitted in the NDA. We recommend that you develop a plan for verifying the accuracy of the data transmitted to you and that you provide it to the Agency in advance of its implementation. If the AVERROES database is being derived from paper CRFs that are scanned using optical character recognition (OCR), attention should be paid to the accuracy of data transfer. We suggest that you perform detailed checks of datasets critical for the assessment of efficacy and safety in a manner that ensures that any errors resulting from OCR scanning are minimized. This may include sorting of laboratory data that enables scrutiny of outliers that may be in error, such as hemoglobin values for assessment of bleeds or liver function tests for safety assessments.

In addition, you should provide a detailed account of the timing of interim analyses, study termination dates, actual study termination dates for each subject, censoring rules, and timing of final database lock.

Finally, we note that you are planning to have the statistician that reports to the DMC perform an unblinded analysis for presentation of "topline" results at ESC in August of 2010. This unblinded analysis will occur prior to the final database lock planned in October 2010. Ideally, you should have completed all follow-up on end points prior to this unblinding. If you have not, please address how your subsequent follow-up cannot be affected by the early unblinding.

In addition, because the study was terminated early, you will need to discuss in detail how adjudicated events, including potential primary events submitted for adjudication prior to termination, but not yet adjudicated, will be handled. It is currently not clear which events will be included in the final analyses as it appears you continue to perform data queries in anticipation of a future database lock.

Discussion During Meeting:
The sponsor noted that they are currently drafting their plan for verifying the accuracy of the data transmitted from PHRI and will submit it to the Agency prior to its implementation.

It was explained that PHRI houses and maintains the clinical database for AVERROES. Data verification and cleaning is done on an ongoing basis by PHRI and sent to the sponsor at predetermined intervals. Upon receipt of the data, the sponsor reviews primary efficacy and safety data, serious adverse events, potential liver events, disposition data and checks for any obvious date errors through programmatical checks. All other information is reviewed and verified by PHRI prior to transmission to the sponsor.

Regarding the Agency's comments on the early unblinding of data to prepare for an upcoming society presentation, please see the sponsor's slide 8 in the appendix of these minutes. The sponsor added that any event that occurred prior to May 28th was still sent to be blindly adjudicated as well as any events identified after the May 28th date. The Agency was concerned about any adjudication after the August 10th date, but the sponsor mentioned that no subject level data were unblinded.

The Division asked how close out of the study would now be handled. The sponsor explained that all patients had the option of being rolled into an extension open-label study after their last AVERROES "in person" visit. If any events were obtained at this close out visit, which could have

occurred after August 10th, those events would still be adjudicated and included in the primary efficacy analysis.

The sponsor mentioned that the Final Statistical Plan was submitted to the Agency on May 10th.

10. Does the FDA agree with the proposal to waive the SCE and SCS?

Preliminary Response:
Yes.

Discussion During Meeting:
There was no further discussion regarding the SCE or SCS.

11. Does the FDA agree with the narrative proposal?

Preliminary Response:
Please refer to the comments on liver data (see "Additional Comments). In addition, please remove the requirement that neurological AEs or SAEs last at least 7 days to qualify for narrative generation.

Discussion During Meeting:
After further discussion at the meeting, the Agency agreed that the sponsor's initial narrative proposal was acceptable. The initial proposal was as follows:

i. Deaths
ii. SAEs related (certainly, possibly, probably, or missing - investigator's judgment)
iii. SAEs for bleeding
iv. Discontinuations due to adverse event
v. AT >3×ULN and total bilirubin >2xULN on the same date
vi. AT >5xULN
vii. SAEs jaundice or hepatitis or liver failure
viii. Platelet count < 50,000/mm3
ix. Neurological AEs or SAEs that lasted at least 7 days or resulted in a neurological consult and for which the severity was moderate or severe or very severe at least once during the duration of the event.
x. Creatine kinase >10xULN

Please also see discussion under liver data in the Additional Comments section.

12. The AVERROES NDA will provide an assessment of blinded safety data from the ongoing ARISTOTLE study. Additional blinded safety data from this study will be provided with the Safety Update Report. In addition, topline efficacy and safety data from the completed study will be made available during AVERROES review (2Q-3Q 2011). Can the FDA comment on what, if any, additional data or information will be needed from the ARISTOTLE study prior to the AVERROES NDA approval?

Preliminary Response:
At this time, we do not anticipate that we will need additional data from ARISTOTLE.

