

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-986 & 22-072

ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE

Bristol-Myers Squibb Company

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
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		NDA NUMBER	
		NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb Company	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) SPRYCEL™			
ACTIVE INGREDIENT(S) Dasatinib		STRENGTH(S) 20 mg, 50 mg, 70 mg	
DOSAGE FORM Tablets			
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 file 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 6,596,746		b. Issue Date of Patent July 22, 2003	c. Expiration Date of Patent April 13, 2020
d. Name of Patent Owner Bristol-Myers Squibb Company		Address (of Patent Owner) 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?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

Bristol-Myers Squibb Company

<p>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.</p>		
<p>2. Drug Substance (Active Ingredient)</p>		
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?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No**(see below)
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).	<input type="checkbox"/> Yes <input type="checkbox"/> 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.)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.6	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>**The patent does not specifically claim any individual polymorphic forms. The patent claims the compound and as a compound claim, it covers all polymorphic forms of the compound.</p>		
<p>3. Drug Product (Composition/Formulation)</p>		
3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
3.2	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes <input type="checkbox"/> No

Bristol-Myers Squibb Company

4. Method of Use	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
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?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 7	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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 approved labeling.) See attached Appendix A.
4. Method of Use	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
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?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 18	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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 approved labeling.) See attached Appendix A.
4. Method of Use	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
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?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 29	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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 approved labeling.) See attached Appendix A.
4. Method of Use	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
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?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 30	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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 approved labeling.) See attached Appendix A.

4. Method of Use	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
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?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 44	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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 approved labeling.) See attached Appendix A.
4. Method of Use	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
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?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 47	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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 approved labeling.) See Appendix A.

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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.	<input type="checkbox"/> Yes

6. Declaration Certification	
<p>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.</p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> <p><i>Mary VanAtten</i></p>	<p>Date Signed</p> <p>12/13/05</p>

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.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input checked="" type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name Mary VanAtten</p>	
<p>Address To the attention of V.P. and Chief Patent Counsel Route 206 & Provinceline Rd. P.O. Box 4000</p>	<p>City/State Princeton, New Jersey</p>
<p>ZIP Code 08543-4000</p>	<p>Telephone Number (609)252-4379</p>
<p>FAX Number (if available) (609)252-4526</p>	<p>E-Mail Address (if available) patents@bms.com</p>

Bristol-Myers Squibb Company

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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 supplemental 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. 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 July 2003) 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://forms.psc.gov/forms/ndahtm/ndahtm.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.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 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 # 21-986

SUPPL #

HFD #

Trade Name SPRYCEL

Generic Name dasatinib

Applicant Name Bristol-Myers Squibb

Approval Date, If Known 6-28-06

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.

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:

d) Did the applicant request exclusivity?

YES NO

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

5

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?

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#

NDA#

NDA#

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#

NDA#

NDA#

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

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:
Title:
Date:

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Amy Baird
6/28/2006 04:18:56 PM

Robert Justice
6/28/2006 04:53:05 PM

EXCLUSIVITY SUMMARY

NDA # 22-072

SUPPL #

HFD # 150

Trade Name SPRYCEL

Generic Name dasatinib

Applicant Name Bristol-Myers Squibb

Approval Date, If Known 6-28-06

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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.

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:

d) Did the applicant request exclusivity?

YES NO

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

5

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?

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)

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YES NO

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

NDA#

NDA#

NDA#

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#

NDA#

NDA#

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

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:
Title:
Date:

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Amy Baird
6/28/2006 04:20:29 PM

Robert Justice
6/28/2006 06:45:01 PM

Bristol-Myers Squibb Company

NDA NO. 21-986

DASATINIB (BMS-354825) TABLETS

CERTIFICATION: DEBARRED PERSONS

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, Bristol-Myers Squibb Company certifies that it has not used and will not use in any capacity the services of any person listed as debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.



Marie-Laure Papi, PharmD
Associate Director
Regulatory Science
5 Research Parkway
Signature 91 Building, 3SIG-5014
Wallingford, CT 06492
203-677-3830



Certification Date

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-986 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 12-28-05 Action Date: 6-28-06

HFD-150 Trade and generic names/dosage form: SPRYCEL™ (Dasatinib) Tablets

Applicant: Bristol-Myers Squibb Therapeutic Class: 5010100

Indication(s) previously approved:

None.

Number of indications for this application(s): 2

Indication #1: The treatment of adults with chronic, accelerated, or blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: _____ Partial Waiver _____ Deferred _____ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: Indication was granted orphan designation.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-986
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: The treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia and lymphoid blast chronic myeloid leukemia with resistance or intolerance to prior therapy.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: Indication was granted orphan designation.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-986
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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this page is the manifestation of the electronic signature.**

/s/

Amy Baird

4/27/2006 03:14:20 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-986	Efficacy Supplement Type SE-	Supplement Number
Drug: SPRYCEL (dasatinib) Tablets		Applicant: Bristol-Myers Squibb
RPM: Amy Baird		HFD-150 Phone # 796-1325
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority 		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<ul style="list-style-type: none"> • Chem class (NDAs only) 		1
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 		Orphan
❖ User Fee Goal Dates		
		6-28-06
❖ Special programs (indicate all that apply)		
		<input type="checkbox"/> None Subpart H <input checked="" type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 		<input type="checkbox"/> Paid UF ID number
<ul style="list-style-type: none"> • User Fee waiver 		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
<ul style="list-style-type: none"> • User Fee exception 		<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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 box below (Exclusivity).

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? () Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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 box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	✓
<ul style="list-style-type: none"> • Exclusivity summary • 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.) 	
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" 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. 	() Yes, Application # _____ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	Filing Review 6-26-06

• Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	<input type="checkbox"/> Materials requested in AP letter <input checked="" type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	6/26/06
• Most recent applicant-proposed labeling	6/23/06
• Original applicant-proposed labeling	12/28/05
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC 5-19-06 & 6-13-06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Gleevec
❖ Labels (immediate container & carton labels)	See labeling tab
• Division proposed (only if generated after latest applicant submission)	"
• Applicant proposed	"
• Reviews	"
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	6/23/06
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	N/A
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	6/15/05 (CMC only)
• Pre-NDA meeting (indicate date)	#1-7/7/05 & #2-10/27/05
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	6/2/06
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	Fed. Register Notice for ODAC

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	
	ONDA A 6/26/06
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	6/22/06
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See tab (taken from MOR)
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	4/27/06
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	6/16/06
❖ Biopharmaceutical review(s) (indicate date for each review)	
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	6/16/06
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	
❖ Facilities inspection (provide EER report)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (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.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).



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

MEMORANDUM

DATE: June 27, 2006

FROM: Dotti Pease, Chief, Project Management Staff
Division of Drug Oncology Products, HFD-150

SUBJECT: NDA 21-986 and 22-072 administrative split of NDA for dasatinib

TO: File

NDA 21-986 was received December 28, 2005 and included the indications of chronic myelogenous leukemia (CML) and acute lymphocytic leukemia (ALL). At the Oncologic Drugs Advisory Committee Meeting June 2, 2006 it was recommended that the CML should be approved as accelerated approval and the ALL approved by regular approval. The Division of Drug Oncology Products agreed with this recommendation.

In order to reflect in COMIS an accelerated and regular approval for this product, it was necessary to administratively split the NDA. Therefore, NDA 21-986 will retain the CML indication, and NDA 22-072 was created for the ALL indication.

All submissions were copied to the second NDA and reviews linked to both in DFS. A separate action package and letter was prepared for each NDA.

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

/s/

Dotti Pease
6/27/2006 12:50:57 PM
CSO

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22, Mail Stop 4447)

DATE RECEIVED: May 1, 2006	DESIRED COMPLETION DATE: June 9, 2006	OSE REVIEW #: 06-0124-1
DOCUMENT DATE: December 28, 2005	PDUFA DATE: June 28, 2006	

TO: Robert Justice, M.D.
Director, Division of Drug Oncology Products

THROUGH: Linda Kim-Jung, Pharm.D. Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Todd Bridges, R.Ph., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: **Sprycel**
(Dasatinib Tablets)
20 mg, 50 mg, and 70 mg

NDA #: 21-986

SPONSOR: Bristol-Myers Squibb Company

- RECOMMENDATIONS:**
1. DMETS has no objections to the use of the proprietary name, Sprycel. DMETS considers this a final review. However, if approval of the application is delayed beyond 90 days from the signature date of this review then the name and its labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
 2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.
 3. DDMAC does not recommend approval of the proposed trade name, Sprycel.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Diane Smith, Project Manager, at 301-796-0538.

**Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
WO 22, MAIL STOP 4447
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 22, 2006

NDA NUMBER: 21-986

NAME OF DRUG: **Sprycel**
(Dasatinib Tablets)
20 mg, 50 mg, and 70 mg

NDA SPONSOR: Bristol-Myers Squibb Company

I. INTRODUCTION

This consult was written in response to a request from the Division of Drug Oncology Products (HFD-150), for assessment of the proprietary name, Sprycel, regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were submitted for review and comment.

Initially, the Division concurred with DDMAC's objection to the name, and thus, DMETS did not complete the name review for Sprycel at that time (see OSE Review #06-0124 dated May 12, 2006). However, subsequently the Division has re-requested that DMETS continue with its safety review of the name, Sprycel, despite DDMAC's objection to the proprietary name, Sprycel.

PRODUCT INFORMATION

Sprycel is an inhibitor of oncogenic kinases indicated for the treatment of adults with chronic, accelerated, or blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including Imatinib. Sprycel is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia and lymphoid blast chronic myeloid leukemia with resistance or intolerance to prior therapy. The usual dose of Sprycel is 70 mg twice daily. Sprycel is proposed to be available as 20 mg, 50 mg, and 70 mg tablets in 60 count bottles. The 20 mg and 50 mg product strengths are utilized for patients that require dose modifications (e.g., patients who did not achieve a response or experienced adverse reactions at the usual dose).