Discussion During Meeting:
The Agency confirmed again that they will not need data from ARISTOTLE in order to review AVERROES.

13. The design and outcome of the AVERROES study is anticipated to satisfy the criteria of 'safe and effective therapy where no satisfactory alternative therapy' for a Priority Review classification. We understand that the review classification will be determined after the NDA submission. Can the FDA provide guidance on expectations of AVERROES outcomes for gaining Priority Review and if the priority review application is under review, are there any conditions that could change that designation?

Preliminary Response:
If the NDA is submitted prior to another product becoming available for patients who cannot take coumadin, your planned NDA would probably be granted priority review status. If such a product became available during the review, we can and probably will change the review status of your planned NDA to standard.

Discussion During Meeting:
The topic of whether the priority review status can change mid cycle was discussed. The Agency mentioned that the final status is determined and communicated to the sponsor at Day 60. The ability to amend the status from priority to standard after Day 60 was debated. The Agency noted that the internal guidance was inconsistent and in the event this was an issue for AVERROES, it would be discussed internally.

14. Top-line results from the second Phase 3 AF study (ARISTOTLE) are anticipated to be available during the AVERROES review period. Does the FDA agree that the ARISTOTLE application can be submitted as a stand-alone NDA in case the approval of the AVERROES application is pending at the time the ARISTOTLE dossier is ready for submission?

Preliminary Response:
Yes. The planned NDA based on ARISTOTLE can be submitted regardless of the review status of the NDA based on AVERROES.

Discussion During Meeting:
No further discussion on this topic at the meeting.

15. If a Priority Review is granted, will the FDA be willing to accept an early Safety Update Report at 3 months instead of the standard 4 months? Given the large extent of unblinded and blinded safety database being provided with the NDA, the Sponsor does not anticipate any substantial difference in data critical to safety assessment between these 2 reports.

Preliminary Response:
Yes, this is acceptable.

Discussion During Meeting:
There was no further discussion on the 120-day safety report.

16. Can the FDA provide comment on how they would manage the potential Medication Guide associated with AVERROES, knowing that the ARISTOTLE data may obviate that rationale for the Medication Guide?

Preliminary Response:
A Risk Evaluation and Mitigation Strategy (REMS) that includes a Medication Guide should be submitted with the NDA. The Medication Guide should include safety information for patients such as

bleeding risk and any other important adverse events. It is unlikely that data from ARISTOTLE would change the need for a Medication Guide.

At the time you are planning to submit the NDA based on AVERROES, there will be no data demonstrating that apixaban is not inferior to warfarin for the prevention of stroke in patients with AF. It may be important to include this information in the medication guide.

You should also consider including a Communication Plan to convey important prescribing and safety information to the physician. The Communication Plan could include information about the indication, limitations of use, dosing considerations, and important contraindications.

Discussion During Meeting:
There was no further discussion beyond the comments outlined in the preliminary comments.

Additional Comments:

- Cover Letters: Please include in your cover letter the approximate size of the submission, technical and alternative point of contact information (i.e. name, telephone/fax numbers, and email address), and the transmission information (i.e. CD, DVD, DLT, ESG).

  Discussion During Meeting:
  This topic was not discussed at the meeting.

- Reviewer's Aid: Please provide a linked reviewer's aid in module 1 as a separate document from the cover letter.

  Discussion During Meeting:
  No further discussion.

- Synopsis of Individual Studies: Please provide a list of synopses and include links from Module 2 to the actual synopses that reside in Module 5.

  Discussion During Meeting:
  No further discussion.

- Module 5: Clinical Study Reports:
  - 5.1 Table of Contents of Module 5 - Please note that in eCTD format, Section 5.1 is not necessary because the eCTD XML backbone (i.e. index.xml; stf.xml) are the TOCs.
  - 5.2 Tabular listing of all clinical studies Sep-2010
    5.2 Tabular listing of all clinical studies - updated with AVERROES and CV185067 1Q2011
    - 5.2 should be submitted as a single pdf file with links to the clinical studies in Module 5.

  Discussion During Meeting:
  There was no further discussion regarding this point.

- Liver Data: Separate from the primary efficacy and safety datasets, additional datasets will need to be provided according to the specifications provided in an email to Porter Layne on 8Aug10. Please provide these in the original submission. Also provide a separate dataset of the patient narratives, via email, to Alison Blaus.