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{i,ii} as well as several FDA databases^{iii,iv} for existing drug names which sound-alike or look-alike to Sprycel to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted^v. The SAEGIS^{vi} Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proposed proprietary name. Potential concerns regarding drug marketing and promotion related to the proposed name are also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC objects to the proposed trade name Sprycel because _____

ⁱ MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

ⁱⁱ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, Missouri.

ⁱⁱⁱ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

^{iv} Phonetic and Orthographic Computer Analysis (POCA)

^v www location <http://www.uspto.gov/tmdb/index.html>.

^{vi} Data provided by Thomson & Thomson's SAEGIS™ Online service, available at www.thomson-thomson.com

Despite DDMAC's objection to the proprietary name, Sprycel, the Division requested that DMETS continue with its safety review.

2. The Expert Panel identified one proprietary name which was thought to have the potential for confusion with Sprycel. This product is listed in Table 1 (see below), along with the dosage forms available and usual dosage.

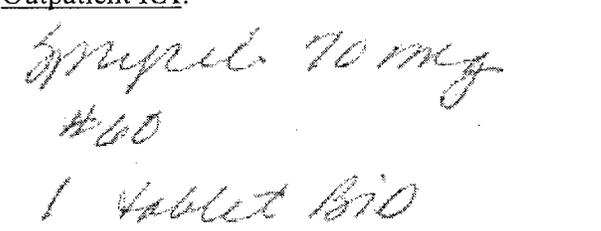
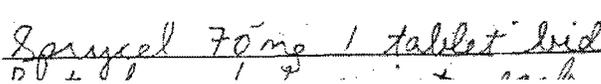
Table 1. Potential Look-Alike Name Identified for Sprycel.

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Sprycel	Tablets, Dasatinib, 20 mg, 50 mg, and 70 mg	70 mg twice daily.	N/A
Synarel	Metered Nasal Spray, Nafarelin Acetate, 0.2 mg/spray	<u>Endometriosis</u> : 1 spray in one nostril every morning, 1 spray in the other nostril every evening. <u>Central precocious puberty</u> : 2 sprays into one nostril every morning and 2 sprays in the other nostril every evening.	LA
*Frequently used, not all-inclusive. **LA (look-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Sprycel with other U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 119 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Sprycel (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<u>Outpatient RX:</u> 	Sprycel 70 mg #60 1 tablet twice daily
<u>Inpatient RX:</u> 	

2. Results:

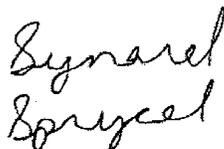
The proposed name was interpreted as “Synyrel” and “Synerel” by two respondents, which can look similar to “Synarel”, an approved drug product currently marketed in the United States. See Appendix A (page 8) for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Sprycel, the primary concerns raised were related to look-alike and/or sound-alike confusion with Synarel.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with the aforementioned name. However, negative findings are not predictive as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Sprycel.

Synarel was identified as a name with similar appearance to Sprycel when scripted. This was evidenced by the outpatient prescription study in which the proposed name was misinterpreted by two respondents as “Synyrel” and “Synerel”, which may look similar to “Synarel”. Synarel is a nasal spray indicated for the treatment of endometriosis and precocious puberty. Both names begin with the letter (S), contain the same letter count (seven), and have the same ending (“el”) which contributes to the visual similarity of this name pair. Orthographic similarities may also be attributed to each name having a downstroke letter (y vs. p) as the second letter. However, the additional downstroke letter “y” in the name Sprycel may help to differentiate Synarel from Sprycel on an order (see below).



Additionally, Sprycel is available in three different strengths and thus, the product strength must either be indicated on a prescription or obtained from the prescriber prior to dispensing which may further differentiate this name pair. Since Sprycel is available in multiple strengths, the necessity to indicate the product strength on a prescription written for Sprycel will help to decrease the potential for confusion between this name pair. Furthermore, Sprycel and Synarel have different routes of administration (orally vs. intranasal), indications for use (leukemia vs. endometriosis or precocious puberty), dosage forms (nasal solution vs. tablet), and dosing units (spray vs. tablet). Moreover, the ordered quantity for Sprycel and Synarel will likely differ as well (e.g., #1 or 10 mL vs. #60) and thus, the ordered net quantity, if included on a prescription order, may help to differentiate these products. Additionally, while an order for Synarel may be written with the instructions “use as directed”, an order for Sprycel will likely be written with a specific dose and frequency of administration (e.g., 1 tab. twice daily or 70 mg twice daily). Furthermore, according to the 2004 annual report for Synarel, the distribution from December 2003 through February 2005 was less than — Despite some orthographic similarities between Synarel and Sprycel, the low distribution levels of Synarel and differentiating product characteristics described above will help to minimize the potential for confusion between the two drug products.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Sprycel, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

1. GENERAL COMMENTS

- a. As currently presented, the “Usual Dosage” statement is lengthier than necessary and takes up too much space on the primary display panel. Revise the “Usual Dosage” statement to read “Usual Dosage: See package insert.”
- b. There should be no interfering matter (i.e., line) between the proprietary and established names. We refer you to 21 CFR 201.10(a) for further guidance.
- c. Revise so that the dosage form (i.e., tablets) and established name are of the same font size and type.

2. CONTAINER LABEL

See General Comments 1a through 1c.

3. CARTON LABELING

See General Comments 1a through 1c.

4. INSERT LABELING

Delete the use of trailing zeros throughout the insert labeling. FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols (e.g., trailing zeros). Thus, we request that the Divisions not approve or use trailing zeros in their labels and labeling as the potential for a ten-fold dosing error exists if the decimal point is not readily apparent. Additionally, the use of terminal zeroes in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "... to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." We further note that the use of trailing zeros are specifically listed as dangerous abbreviations, acronyms, or symbols in the 2006 National Patient Safety Goals of The Joint Commission for Accreditation of Hospitals (JCAHO). Lastly, safety groups, such as the Institute for Safe Medication Practices (ISMP), also list trailing zeros on their dangerous abbreviations and dose designations list.

5. PATIENT INFORMATION

For the benefit of lactose intolerant patients, include a prominent statement stating that this product contains lactose.

Appendix A. DMETS prescription study results for Sprycel.

Voice	Inpatient	Outpatient
Bricel	Sarycel	Smyril
Bricel	Spraycel	Snyreb
Bricell	Spregeel	Spnpeb
Brycel	Sprycel	Sripel
Brycell	Sprycel	Sripel
Brysel	Sprycel	Sripib
Bryso	Sprycel	Sripil
Prizel	Sprycel	Sripil
Snipel	Sprycel	Sripil
Spricel	Sprycel	Sripil
Sprycell	Sprycel	Spryrel
	Sprycel	Spryrel
	Sprycel	Spryiril
	Sprycel	Spupil
	Sprycel	Synerel
		Synyrel

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

/s/

Todd Bridges
6/27/2006 03:20:19 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
6/27/2006 03:42:58 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/27/2006 04:03:09 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, Director DMETS, in her
absence

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-986

Supplement #

Efficacy Supplement Type SE-

Trade Name: **Dasatinib**
Established Name: **SPRYCEL (Dasatinib) Tablets**
Strengths: **20 mg, 50 mg, 70 mg**

Applicant: **Bristol-Myers Squibb**
Agent for Applicant:

Date of Application: **December 28, 2005**
Date of Receipt: **December 28, 2005**
Date clock started after UN: **N/A**
Date of Filing Meeting: **February 13, 2006**
Filing Date: **February 24, 2006**
Action Goal Date (optional):

User Fee Goal Date: **June 28, 2006**

Indication(s) requested: **Treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib.**

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application is a (b)(2), complete Appendix B.*
- (2) *If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) **1**
Other (orphan, OTC, etc.) **Orphan**

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient*

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? **All sections.**

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO

- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, 5 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act 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"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO

- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: **66,971**

- End-of-Phase 2 Meeting(s)? Date(s) 6-15-05 (CMC EOP2) NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 7-7-05 NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO

- Risk Management Plan consulted to ODS/IO? N/A YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application: N/A for NDA 21-986

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 13, 2006

BACKGROUND: NDA 21-986 SPRYCEL (dasatinib) Tablets is a new molecular entity submitted for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib.

ATTENDEES: Dagher, Kaminskas, Farrell, Pope, Men, Justice, Rothmann, Jiang

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Dr. Kaminskas, Dr. Brave, Dr. Goodman
Secondary Medical:	Dr. Farrell
Statistical:	Dr. Janet Jiang
Pharmacology:	Dr. Haleh Mahloogi
Statistical Pharmacology:	N/A
Chemistry:	Dr. Timmer, Dr. Wang
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Dr. Men, Dr. Bullock
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Dr. Iacono-Connors
Regulatory Project Management:	Amy Baird
Other Consults:	Joseph Grillo, Carol Holquist, Diane Toyer

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site inspection needed? YES NO
- Advisory Committee Meeting needed? YES, date if known June, 2006 NO
- 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? N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. inspection needed? YES NO

PHARMACOLOGY	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• GLP inspection needed?			YES <input type="checkbox"/> NO <input type="checkbox"/>
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Establishment(s) ready for inspection?			YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>
• Microbiology			YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>

ELECTRONIC SUBMISSION:
Any comments: None.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Convey document filing issues/no filing issues to applicant by Day 74.