Please be aware that we wish to use eDISH to assess the likelihood that your new compound causes liver toxicity and identifying potential "Hy's Law" cases of elevated ALT or AST >3xULN and TBL >2xULN (or more in Gilbert syndrome) is just the first step. The next two steps are: 1) looking at all the liver test data for patients of interest over the time of observation, to appreciate the time-related elevations and which of the tests rises first, and then 2) evaluating the narrative data gathered to adjudicate the probable cause of the abnormal findings. This may require additional questions, tests, examinations to search for the cause, and only after ruling out other causes can a presumptive diagnosis of probable drug- related liver injury (DILI) be made. Liver biopsy is not definitive, and there is no single test or finding that proves DILI. For the adjudication to be successful, your investigators must search actively for the cause of all cases of elevated ALT or AST >3xULN and TBL >2xULN. Finding a probable, very likely, or definite cause of the liver injury other than the drug is very important. The eDISH system, as used by medical reviewers at CDER, includes the capability to create time-course graphs for each subject, and to read the narrative summaries, helping them in drawing their own conclusions as to whether the drug may have caused the abnormal findings. We will want to review the data independently. Estimation of the likelihood that the liver injury was caused by the drug being studied is frequently difficult and requires information to rule out or rule in other possible causes.

Therefore, we recommend that the narratives should be written by *physicians or other medical personnel* skilled in medical differential diagnosis. Pertinent negative findings should be included in any narrative. The data that needs to be gathered by the investigator are those that can establish or rule out other causes, such as acute viral hepatitis A or B (less often C or E), biliary disease such as stones or tumors, cardiac failure or shock, acute alcoholic or autoimmune hepatitis.

Discussion During Meeting:
The sponsor agreed to provide the data as outlined above, but asked if AVERROES was the only trial of interest. The Office of Surveillance and Epidemiology was not at the meeting, but was to be contacted for this feedback after the meeting.

Post-meeting Note:
In addition to AVERROES, the Office of Surveillance and Epidemiology confirmed that they would like to see all cases that fit the algorithm (specified in the preliminary comment) from the 6-month ACS, the 3-month atrial fibrillation, and the 3-month VTE treatment studies.

Meeting recorder: _____
Alison Blaus

Meeting concurrence: _____
Robert Temple, M.D.

Draft: ab 25Aug10
Final: ab 10Sep10

RD:
Liu 30Sep10
Madabushi 30Sep10
Fiorentino 31Sep10
Karkowsky 31Sep10
Fromm 1Sep10

Grant 2Sep10
Stockbridge 3Sep10
Temple 9Sep10

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-68598	GI-1	BRISTOL-MYERS SQUIBB	APIXABAN

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/s/

ALISON L BLAUS
09/16/2010

ROBERT TEMPLE
09/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 68,598

ADVICE/INFORMATION REQUEST

Bristol-Myers Squibb
ATTENTION: Porter P. Layne, Ph.D., M.B.A.
Group Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Layne:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for apixaban (BMS-562247).

We also refer to your amendment dated February 16, 2010, containing the statistical analysis plan (SAP) for the protocol, CV185048, entitled "Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or are Unsuitable for Vitamin K Antagonist Treatment: A Randomized Double Blind Trial".

Upon review of the above mentioned SAP, we have the following comments:

1. The interim analysis plan seems to propose using the Haybittle-Peto boundary for two interim analyses. On the other hand, Whitehead's procedure appears to be used as well. Please clarify what the formal stopping boundary you are using and provide the technical details about Haybittle-Peto boundary and Whitehead's method. These technical details need to be provided in the SAP.
2. Please also provide all details regarding simulation.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, please contact Alison Blaus, Regulatory Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-68598	ORIG-1	BRISTOL-MYERS SQUIBB	APIXABAN

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/s/

NORMAN L STOCKBRIDGE
05/03/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 68,598

ADVICE/INFORMATION REQUEST

Bristol-Myers Squibb
ATTENTION: Porter P. Layne, Ph.D., M.B.A.
Group Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Layne:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for apixaban (BMS-562247).

We also refer to your amendment dated December 17, 2009, containing a revised statistical analysis plan (SAP) and protocol amendment. The SAP and protocol are for the Phase 3 study entitled, "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 Nonvalvular Atrial Fibrillation (The ARISTOTLE study)".

Upon review of the abovementioned submission, we have the following comments and recommendations:

1. At the interim analysis, your sequential testing strategy using the same significance level (≤ 0.0001) as the primary efficacy endpoint to test all cause mortality as the secondary endpoint is acceptable. However, to increase the chance of success for the secondary endpoint, you may consider allocating a more liberal alpha (larger than 0.0001) for the interim analysis and a more stringent alpha at the end with the overall alpha for this endpoint no more than 0.025. We recommend that simulation be done to determine an efficient allocation. Please send in the simulation as an amendment to the IND.
2. For a non-inferiority claim of apixaban, only the margin of 1.38 is acceptable.
3. For non-inferiority testing, ITT analysis is known to be prone to bias in favor of falsely concluding non-inferiority. You need to propose a number of sensitivity analyses, one of which is "on-treatment" analysis that counts the events that occur only within a prespecified treatment window. A number of time windows of varying length need to be prespecified.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

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Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-68598	ORIG-1	BRISTOL-MYERS SQUIBB	APIXABAN

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
02/23/2010

NORMAN L STOCKBRIDGE
02/23/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 68,598

ADVICE/INFORMATION REQUEST

Bristol-Myers Squibb
ATTENTION: Porter P. Layne, Ph.D., M.B.A.
Group Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Layne:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for apixaban (BMS-562247).

We also refer to your amendment dated June 25, 2009, containing an update to your phase 3 protocol (CVI85030) entitled, "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". This protocol was initially submitted to the Division as a Special Protocol Assessment (SPA), dated November 9, 2006.

We have completed our review of the above amendment and have the following comments and recommendations:

1. Discretionary late changes in the protocol - like increasing the sample size from 15,000 to 18,000 patients - are a concern to us because of the difficulty in establishing the true state of knowledge about interim results. Our concern here is mitigated somewhat by preserving the original event count, but you should plan to provide all available documentation concerning the decision-making process in your final complete study report.
2. The following comments, relayed to you in the advice letter dated September 28, 2007, have not been addressed in this revised protocol.
    a. A plan should be made to control the family-wise error rate for the primary endpoint (two hypotheses), the first secondary endpoint (tested in two populations) and 8 remaining secondary endpoints. The family-wise error rate will be larger than 5% if the analyses are conducted as currently planned.
    b. For the interim analysis, the sponsor should provide details on how the estimate of the treatment effect and the confidence intervals will be adjusted and how the secondary endpoints will be tested if the study stops early.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug

that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, please contact Alison Blaus, Regulatory Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IND 68598	ORIG 1	BRISTOL-MYERS SQUIBB	APIXABAN

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/s/

ALISON L BLAUS
08/18/2009

NORMAN L STOCKBRIDGE
08/18/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,598

Britol-Myers Squibb
ATTENTION: Porter P. Layne, Ph.D., M.B.A.
Group Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Layne:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for apixaban (BMS-562247).

We also refer to your amendment dated January 13, 2009, containing an update to your phase 3 protocol (CVI85030) entitiled, "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". This protocol was initially submitted to the Division as a Special Protocol Assessment (SPA), dated November 9, 2006.

Upon review of the above mentioned amendment, we have the following comments:

1. You propose to (b) (4)
2. Please plan to analyze separately the efficacy in the subgroup of subjects enrolled under the new eligibility criteria and the prior eligibility criteria.
3. The statement in your revised eligibility criteria "would likely to be treated with warfarin or another VKA if not enrolled in a clinical trial" is vague and therefore subject to variability in investigator interpretation. Please make clearer the population you wish to enroll.

We also acknowledge the other changes to this protocol and note that they appear to be acceptable.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, please contact Alison Blaus, Regulatory Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name / Subject
IND 68598	BRISTOL-MYERS SQUIBB	APIXABAN

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/s/

ALISON L BLAUS
02/17/2009

NORMAN L STOCKBRIDGE
02/17/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,598

Bristol-Myers Squibb Company
Attention: Porter P. Layne, Ph.D.,
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Layne:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Apixaban.

We also refer to your October 27, 2006, request for a special clinical protocol assessment. The protocol is entitled "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 Nonvalvular Atrial Fibrillation."

We have completed our review of your submission and have the following responses to your questions.

1. Does the Division agree that the study as designed and described in the attached protocol will provide the information needed to make a regulatory decision regarding the approval of apixaban in the identified indication?