Regulatory Project Manager, HFD-

Appendix A to NDA Regulatory Filing Review

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (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.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, YES NO
ORP?

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO
6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).)?
N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# _____ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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

/s/

Amy Baird
6/26/2006 01:00:41 PM
CSO

Amy Baird
6/26/2006 01:03:36 PM
CSO

B

2 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

Baird, Amy

From: Baird, Amy
ent: Friday, June 23, 2006 4:31 PM
fo: 'marie-laure.papi@bms.com'
Subject: Dasatinib Phase 4 Commitments

Here are the updated phase 4 commitments.

Required Phase 4 Commitments

1) You have agreed to submit the completed study report and data from the study, CA-180-002, a bicenter, dose escalation study to determine the safety, pharmacokinetics, and pharmacodynamics of BMS-354825 in the treatment of patients with Chronic, Accelerated, or Blast Phase Chronic Myelogenous Leukemia, or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia who have hematologic resistance to Imatinib Mesylate.

Protocol Submission: xx/xx
Study Start: 11/03
Final Report Submission: xx/xx

2) You have agreed to submit the completed study report and data from the study, CA-180-005, a phase 2 multicenter study of dasatinib (BMS-354825) in subjects with Accelerated Phase Chronic Myeloid Leukemia resistant to or intolerant of Imatinib Mesylate.

Protocol Submission: xx/xx
Study Start: 12/04
Final Report Submission: xx/xx

3) You have agreed to submit the completed study report and data from the study, CA-180-006, a phase 2 multicenter study of dasatinib (BMS-354825) in subjects with Myeloid Blast Phase Chronic Myeloid Leukemia resistant to or intolerant of Imatinib Mesylate

Protocol Submission: xx/xx
Study Start: 12/04
Final Report Submission: xx/xx

4) You have agreed to submit the completed study report and data from the study, CA-180-013, a phase 2 multicenter study of dasatinib (BMS-354825) in subjects with Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia who have disease that is resistant to high dose Imatinib Mesylate or who are intolerant of Imatinib

Protocol Submission: xx/xx
Study Start: 02/05
Final Report Submission: xx/xx

5) You have agreed to submit the completed study report and data from the study, CA-180-017, a randomized, open-label multicenter study of dasatinib (BMS-354825) versus Imatinib Mesylate (Gleevec, Glivec) 800 mg/d in subjects with Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia who have disease that is resistant to Imatinib at a Dose of 400 - 600 mg/d

Protocol Submission: xx/xx
Study Start: 02/05
Final Report Submission: xx/xx

6) You have agreed to submit the study report and data from the study, CA-180-015, a phase 2 multicenter study of dasatinib (BMS-354825) in subjects with Lymphoid Blast Phase Chronic Myeloid Leukemia or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia resistant to high dose Imatinib Mesylate (Gleevec) or who are intolerant of Imatinib

Protocol Submission: xx/xx
Study Start: 01/05
Final Report Submission: xx/xx

) You have agreed to submit the completed study report and data from the study, CA-180-051, a single-dose, pharmacokinetic study of BMS-354825 in subjects with hepatic impairment compared to healthy adult subjects.

Protocol Submission: 05/06
Study Start:
Final Report Submission:

8) You have agreed to submit the completed study report and data from the study, CA-180-021, an open-label, single-sequence study to evaluate the effect of ketoconazole on the pharmacokinetics of BMS-354825 in patients with advanced solid tumors.

Protocol Submission: NA
Study Start: NA
Final Report Submission:

Other Phase 4 Commitments

9) You have agreed to submit the completed study report and data from the study, CA-180-034, a randomized, two-by-two, open-label study of dasatinib (BMS-354825) in subjects with Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia resistant to or intolerant of Imatinib Mesylate

10) You have agreed to complete a study evaluating the effects of a p-glycoprotein inhibitor on the pharmacokinetics of BMS-354825 and to submit a study report and the data.

Protocol Submission:
Study Start:
Final Report Submission:

Amy Baird
Consumer Safety Officer
Division of Drug Oncology Drug Products
Phone: 301-796-1325
Fax: 301-796-9867
Email: bairda@cder.fda.gov

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: June 16, 2006

TO: Amy Baird, Regulatory Project Manager
Edvardas Kaminskas, M.D., Clinical Reviewer
Division of Oncology Drug Products, HFD-150

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Lauren Iacono-Connors, Ph.D.
Reviewer, Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

SUBJECT: Preliminary Evaluation of Clinical Inspections, Pending Receipt of all EIRs

NDA: 21986/000

NME: Yes

APPLICANT: Bristol-Myers Squibb

DRUG: Dasatinib (BMS-354825)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of adults with chronic myeloid leukemia (chronic, accelerated, and blast phases) or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (PH+ALL)

CONSULTATION REQUEST DATE: March 10, 2006

DIVISION ACTION GOAL DATE: May 26, 2006

PDUFA DATE: June 28, 2006

I. BACKGROUND:

Drug Product:

Dasatinib (BMS-354825) is a potent inhibitor of multiple oncogenic kinases that are linked to multiple forms of human malignancies. Dasatinib binds to both active and inactive forms of a specific oncogenic kinase and through this binding action is thought to mediate efficacy via antiproliferation of leukemic cells. This drug is a new molecular entity and is purported by the

sponsor to provide a critical treatment option for patients with advanced Chronic Myeloid Leukemia who are either refractive or intolerant to Imatinib (Gleevec®). The safety and efficacy data submitted to the agency, NDA 21986/000, to support the above indication are drawn in part from 5 studies. One study is a phase I (dose escalation study/safety), and 4 are phase II clinical safety and efficacy studies that each represents a different stage of disease in these rare patient populations. All studies were open labeled, single-arm and multicenter.

The sponsor chose to keep the efficacy data generated by the phase II studies unbundled in order to demonstrate comparative dasatinib safety and efficacy by disease stages as follows:

- Accelerated Phase CML (Imatinib-Resistant or IM-Intolerant): CA180-005 (197 Enrolled/40 CIs)
- Myeloid Blast Phase CML (IM-R or IM-I): CA180-006 (124 Enrolled/35 CIs)
- Chronic Phase CML (IM-R or IM-I): CA180-013 (424 Enrolled/41 CIs)
- Ph+ ALL of Lymphoid Phase CML (IM-R or IM-I): CA180-015 (101 Enrolled/34 CIs)

The phase I study, CA180-002, is a dose escalation study in patients with chronic, accelerated, or blast phase chronic myelogenous leukemia, or PH+ALL who have hematologic resistance to imatinib mesylate (Gleevec®). This study was also, open-labeled, multi-cohort and multicenter (2 sites). Study CA180-002 had 92 subjects enrolled as of the study date closure of May 11, 2005.

The phase I and II protocols and their execution by Hagop M. Kantarjian, M.D., University of Texas MD Anderson Cancer Center, Charles Sawyers, MD., UCLA, Andreas Hochhaus, MD., at Fakultät fuer Klinische Medizin, Mannheim, Germany and Michele Baccarani, MD., at Università di Bologna, Istituto di Ematologia, Bologna, Italy participated as primary investigators on the 5 protocols audited. In addition, an inspection of the sponsor-monitor was conducted on the listed studies performed by the investigators mentioned above, completing the sponsor and monitor compliance program (CP 7348.810).

II. RESULTS:

Inspected Entity	City, State\Country	Protocol(s)	Inspection Dates	EIR Received Date	Final Classification
Hagop Kantarjian, M.D.	Houston, TX	CA180-002 CA180-005 CA180-006 CA180-013 CA180-015	May 2006	Pending DAL-DO	Pending
Charles Sawyers, M.D.	Los Angeles, CA	CA180-002	April 17-26, 2006	May 9, 2006	NAI
Andreas Hochhaus, M.D.	Mannheim, Germany	CA180-005 CA180-006 CA180-013 CA180-015	May 2006	Pending FLA-DO	Pending
Michele Baccarani, M.D.	Bologna, Italy	CA180-005 CA180-006 CA180-013	May 2006	Pending FLA-DO	Pending
Bristol-Myers Squibb	Wallingford, CT	CA180-002 CA180-005 CA180-006 CA180-013 CA180-015	May 2006	Pending NWE-DO	Pending

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

1. **Charles Sawyers, M.D.**
 UCLA
 11-934 Factor Building
 10833 Leconte Avenue
 Los Angeles, California 90095

Protocol Number	Subjects Randomized	Subjects Audited
CA180-002	41	10

a. What was inspected?

The study records of 10 of the 41 subjects enrolled into the phase I study, and under the care of Dr. Sawyers, were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these 10 subjects the record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed the date and cause of death and informed consent forms for all randomized subjects.

b. Limitations of inspection: None

c. General observations/commentary:

The site was found to be adequate in the execution of the study CA180-002. The study was well controlled and documented. No FDA Form 483 was issued. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. Source data were audited for 10 subjects. IRB compliance was verified and test article accountability records were found to be sufficient. All AEs were reported and followed up. All serious AEs were reported immediately to the sponsor and the IRB. There were no deaths related to the study drug.

d. Assessment of data integrity: The data from Dr. Sawyers' site, associated with protocol CA180-002, submitted to the agency in support of NDA 21986, is reliable.

2. **Hagop M. Kantarjian, M.D. (Current CI; As of Jan 2006)**
 University of Texas
 MD Anderson Cancer Center
 1515 Holcombe Blvd
 Houston, Texas 77030

Protocol Number	Subjects Randomized	Subjects Audited
CA180-002	48	8
CA180-005	11	2
CA180-006	2	2
CA180-013	22	2
CA180-015	2	2

a. What was inspected?

The study records of 8 subjects for study CA180-002 and 2 subjects each from the remaining 4 studies were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these audited subjects the record audit included comparison of source documentation to CRFs with particular attention paid to eligibility criteria satisfaction, confirmation of diagnosis. The FDA investigator also assessed the date and cause of death, and any SAEs and AEs and informed consent forms.

b. Limitations of inspection: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator.

c. General observations/commentary



The EIR is currently being finalized and will be submitted to DSI upon completion. The observations noted above are based on the preliminary EIR and communication from the field investigator, Ms. Andrea Branche. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. Assessment of data integrity: The data from Dr. Kantarjian's site, associated with the 5 protocols listed above, submitted to the agency in support of NDA 21986, are reliable.

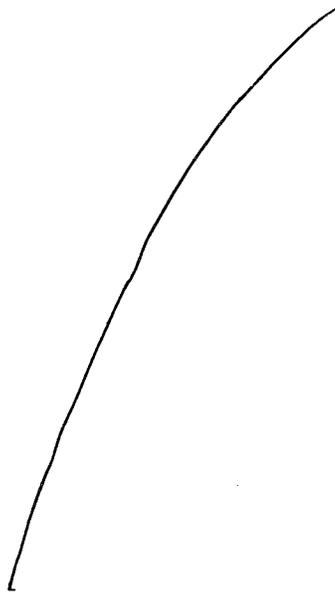
3. **Dr. Andreas Hochhaus**
Fakultaet Fuer Klinische Midizin Mannheim
Theodor-Kutzer-Ufer 1-3
Mannheim 68163
Germany

Protocol Number	Subjects Randomized	Subjects Audited
CA180-005	5	2
CA180-006	3	2
CA180-013	30	12
CA180-015	4	3

a. What was inspected? The study records of a subset of subjects for the studies listed in the table above were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these audited subjects the record audit included comparison of source documentation to CRFs with particular attention paid to eligibility criteria satisfaction, confirmation of diagnosis. The FDA investigator also assessed the date and cause of death, and any SAEs and AEs and informed consent forms.

b. Limitations of inspection: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. Also, the majority of the audited documents were in the native language of German. Field investigator Ms. Shari Shambaugh had the benefit of an interpreter who was present for the inspection. However, the language barrier required that Ms. Shambaugh accept the interpretation support and products provided in support of the CI inspection and the outcome.

c. General observations/commentary:



The EIR is currently being finalized and will be submitted to DSI upon completion. The observations noted above are based on the preliminary EIR and communication from the field investigator, Ms. Shari Shambaugh. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. Assessment of data integrity: The data from Dr. Hochhaus' site, associated with the 4 protocols listed above, submitted to the agency in support of NDA 21986, may be considered reliable.

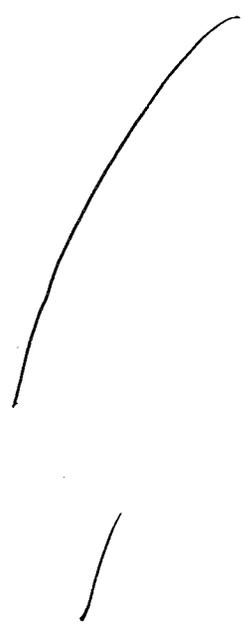
4. **Dr. Michele Baccarani**
Universita Di Bologna
Istituto Di Ematologia
Lorenzo E Ariosto Seragnoli
Ospedate S. Orsola
Via Massarenti 9
Bologna 40138
Italy

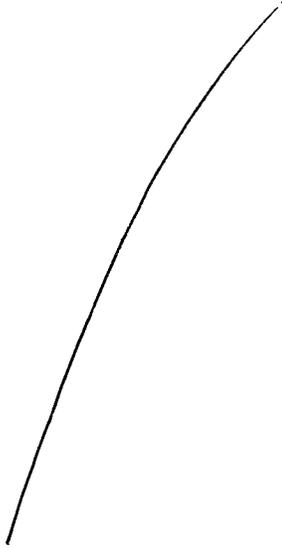
Protocol Number	Subjects Randomized	Subjects Audited
CA180-005	7	3
CA180-006	5	3
CA180-013	14	9
CA180-015	12	0

a. What was inspected? The study records of a subset of subjects for the studies listed in the table above were audited in accordance with the clinical investigator compliance program, CP 7348.811. It should be noted that for study CA180-015 no subjects were audited. There was not sufficient time to conduct the audit for a subset of subjects randomized into study CA180-015. The DSI reviewer was informed by the FDA field investigator of the time constraints on-site. The DSI reviewer, Dr. Lauren Iacono-Connors, instructed the field investigator to eliminate study CA180-015 from the audit objectives provided in the inspection assignment. For audited subjects the record audit included comparison of source documentation to CRFs with particular attention paid to eligibility criteria satisfaction and confirmation of diagnosis. The FDA investigator also assessed the date and cause of death, and any SAEs and AEs and informed consent forms.

b. Limitations of inspection: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. Also, the majority of the audited documents were in the native language of Italian. Field investigator Ms. Shari Shambaugh had the benefit of an interpreter who was present for the inspection. However, the language barrier required that Ms. Shambaugh accept the interpretation support and products provided in support of the CI inspection and the outcome.

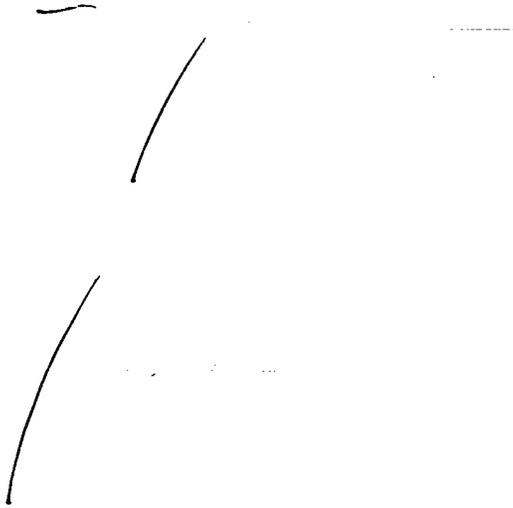
c. General observations/commentary:





The EIR is currently being finalized and will be submitted to DSI upon completion. The observations noted above are based on preliminary communications from the field investigator, Ms. Shari Shambaugh. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. Assessment of data integrity:



Therefore, while the observations are notable their impact on data reliability from this site and more importantly the overall impact on the study efficacy analyses, is believed, by this reviewer and Dr. Kaminskas, to be negligible.

5. **Bristol-Myers Squibb**
5 Research Parkway
Wallingford, Connecticut 06492

a. **What was inspected?** The FDA Investigator reviewed sponsor procedures and records for protocols CA180-002, CA180-005, CA180-006, CA180-013 and CA180-015.

b. **Limitations of inspection:** The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator.

c. **General observations/commentary:**

The EIR is currently being finalized and will be submitted to DSI upon completion. The observations noted above are based on the preliminary EIR and communication from the field investigator, Ms. Pat Murphy. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. **Assessment of data integrity:** The data collected and maintained at the sponsor's site, as it pertains to the 4 clinical sites audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810, associated with the 5 protocols listed above are consistent with that submitted to the agency as part and in support of NDA 21986.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The study data collected by Dr. Sawyers, Dr. Kantarjian and Dr. Hochhaus, appear reliable. The data collected by Dr. Baccarani are acceptable. The inspection of Bristol-Myers Squibb did not identify any issues.

Inspection of Dr. Baccarani's site found

by this site may be considered acceptable by the product review division. in general, the data generated

Inspection of Dr. Kantarjian's site found

Observations noted above are based in part on the preliminary communications provided the field investigators. Only the findings at Dr. Sawyers' site are based on a final EIR. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final remaining EIRs.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIRs and the supporting inspection evidence and exhibits.

Lauren Jacono-Connors, Ph.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Lauren Iacono-Connors
6/16/2006 10:54:48 AM
UNKNOWN

Leslie Ball
6/16/2006 04:19:41 PM
MEDICAL OFFICER

Fax



DIVISION OF DRUG ONCOLOGY PRODUCTS

Center for Drug Evaluation and Research
White Oak Bldg. 22, Room 2173
10903 New Hampshire Avenue, Silver Spring, MD 20903

To: Marie-Laure Papi, Pharm.D.

From: Amy Baird, CSO

Fax: 203-677-3818

Fax: 301-796-9845

Phone: 203-677-3830

Phone: 301-796-1325

Pages (including cover): 1

Date: June 13, 2006

Re: NDA 21-986 Dasatinib (BMS-354825).

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Per the request of the Dasatinib review team, please provide the following information:

Please provide links or source materials for all claims made in the MOA section of the label. Some links in the nonclinical overview do not appear to connect to the relevant original study reports.

Please call should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
6/13/2006 09:10:57 AM
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✓ § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

MEMO

To: Robert Justice, M.D.
Acting Director, Division of Drug Oncology Products
HFD-150

Through: Linda Y. Kim-Jung, Pharm.D., Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420; White Oak Bldg. 22, Mail Stop 4447

From: Todd D. Bridges, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420; White Oak Bldg. 22, Mail Stop 4447

Date: May 12, 2006

Re: ODS Consult 06-0124
Sprycel (Dasatinib Tablets) 20 mg, 50 mg, and 70 mg
NDA #: 21-986

This memorandum is in response to an April 27, 2006 request from your Division for a review of the proprietary name, Sprycel (NDA # 21-986). Upon the initial steps in the proprietary name review process, the Division of Drug Marketing, Advertising and Communications (DDMAC) did not recommend the use of the proposed proprietary name, Sprycel.