   FDA response: In general, we agree that the study, as designed and described in the proposed protocol, would provide the information necessary to make a regulatory decision on the approvability of apixaban for the prevention of stroke and other thromboembolic complications associated with atrial fibrillation.

2. Does the Division agree that the warfarin-naive subgroup (which is the subject of the second key secondary objective named in the protocol) is a clinically meaningful population as defined in the labeling guidance, and that a significant finding in this group could support a labeling claim?

   FDA response: Any population of "treatment naive" patients could be considered clinically meaningful. Certainly, "warfarin/Vitamin K antagonist naïve" patients would be no exception. A statistically significant and robust finding of superiority of apixaban relative to warfarin/Vitamin K antagonists in this subgroup of patients could support a labeling claim.

3. At the end-of-phase 2 meeting, there was some discussion regarding an acceptable weighting of the major bleeding and stroke components of the composite endpoint for two key secondary objectives. It was agreed that BMS would submit a proposal for the Division's consideration. Section 8.4.3, "Efficacy Analyses" of the protocol indicates that for the two key secondary objectives, sensitivity analyses will be performed to assess the effects of using different weights for each of the components

of the composite endpoint, i.e., ischemic stroke, hemorrhagic stroke, systemic embolism and major bleeding. Does the Agency agree with this approach?

FDA response: We cannot offer comments on this question until a more detailed description of how each endpoint is to be weighted is provided. Section 8.4.3 of the protocol does not currently allow us to make such a determination.

4. If one or both of the two key secondary objectives are achieved, BMS would like to describe the composite endpoint, i.e., ischemic stroke, hemorrhagic stroke, systemic embolism and major bleeding in labeling as follows: (b) (4) Does the Division agree?

FDA response: At this time, we cannot agree to any specific labeling language (e.g. "(b) (4)") because we do not know how the components of the composite endpoint will be weighted. In addition, please note that if there are serious adverse events that are associated with apixaban and not captured in the composite endpoint, a claim of (b) (4)" would be difficult to grant.

5. At the end-of-phase 2 meeting, the Division recommended that the non-inferiority margin be 1.38 and that testing for non-inferiority be performed at the one-sided α=0.025 (non-inferiority demonstrated if upper bound of the two-sided 95% CI < 1.38). (b) (4) Section 8.1 "Sample Size Determination" and Section 8.4.3 "Efficacy Analyses" describe our approach for satisfying the differing regulatory requirements. Does the Division agree with this approach?

FDA response: The Division has confirmed that the study will have at least 90% power to meet both regulatory definitions of non-inferiority with 448 expected events. In fact, a margin of 1.38 at 0.05 levels will need 405 events and a margin of (b) (4) levels will need 448 events. When the application is eventually filed, we expect to judge success for the primary endpoint on the basis of excluding the non-inferiority margin of 1.38 at an alpha of 0.05.

Regarding the question of analyzing both possible superiority on the primary endpoint and superiority of all three secondary objectives, we have not yet come to a conclusion on the appropriate statistical strategy. We note, however, that this should not affect the design and conduct of the trial at this point and we intend to have further internal (and perhaps external) discussion of the question.

Regarding your proposed interim analysis, which will be performed once 50% of the primary efficacy endpoint events have been confirmed by CEC, we have the following comment. The boundaries associated with a one-sided superiority test at (b) (4) will be used. We are concerned that such a loose boundary could have a substantial impact on the significance level of the final analysis. For instance, suppose the interim analysis for superiority showed nominal significance of 0.08. This would clearly not be sufficient evidence for superiority, but the 95% CI would strongly rule out the NI margin, perhaps forcing the trial to stop for non-inferiority, but in any case, representing an interim assessment of NI. The impact of this analysis on total alpha for non-inferiority, however, has not been accounted for. We suggest you use a much smaller and more conservative α (<0.001) or O-F boundary for the interim analysis.