Specifically, DDMAC states:



As per email correspondence with the Division of Drug Oncology Products, on May 12, 2006, the Division concurs with DDMAC's comments. Therefore, DMETS will not proceed with the safety review of the proposed proprietary name, Sprycel, since the Division supports DDMAC's objection of the name based on

— We recommend the sponsor be notified immediately of the decision to reject the name based on the promotional concerns and request submission of an alternative proprietary name for NDA # 21-986. Please forward the alternate name for DMETS review upon submission.

If you have any questions for DDMAC, please contact Catherine Gray or Suzanne Berkman at 301-796-1200. If you have any other questions or need clarification, please contact the medication errors Project Manager, Diane Smith, at 301-796-0538.

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/s/

Todd Bridges
5/16/2006 04:37:22 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
5/16/2006 04:40:13 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/19/2006 02:16:29 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/19/2006 02:59:44 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 WO22, RM 4447		FROM: Amy Baird CDER/OODP/DDOP WO22, Room 2137		
DATE 4-27-06	IND NO.	NDA NO. 21-986	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 12-28-05
NAME OF DRUG Sprycel (dasatinib) Tablets		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE June 9, 2006
NAME OF FIRM: Bristol-Myers Squibb				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE. ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE. DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please conduct a review of the proposed tradename "SPRYCEL (dasatinib) Tablets". Attached is the proposed package insert, container and carton labels.				
PDUFA DATE: 6-28-06 ATTACHMENTS: Draft Package Insert, Container and Carton Labels CC: Archival IND/NDA NDA 21-986 HFD-150/Division File HFD-150/RPM HFD-150/Reviewers and Team Leaders				
NAME AND PHONE NUMBER OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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OFFICE OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research

White Oak

Building 22, Room 2204

10903 New Hampshire Avenue, Silver Spring, MD 20903

To: Marie-Laure Papi, Pharm.D.

From: Amy Baird, CSO

Fax: 203-677-3818

Fax: 301-796-9845

Phone: 203-677-3830

Phone: 301-796-1325

Pages (including cover): 2

Date: April 21, 2006

Re: NDA 21-986 Dasatinib (BMS-354825).

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● **Comments:**

Per the request of the Dasatinib review team, please provide the following information:

In reviewing the healthy volunteer PK studies in NDA 21-986, we note the following:

1. The clinical synopsis of Study CA180009 states "Thirty-eight subjects had at least 1 laboratory abnormality that was higher on-treatment relative to prestudy. Treatment-emergent laboratory abnormalities seen in $\geq 10\%$ of subjects were anemia (9, 17%); elevated creatine kinase, lymphopenia, and bilirubinemia (8 each, 15%); and hypoglycemia (7, 14%). No laboratory abnormality was reported as an AE."
2. The clinical synopsis of Study CA180020 states "Twenty-one subjects had at least 1 treatment-emergent laboratory abnormality. Those seen in $\geq 10\%$ of subjects were prolonged prothrombin time (7), hyponatremia (7), anemia (5), neutropenia (3), and hypocalcemia (3). Five subjects had grade 2 laboratory abnormalities (2 hyperkalemia, 1 neutropenia, 1 hyponatremia, 1 hypophosphatemia).

No datasets were submitted for these AEs.

Please provide datasets containing all laboratory values for patients in Studies CA180009 and CA180020. Although the clinical synopses of Studies CA1800019, CA180022, and CA180032 do not specifically mention the occurrence of abnormal laboratory values, please provide the corresponding datasets for those three studies as well, if available.

Please call should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
4/21/2006 04:06:05 PM
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DIVISION OF DRUG ONCOLOGY PRODUCTS

Center for Drug Evaluation and Research

White Oak

Building 22, Room 2204

10903 New Hampshire Avenue, Silver Spring, MD 20903

To: Marie-Laure Papi, Pharm.D.

From: Amy Baird, CSO

Fax: 203-677-3818

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Pages (including cover): 1

Date: April 21, 2006

Re: NDA 21-986 Dasatinib (BMS-354825).

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Please refer to BMS e-mail dated March 30, 2006, wherein you provided a proposal for the submission of the long-term stability studies update. After reviewing your email, the FDA Dasatinib CMC team has the following comment:

The proposed submission of updated long term stability data (for both drug substance and drug product) without statistical analysis is acceptable. However, in the event that such statistical analysis should become required for review, this will be requested by the Agency and will need to be submitted in a timely fashion. If this analysis is requested, the promptness and quality of the submission will determine whether or not it can be reviewed prior to the NDA's PDUFA date.

Please call should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
4/21/2006 04:36:00 PM
CSO

Fax



OFFICE OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research

White Oak

Building 22, Room 2204

10903 New Hampshire Avenue, Silver Spring, MD 20903

To: Marie-Laure Papi, Pharm.D.

From: Amy Baird, CSO

Fax: 203-677-3818

Fax: 301-796-9845

Phone: 203-677-3830

Phone: 301-796-1325

Pages (including cover): 1

Date: April 7, 2006

Re: NDA 21-986 Dasatinib (BMS-354825).

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● **Comments:**

Per the request of the Dasatinib review team, please provide the following request for information:

BMS-354825 (Dasatinib), BMS-354825-02, and BMS-354825-03 were used in your nonclinical studies. Please clarify how these substances differ from each other. If they are structurally different, please provide the structure for all 3 substances. This information will be needed in order to make decisions regarding the outcome of the studies.

Please call should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
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OFFICE OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research

White Oak

Building 22, Room 2204

10903 New Hampshire Avenue, Silver Spring, MD 20903

To: Marie-Laure Papi, Pharm.D.

From: Amy Baird, CSO

Fax: 203-677-3818

Fax: 301-796-9845

Phone: 203-677-3830

Phone: 301-796-1325

Pages (including cover): 1

Date: March 30, 2006

Re: NDA 21-986 Dasatinib (BMS-354825).

Urgent For Review Please Comment Please Reply Please Recycle

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● **Comments:**

Per the request of the Dasatinib review team, please provide the following request for information:

The Division would like to review the results from Study 180003 in order to compare the toxicity profile of Dasatinib in solid tumor patients with that in leukemia patients. Please provide an update of Study 180003 including the number of patients enrolled, the maximum tolerated dose and dose limiting toxicities. Please indicate when you expect to submit a preliminary clinical study report and datasets.

Please call should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
3/30/2006 02:53:37 PM
CSO



NDA 21-986

INFORMATION REQUEST LETTER

Bristol-Myers Squibb Company
Attention: Marie-Laure Papi, Manager, Global Regulatory Science
5 Research Parkway
P.O. Box 5100, Mailstop 3SIG-5014
Wallingford, CT 06492-7660

Dear Ms. Papi,

Please refer to your December 28, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sprycel™ (dasatinib) tablets.

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

1. The CMC information presented on the *proposed* starting material _____ as included in the NDA in Section 3.2.S.2.3.1, is inadequate. Note that this material has been previously discussed in a CMC EOP2 teleconference between BMA and the FDA on 15-JUN-05. A review of the details of the conversation reveals that no concrete decisions were reached regarding this material. Accordingly, the following information regarding _____ is requested:
 - a. The name and address of the vendor which supplies this material. It is noted that two vendors are listed in the NDA; however, it is never stated which vendor BMS intends to use.
 - b. Information on the extent of change controls in the quality system to qualify and recertify the vendor(s) including vendor's obligations to report to the firm any changes made to the synthesis of the starting materials.
 - c. The route of synthesis of _____
As noted in the _____ NDA, there are several routes that may be used to synthesize _____ In order to have the option of using any of the listed synthetic schemes for _____, the analytical method for the starting material should have been shown to resolve and quantify the process impurities from each of the synthetic schemes.
 - d. The procedure by which BMS will use to _____

- e. If one exists, a DMF number for the _____ as supplied by the vendor(s).
- f. A specific and unequivocal identify test for the starting material including a well characterized and well established reference standard for _____
- g. The _____ assay for _____ is _____ as listed on the *Testing Standard Specification*. Please propose a tighter specification for the assay; note that this was previously agreed to during the 15-JUN-05 meeting.
- h. Quantitative proof that the impurities and/or degradants in the vendor supplied _____ do not carry over into the drug substance at levels more than _____ w/w if the impurities are not considered the structural alerts for mutagenicity.
2. Provide a summary of the results of the _____ study for the drug substance dasatinib.
3. It is stated that “ _____
4. _____
5. Add individual _____ specifications for both _____ in the drug substance.
6. Add a heavy metal specification for the drug substance or provide assurance that no heavy metal will come from starting materials, reagents, solvents, or process conditions.
7. The proposed drug substance specification has the following:
- /
- /

8.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Karl Stiller, Regulatory Health Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Ravi Harapanhalli, PhD.
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Evaluation
Center for Drug Evaluation and Research

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/s/

Ravi Harapanhalli
3/30/2006 03:51:37 PM

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OFFICE OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research

White Oak

Building 22, Room 2204

10903 New Hampshire Avenue, Silver Spring, MD 20903

To: Marie-Laure Papi, Pharm.D.

From: Amy Baird, CSO

Fax: 203-677-3818

Fax: 301-796-9845

Phone: 203-677-3830

Phone: 301-796-1325

Pages (including cover): 3

Date: March 23, 2006

Re: NDA 21-986 Dasatinib (BMS-354825).

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Per the request of the Dasatinib review team, please provide the following request for information:

This request is in reference to your report entitled, "INTEGRATED ANALYSIS FOR DASATINIB OF CHANGES IN ECG INTERVALS, AND OF ADVERSE EVENTS POTENTIALLY RELATED TO QT/QTc INTERVALS PROLONGATION AND ARRHYTHMIAS", dated December 12, 2005.

1. Please submit all analysis datasets used to perform the analyses described in the aforementioned report. Submit these datasets in SAS transport file format. Please also submit an electronic copy of all computer code used to perform the analyses.

2. Please submit the following datasets in SAS transport file format.

(A) For each study***, please submit a dataset with the following columns. Please use a consistent format between the studies for each column in the dataset.

***Studies: CA 180002, CA180003, CA180005, CA180006, CA180013, CA180015, CA180017, CA180016, CA180009, CA180032, CA180019, CA180020, CA180022

SubjectID Unique Identifier for patient
StudyID Study Number
Study Regimen Regimen: character value describing (e.g. "Dasatinib 70 mg BID")

Dose	Dose of drug given at each dosing event (numeric value)
DailyDose	Daily dose administered on dosing days (numeric value)
Study Day	Day of study relative to administration of 1 st dose in patient (numeric value)
TimeSFD	Nominal time since 1 st dose in hours (numeric value)
Time	Nominal time relative to 1 st dose on a particular study day (numeric value; clock is reset each day, so all values ≤ 24)
QT	Measured QT interval in milliseconds
RR	Measured RR interval in milliseconds
QTcF	Fridericia corrected QT interval in milliseconds
BaselineQTcF	Baseline QTcF in milliseconds
delQTcF	Baseline subtracted QTcF in milliseconds
ConcDasatinib	Concentration of dasatinib (ng/mL)
ConcBMS-573188	Concentration of metabolite (ng/mL)
ConcBMS-582691	Concentration of metabolite (ng/mL)
ConcBMS-606181	Concentration of metabolite (ng/mL)
SubjectAge	Age of subject (Years)
SubjectWT	Weight of subject (kilograms)
SubjectSex	Sex of subject (0=female, 1=male)

If any particular data item is not available at a given time point in a particular patient, indicate that the data are not available by providing an "NA" value in the dataset where the data should be listed, e.g. do not eliminate a row of data just because concentration is not available, just list concentration as "NA".

Please specify how baseline is computed (i.e. the value in the BaselineQTcF column).

(B) Please submit a single SAS transport format dataset for all of the studies listed in part (A) of this request with the columns listed in part (A). This should be simple to do once all of the data are gathered for part (A) of this request (i.e. combine data sets).

3. Please perform the following analyses on all of the studies listed in request #2 of this letter. Please submit the analysis datasets in SAS transport format and also submit the data analysis code.

Note that:

QTcF = Fridericia corrected QT interval in milliseconds

Δ QTcF = Baseline subtracted, Fridericia corrected QT interval in milliseconds

(A) For a given study day, at a given time, for each dose group, compute the mean **QTcF** and upper 95% confidence interval (one-sided t test) across subjects.

- Provide a table of the results
- Plot the data: mean (with upper 95% CI) Δ QTcF vs. time for each dose group/day
- Indicate the maximum effect and time of maximum effect for each day and dose

(B) For a given study day, at a given time, for each dose group, compute the mean **QTcF** and upper 95% confidence interval (one-sided t test) across subjects.

- Provide a table of the results
- Plot the data: mean (with upper 95% CI) QTcF vs. time for each dose group/day
- Indicate the maximum effect and time of maximum effect for each day and dose

(C) Fit a linear mixed effects model (estimate slope and intercept) to the parent concentration- Δ QTcF data

- Plot baseline corrected QTcF (Δ QTcF) vs. concentration of Parent; overlay the mixed effects regression line
- Compute Δ QTcF at mean C_{max} (w/ upper 95% CI; one-sided t test)
- Provide diagnostics of model goodness of fit (e.g. residual plots, plot individual data with individual predicted and population predicted slope)

(D) Fit a linear mixed effects model (estimate slope and intercept) to metabolite concentration- Δ QTcF data

- i. Plot baseline corrected QTcF (Δ QTcF) vs. concentration of metabolite; overlay the mixed effects regression line
- ii. Compute Δ QTcF at mean C_{max} (w/ upper 95% CI; one-sided t test)
- iii. Provide diagnostics of model goodness of fit (e.g. residual plots, plot individual data with individual predicted and population predicted slope)

5. Please submit the study report(s) for the hERG assay(s) used.

6. Please submit the study report for the nonclinical in vivo QT effects.

Please call should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
3/27/2006 04:12:32 PM
CSO

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OFFICE OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research

White Oak

Building 22, Room 2204

10903 New Hampshire Avenue, Silver Spring, MD 20903

To: Marie-Laure Papi, Pharm.D.

From: Amy Baird, CSO

Fax: 203-677-3818

Fax: 301-796-9845

Phone: 203-677-3830

Phone: 301-796-1325

Pages (including cover): 1

Date: March 22, 2006

Re: NDA 21-986 Dasatinib (BMS-354825).

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Per the request of the Dasatinib review team, please provide the following request for information ASAP:

The AESAE tables in your submission do not appear to contain sufficient data for determining whether a patient was within 30 days of treatment at the start of an adverse event. Although events occurring during visits labeled "on treatment" may be presumed to meet the criteria, some of those visits listed as "follow-up", "unscheduled" or "SAE" may also have occurred on treatment or within 30 days of last dose. Please provide updated tables for all CML/ Ph+ ALL studies containing data of last dose and/or number of days since last dose, or instructions on how to retrieve this data from the original submission.

Please call should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
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OFFICE OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research

White Oak

Building 22, Room 2204

10903 New Hampshire Avenue, Silver Spring, MD 20903

To: Marie-Laure Papi, Pharm.D.

From: Amy Baird, CSO

Fax: 203-677-3818

Fax: 301-796-9845

Phone: 203-677-3830

Phone: 301-796-1325

Pages (including cover): 2

Date: March 22, 2006

Re: NDA 21-986 Dasatinib (BMS-354825).

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Per the request of the Dasatinib review team, please provide the following request for information:

1. The table below contains a list of patients enrolled on study CA180015 for whom the reviewer's assessment of the response duration and/or progression date differs from the data presented in appendix 4.1.1 of the study report. Please review the revised progression and censoring dates. In your response, please agree or disagree with each revised date or outcome and provide an explanation for any disagreements.

Subject ID	Progression or Censored	Date
0004-15021	progression	9/1/05 ^a
0022-15037	censored	9/8/05
0021-15061	progression	7/21/05 ^b
0021-15076	progression	10/5/05 ^c
0023-15046	censored	10/19/05
0039-15050	progression	10/3/05
0052-15052	censored	10/25/05
0096-15075	censored	11/3/05
0056-15066	censored	10/26/05
0001-15047	censored	10/28/05

0013-15011	censored	9/9/05
0016-15072	censored	10/27/05
0044-15015	progression	9/1/05 ^d
0044-15054	censored	10/26/05
0044-15059	progression	10/18/05 ^e
0095-15071	censored	10/25/05
0103-15028	progression	7/6/05

- a. progression based on appearance of BM blasts
- b. based on BM blasts
- c. progression based on peripheral blasts
- d. progression based on reappearance of extramedullary disease
- e. based on recurrence of BM blasts

2. Patient 0021-15060 did not meet criteria for no evidence of leukemia for a two week period from 8/3/05-8/17/05 based on a white blood cell count outside the institutional upper limit of normal, yet this patient continued to be classified as a responder. Please explain.

Please call should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
3/22/2006 02:46:30 PM
CSO

March 10, 2006

To: Ni Aye Khin, M.D., Branch Chief, GCP1, HFD-476
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

cc: Joanne L. Rhoads, M.D., Director, DSI, HFD-45
Robert Justice, M.D., Acting Director

From: Amy Baird, Consumer Safety Officer
Division of Drug Oncology Products

Subject: **Request for Clinical Site Inspections**
NDA 21-986
Bristol-Myers Squibb
Dasatinib (BMS-354825)

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
— Univ. of Texas MD Anderson Cancer Center 1515 Holcombe Blvd Houston, TX 77030	CA180002 CA180005 CA180006 CA180013 CA180015	46 (CA180002) Phase 1 8 (CA180005) Phase 2 2 (CA180006) Phase 2 17 (CA180013) Phase 2 1 (CA180015) Phase 2	Chronic myeloid leukemia (chronic, accelerated, and blast phases) and Ph+ ALL.
Dr. Charles Sawyers UCLA 11-934 Factor Building 10833 Leconte Avenue Los Angeles, CA 90095	CA180002	38 (CA180002) Phase 1 2 (CA180005) 2 (CA180006) 2 (CA180013) 3 (CA180015)	Chronic myeloid leukemia (chronic, accelerated, and blast phases) and PH+ ALL.
Dr. Michele Baccarani Universita di Bologna Istituto di Ematologia Lorenzo E Ariosto Seragnoli Ospedale S. Orsola Via Massarenti 9 Bologna 40138 Italy	CA180005 CA180006 CA180013 CA180015	6 (CA180005) 5 (CA180006) 12 (CA180013) 3 (CA180015)	Chronic myeloid leukemia (chronic, accelerated, and blast phases) and Ph+ ALL.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Dr. Andreas Hochhaus Fakultaet Fuer Klinische Medizin Mannheim Theodor-Kutzer-Ufer 1-3 Mannheim 68163 Germany	CA180005 CA180006 CA180013 CA180015	4 (CA180005) 3 (CA180006) 28 (CA180013) 3 (CA180015)	Chronic myeloid leukemia (chronic, accelerated, and blast phases) and Ph+ ALL.

Domestic Inspections:

We have requested inspections because (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify: Dasatinib is potentially a very important drug for CML patients – the population is resistant to or intolerant of Gleevec)
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other: SPECIFY

International Inspections:

We have requested inspections because (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: This is a very large world-wide trial. Data is presented for 565 subjects with a relatively rare condition. Even though a significant part of the study population is from the US, a large part is from Europe and the Far East.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) June 5, 2006. We intend to issue an action letter on this application by (division action goal date) June 28, 2006. The PDUFA due date for this application is June 28, 2006.