6. The criteria for describing the effect of apixaban in labeling as comparable to warfarin were briefly discussed at the end-of-phase 2 meeting. The Division suggested that retaining something on the

order of 90% of the warfarin effect might be sufficient basis for granting a claim of comparable effectiveness, but indicated that the criteria for granting such a claim have not been defined. We have given some thought to what the criteria for a claim of comparable effectiveness should be. We suggest that satisfaction of the following criteria would justify the granting of a comparable effectiveness claim for apixaban versus warfarin in atrial fibrillation:

1. a point estimate for the RR that is < 1 and
2. preservation of a substantial amount of the effect of warfarin and
3. a high level of confidence for the finding and
4. an acceptable safety profile

BMS is requesting that the Division consider the following proposal which satisfies all the above criteria. We propose that the criteria for granting a claim of comparable efficacy of apixaban to warfarin be an outcome where, for the primary efficacy endpoint, the observed RR is <1 which translates to the upper bound of a two-sided (b)(4)% CI for RR being < (b)(4) Meeting this criterion preserves (b)(4)% on a log scale (b)(4)% on a linear scale) of the effect of warfarin. Does the Division find this proposal acceptable?

If the Division agrees to this criterion and the criterion is achieved, BMS would like to describe this finding in labeling as follows: "(b)(4) ". Does the Division find this acceptable?

FDA response: We previously suggested preservation of 90% of the effect expected from warfarin (with α=0.05) would suffice. We do not believe that preserving (b)(4)% is adequate for α=0.05.

7. Another possible outcome of the study is that apixaban is superior to warfarin for the primary efficacy endpoint, i.e., the upper bound of the two-sided 95% CI for RR is < 1 (which translates to an observed RRR > 16.9%). BMS proposes that this outcome be considered a reasonable criterion for granting the following efficacy claim "(b)(4)". We realize that this outcome is a very high hurdle, considering the efficacy of warfarin that is expected to be observed in a blinded clinical trial setting with close INR monitoring. Does the Division find this acceptable?

   FDA response: Generally, a claim that (b)(4) could be made based on consistent and convincing findings from at least two adequate and well-controlled studies. Alternatively, a robust finding from a single outcome study (e.g., P value around 0.001) could also be a basis for a claim of superiority from a single study. Both of the above scenarios assume, of course, that the active control was used optimally with respect to dose and dosing regimen.

8. The primary safety endpoint of this study is major bleeding (as defined in Section 6.4.1). BMS has pre-specified a second category of bleeding events, i.e., clinically relevant non-major bleeding" (as defined in Section 6.4.1), which includes bleeding events that do not meet the criteria for major bleeding, but nonetheless are considered clinically important. All suspected major and clinically important bleeding events will be adjudicated by a Clinical Events Committee. It is anticipated that the trial data for bleeding events (major, clinically relevant non-major and other) will be presented in labeling in a tabular summary as it is for most anticoagulant drugs. It is also anticipated that the statistical assessments associated with major bleeding and clinically relevant non-major bleeding would appear in the tabular summary in the label similar to the presentation of bleeding data in the Angiomax package insert. Does the Division agree?

If apixaban-treated subjects have a statistically significant lower rate of major bleeding versus warfarin-treated subjects ($p<0.05$), would this finding support language such as the following in the label: [redacted (b) (4)]? In addition, if apixaban-treated subjects also have a statistically significant lower rate of clinically relevant, non-major bleeding, would this finding support language such as the following in the label: "[redacted (b) (4)]"?

FDA response: We have not consistently accepted any single definition of major bleeding. The definition of major bleeding in the proposed protocol is adapted from the ISTH. While we do not object to this definition, the study case report form should allow for capture of alternative definitions of major bleeding (e.g., TIMI major bleeding). A tabular summary of the major bleeding events could be included in labeling as this is an expected adverse event based on the drug's pharmacology. A statement of [redacted (b) (4)] would depend on the strength of the evidence and the nature of the events. With respect to non-major bleeding adverse events, any labeling description or presentation of such events would depend on the strength and consistency of the findings.

In addition, we have the following comments.

- While data on clinical outcomes in subjects post study drug discontinuation may be collected, the primary endpoint analysis should be limited to endpoints that occur on treatment (or within a short period of time, e.g., 15-30 days post study drug discontinuation). The inclusion of endpoint events that are substantially delayed relative to study drug discontinuation in the primary endpoint analysis may confound the interpretability of a non-inferiority analysis.

- The CRF currently contains codes to capture reasons why study subjects were discontinued from study drug (e.g., adverse event, dosing error, subject's choice, other, etc.). There should also be codes for subjects who discontinue study drug due to endpoint events (e.g., stroke, death, bleeding, etc.); these should not be lumped as "other."

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at http://www.fda.gov/cder/guidance/index.htm. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, please contact:

Mr. Russell Fortney
Regulatory Health Project Manager
(301) 796-1068

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
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