Should you require any additional information, please contact Amy Baird at 301-796-1325.

Concurrence: (if necessary)

Dr. Ann Farrell, Medical Team Leader
Dr. Edvardas Kaminskas, Medical Reviewer
Dr. Robert Justice, Acting Division Director

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/s/

Robert Justice
3/17/2006 01:44:58 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-986

Bristol-Myers Squibb Company
Attention: Marie-Laure Papi, Pharm.D.
Associate Director, Regulatory Science
5 Research Parkway
P.O. Box 5100, Mailstop 3SIG-5014
Wallingford, CT 06492

Dear Dr. Papi:

Please refer to your December 28, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SPRYCEL™ (Dasatinib) Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 24, 2006, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Updated stability data should be provided as soon as possible, for both the drug substance and drug product. Stability data analysis and the appropriate SAS transport files should also be provided in this update.

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.

Please respond only to the above requests for additional 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.

NDA 21-986

Page 2

If you have any questions, call Amy Baird, Consumer Safety Officer, at (301) 796-1325.

Sincerely,

(See appended electronic signature page)

Robert L. Justice, M.D.
Acting Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Robert Justice
3/10/2006 04:18:49 PM

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OFFICE OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research

White Oak

Building 22, Room 2204

10903 New Hampshire Avenue, Silver Spring, MD 20903

To: Marie-Laure Papi, Pharm.D.

From: Amy Baird, CSO

Fax: 203-677-3818

Fax: 301-796-9845

Phone: 203-677-3830

Phone: 301-796-1325

Pages (including cover): 1

Date: March 9, 2006

Re: NDA 21-986 Dasatinib (BMS-354825).

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Per the request of the Dasatinib review team, please provide the following request for information:

In the dose escalation study CA180002, there was intra-subject dose escalation in attempt to maximize response rates. What was the dose-response relationship for MCyR and CHR? Subject listings in Appendix sections 4.1.1, 4.1.2, etc., are inadequate to answer that question. For example, in CA180017 Appendix 4.1, Patient Profiles are easy to figure out the temporal relationship between MCyR, CHR and drug dose. Do you have a clear idea what the dose-relationship is?

Please call me should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
3/9/2006 12:50:03 PM
CSO



NDA 21-986

NDA ACKNOWLEDGMENT

Bristol-Myers Squibb Company
Attention: Marie-Laure Papi, Pharm.D.
Associate Director Regulatory Science
5 Research Parkway
P.O. Box 5100, Mailstop 3SIG-5014
Wallingford, CT 06492

Dear Dr. Papi:

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

Name of Drug Product: SPRYCEL™ (Dasatinib) Tablets

Review Priority Classification: Priority (P)

Date of Application: December 28, 2005

Date of Receipt: December 28, 2005

Our Reference Number: NDA 21-986

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 February 24, 2006, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be June 28, 2006.

We will review this application under the provisions of 21 CFR 314 Subpart H (accelerated approval). Before approval of this application, you must submit copies of all promotional materials, including promotional labeling as well as advertisements, to be used within 120 days after approval.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

NDA 21-986

Page 2

Please cite the NDA number listed above 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 Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Amy Baird, Consumer Safety Officer, at (301) 796-1325.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Amy Baird
3/6/2006 02:00:13 PM
for Dotti Pease

Fax



OFFICE OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research

White Oak

Building 22, Room 2204

10903 New Hampshire Avenue, Silver Spring, MD 20903

To: Marie-Laure Papi, Pharm.D.

From: Amy Baird, CSO

Fax: 203-677-3818

Fax: 301-796-9845

Phone: 203-677-3830

Phone: 301-796-1325

Pages (including cover): 1

Date: March 2, 2006

Re: NDA 21-986 Dasatinib (BMS-354825).

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Per the request of the Dasatinib review team, please provide the following request for information:

In reviewing hematologic data for CA180013 and CA180017, it has been found that sometimes the spaces for the % of myelocytes, promyelocytes, etc., are blank and sometimes they are 0. Did you always do differentials with WBC counts? Is a blank space and a 0 the same?

Please call should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
3/6/2006 03:34:40 PM
CSO

Fax



OFFICE OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research

White Oak

Building 22, Room 2204

10903 New Hampshire Avenue, Silver Spring, MD 20903

To: Marie-Laure Papi, Pharm.D.

From: Amy Baird, CSO

Fax: 203-677-3818

Fax: 301-796-9845

Phone: 203-677-3830

Phone: 301-796-1325

Pages (including cover): 1

Date: February 13, 2006

Re: NDA 21-986 Dasatinib (BMS-354825). Specifically, your submission dated December 28, 2005.

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Per the request of the Dasatinib review team, please provide the following requests for information:

We are unable to locate PK reports for five phase 2 studies conducted (ca180-005, ca180-006, ca180-013, ca180-015, ca018-017). Please let us know when you will be able to provide these PK reports and the PK raw data.

Also, please provide a statement that all proposed manufacturing sites are ready for assessment of cGMP compliance.

Please call should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
2/13/2006 01:27:20 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): DDMAC Attention: Joseph Grillo, Pharm.D.		FROM: Amy Baird, DDOP		
DATE 3-13-06	IND NO.	NDA NO. 21-986	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 12-28-05
NAME OF DRUG SPRYCEL (Dasatinib) Tablets		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 5-15-06
NAME OF FIRM: Bristol-Myers Squibb				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY				
<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT				
<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS:				
<p>The Division of Oncology Drug Products requests DDMAC review the proposed product labeling and any relevant advertising for this NDA. Attached to this consult is the proposed labeling along with the container/vial labels. Please see the submissions in the electronic document room for any other pertinent information you may need.</p> <p>Clinical Reviewer: Dr. Edvardas Kaminskas CSO: Amy Baird</p>				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

MEETING MINUTES

DATE: October 27, 2005 **TIME:** 9:30 am **LOCATION:** Room 2327

IND/NDA: IND 66,971

Meeting Request Submission Date: 08-15-05

FDA Response Date: 08-30-05

Briefing Document Submission Date: 10-14-05

Additional Submission Dates: 10-17-05

DRUG: BMS-354825

SPONSOR/APPLICANT: Bristol-Myers Squibb Company

TYPE of MEETING:

1. Pre-NDA meeting
2. Proposed Indication: Treatment of patients with CML who are resistant or intolerant to imatinib mesylate and Ph+ ALL refractory patients

FDA PARTICIPANTS:

Dr. Robert Justice, Acting Director
Dr. Ann Farrell, Clinical Team Leader
Dr. Michael Brave, Clinical Reviewer
Dr. Rajeshwari Sridhara, Statistical Team Leader
Dr. Brian Booth, Clinical Pharmacology Team Leader
Christy Cottrell, Consumer Safety Officer

INDUSTRY PARTICIPANTS:

Dr. Renzo Canetta, VP, Global Clinical Development
Dr. Claude Nicaise, VP, Global Clinical Development
Dr. Maurizio Voi, Exec. Dir., Global Clinical Development
Dr. Donna Morgan Murray, Exec. Dir., Global Regulatory Science
Dr. Antonella Maniero, Group Director, Biostatistics and Programming
Tai-Tsang Chen, Research Biostatistician, Biostatistics and Programming
Cliff Bechtold, Group Director, Project Planning and Management
Dr. Marie-Laure Papi, Associate Director, Global Regulatory Science

BACKGROUND:

BMS plans to submit an NDA in chronic, accelerated and blast CML and Ph+ ALL based primarily on safety and efficacy data from the following 6 studies:

- ◆ CA180002: Phase 1 dose escalation study in CML and Ph+ ALL subjects
- ◆ CA180013: a single arm Phase 2 study of BMS-354825 in chronic CML subjects resistant to imatinib > 600 mg or intolerant to imatinib at any dose
- ◆ CA180005 and CA180006: two single arm Phase 2 studies of BMS-354825 in accelerated and myeloid blast CML patients respectively resistant or intolerant to imatinib
- ◆ CA180015: a single arm Phase 2 study in Ph+ ALL and lymphoid blast CML subjects resistant or intolerant to imatinib
- ◆ CA180017: a randomized Phase 2 study (2:1 randomization) of BMS-354825 and imatinib 800 mg in chronic CML subjects resistant to ≤ 600 mg imatinib

An End-of-Phase 1 meeting was held in December 2004. This meeting was requested to review the results from available registration studies and to review the proposed content of the NDA, label and Safety Update.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Suitability for filing for the proposed indication

1. This background document summarizes the preliminary data (pending final analysis to be included in the NDA) from 3 Phase 2 non-randomized trials (CA180005, CA180013 and CA180015) and provides an update on the status of studies CA180006 (Phase 2 in myeloid blast CML) and CA180017 (randomized Phase 2 in chronic CML). Together along with results from CA180002 previously presented to the Division, the data demonstrate the importance of dasatinib in the treatment of patients with CML and Ph+ ALL. Based on the results from these trials, the proposed indication for dasatinib is for the treatment of adults with chronic, accelerated, or blast phase CML who do not benefit from imatinib mesylate and for Ph+ ALL refractory patients.

Is the proposed clinical data package adequate to support submission of an NDA for dasatinib?

FDA RESPONSE:

- The proposal appears adequate for submission; however, fileability will be a review decision.

Are the proposed indications acceptable?

FDA RESPONSE:

- This will be a review issue.

Duration of Efficacy

2. As described in Section 4, in addition to the efficacy data after a minimum of 3 months follow-up for CA180005, CA180006, CA180013 and CA180015, BMS proposes to provide additional efficacy data (i.e., at least 6 months) for the same patients from the above 4 trials in a single abbreviated report. This report is intended to update efficacy information at 6 months and to confirm the efficacy observed at the earlier 3 month cut-off.

Is this proposal acceptable?

FDA RESPONSE:

- We recommend that you submit the initial efficacy data when patients have had a minimum of 6 months follow-up.

Discussion: Sponsor will submit a minimum of 3 months follow-up data on safety and efficacy for NDA cohort, with a minimum of 6 months follow-up efficacy data on the same patients for all studies except 017 (in one document). The safety update will include a minimum of 6-8 months follow-up on all patients including overenrolled patients. Full Phase 1 data will also be submitted. The Division agrees that this is generally acceptable but the adequacy of the duration of follow-up is a review issue especially for the chronic phase.

Labeling Submissions

3. The proposed labeling in the original NDA for dasatinib will

Is this proposal acceptable?

FDA RESPONSE:

- This would be a review issue. Please see question #2 above.

Discussion: Original submitted label will include

Pediatric Studies

4. As discussed at the December 15, 2004, End-of-Phase 1 meeting, BMS

Is this still acceptable?

FDA RESPONSE:

- Yes. Please refer to the minutes from the December 15, 2004 EOP1 meeting (Question #6).

Rolling Submission

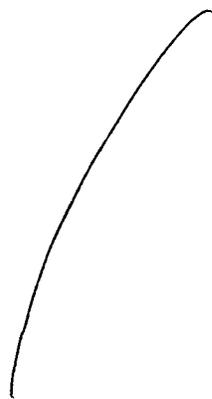
5. BMS would be able to provide the Division with final Clinical Pharmacology and Nonclinical NDA sections prior to the submission of the Clinical and CMC sections, as a rolling submission.

Would this be helpful to FDA reviewers?

FDA RESPONSE:

- If you are proposing a simple rolling submission, then your proposal is acceptable. However, if you are planning to pursue a CMA Pilot 1 submission, please submit the Clinical Pharmacology section at the same time as the Clinical section.

Discussion: The sponsor proposes to submit the nonclinical and clinical pharmacology sections of the NDA in November with clinical and CMC sections proposed for submission in December. The sponsor clarified that this would be a rolling NDA only, not CMA.



Orphan Designation

7. BMS submitted a request for Orphan Product Designation for CML (on August 31, 2005) to the FDA Office of Orphan Drug Products. The review cycle for these requests is usually 90 days or less.

Does the Division have any update on the status of this request?

FDA RESPONSE:

- Please contact Jeff Fritsch in the Office of Orphan Drug Products at (301) 827-0989 for a status update on your request.

Additional Comment

We would like to know why you want to enroll more patients into your studies than was originally planned. Also, what are the percentages of resistant and intolerant patients, respectively, for the CA180013 study?

Discussion: See slides. These questions have been addressed to FDA's satisfaction.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- Adequacy of the duration of follow-up remains a review issue for the chronic phase.
- The sponsor submitted additional background material regarding the core statistical analysis plan along with additional questions on October 17, 2005 (received by the Division by email on October 20, 2005). The Division did not have adequate time to review and address these questions prior to the October 27, 2005, sponsor meeting. The material and questions covered in this submission will be addressed separately at a later date.

There were no action items.

Christy Cottrell
Consumer Safety Officer

Concurrence Chair:

Ann Farrell, M.D.
Clinical Team Leader

Sponsor slides will be attached to final version

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/s/

Christy Cottrell
11/22/2005 10:45:16 AM

Ann Farrell
11/22/2005 10:52:02 AM

- CA180015: A single arm Phase 2 study in Ph+ ALL and lymphoid blast CML subjects resistant or intolerant to imatinib
- CA180017: A randomized Phase 2 study (2:1 randomization) of BMS-354825 and imatinib 800 mg in chronic CML subjects resistant to \leq 600 mg imatinib

The primary endpoints for these studies are major cytogenetic response (MCyR) and complete hematologic response (CHR).

The Division's draft responses were sent to the sponsor on July 5, 2005.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. **At the end of 2005, Bristol-Myers Squibb (BMS) plans to submit an NDA for dasatinib (BMS-354825) and request priority review for this application. The NDA will be based on 6 clinical pharmacology studies, safety and efficacy from 5 Phase 2 (CA180005, CA180006, CA180015, CA180013, CA180017) and one Phase 1 (CA180002) studies and safety from other ongoing studies (CA180003, CA180035, CA180034) (Appendix 2). All of the Phase 2 studies will be ongoing at the time of submission of the NDA; for these studies, the data cut-off for the NDA has been chosen based on the accrual rates in the different studies (Section 4.2). BMS proposes to include updated safety information (i.e., summary of discontinuations due to AEs, SAEs and deaths within 30 days) from the ongoing studies as part of the Safety Update (Appendix 2).**
 - a. **Is the proposed content of the NDA sufficient in scope to support the filing of the NDA for chronic myelogenous leukemia in subjects resistant or intolerant to imatinib?**

FDA RESPONSE:

- If you are seeking accelerated approval, you must show that your product is better than available therapy (see previous discussion during the December 14, 2004, EOP1 meeting regarding the need to show that your product is better than interferon).

Discussion: The sponsor updated the Division on the accrual of their ongoing studies (Study 005: 195 patients, Study 006: 123 patients, Study 013: 413 patients, Study 015: 100 patients, and Study 017: 70 patients). The sponsor stated that they had discussed not conducting a trial against interferon and explained that they plan to use published data and the interferon label. The Division agreed that this approach is acceptable. The sponsor noted that most published data on interferon is post-chemotherapy, but prior to Gleevec and stated that not much data is available on post-Gleevec interferon treatment. The Division acknowledged this but stated that the sponsor should still submit the literature.

b. Is the proposed content of the Safety Update acceptable to FDA?

FDA RESPONSE:

- Yes, your proposed content is acceptable.

c. Assuming priority review will be granted, when should we plan to submit the Safety Update?

FDA RESPONSE:

- At 120 days, per the regulations.

2. Draft Statistical Analysis Plans (SAP) including the core SAP for five Phase 2 studies, one study specific SAP for CA180017 and the summary of clinical safety SAP are included in this submission (Appendix 4, 5 and 6). The core SAP contains response criteria as presented in the Phase 2 protocols submitted for the End-of-Phase 1 discussion of December 15, 2004. BMS proposes to change these response criteria via protocol amendment as described in Section 4.2.3 of this document.

a. Is this proposal acceptable to FDA?

FDA RESPONSE:

- Yes.

b. Are the proposed SAPs acceptable for NDA submission?

FDA RESPONSE:

- Yes, but you should be aware that . —

3. BMS proposes to include patient profiles (i.e., medical history and prior imatinib therapy in the form of a written summary) for each patient enrolled in a Phase 2 trial (Appendix 7). The information in these profiles will be derived from primary source documents and will not be accompanied by datasets. This information is not a part of the usual NDA submission; however, BMS believes that it will provide valuable information to the FDA in their assessment on the subjects' status as imatinib-resistant or imatinib-intolerant.

Is the proposed format and content acceptable to FDA?

FDA RESPONSE:

- Yes, the proposed format and content of the patient profiles are acceptable to the FDA. Do you plan to submit a dataset summarizing the prior imatinib therapy for patients? You should submit complete datasets for each clinical study that you plan to use to support the NDA. These datasets should support individually each clinical indication for which you seek approval. We anticipate that patient narratives will be very helpful in the review process.

Discussion: With regard to the last sentence, the sponsor explained that some data is in the dataset, but some details on medical history come from source documents. The dataset includes date of the first and last dose, highest dose, best response, date of progression, CML treatment, intolerance to Gleevec and reason for intolerance. The sponsor stated that they believe the Division will have all of the standard "denominations"; only the details will be missing. The sponsor also described a "reviewing tool" to be submitted that includes a summary of chemotherapy history. The Division replied that this would be helpful.

4. **Narratives, CRFs and ECG data will be included in the NDA as described in Sections 7 and 8 and Appendix 9 of this document respectively.**

Is this proposal acceptable to FDA?

FDA RESPONSE:

- Yes.
5. **This NDA will be submitted entirely in electronic format following the electronic NDA structure specified in the FDA Guidance document (Providing Regulatory Submissions in Electronic Format – General Considerations and NDAs, dated January 1999) with caveats as specified in Appendix 9 (Proposal for Electronic NDA Submission) and Appendix 10 (draft NDA Table of Contents).**

Is the format and content of the proposed electronic submission plan acceptable to the FDA?

FDA RESPONSE:

- Yes.
6. **Datasets from all of the Clinical Pharmacology and Phase 2 studies will be included in the NDA (Appendix 9) except for studies CA180003, CA180034 and CA180035. Integrated datasets for summary of clinical safety for the six clinical studies (CA180002, CA180005, CA180006, CA180013, CA180015, and CA180017) will also be provided. The datasets will be prepared according to the guidance for electronic submissions (Providing Regulatory Submissions in Electronic Format – General Considerations and NDAs, dated January 1999).**

Does the FDA agree with this proposal?

FDA RESPONSE:

- Yes. See response to Question #3.
7. **Efficacy programs for the six clinical studies (CA180002, CA180005, CA180006, CA180013, CA180015, and CA180017) will also be included in the NDA as described in Appendix 9.**

Does the FDA agree with this proposal?

FDA RESPONSE:

- Yes.

ADDITIONAL COMMENTS

We remind you that at our EOP1 meeting on December 14, 2004, we strongly recommended that

Discussion: The sponsor stated that they intend to come in for another Pre-NDA meeting in October 2005 and agreed to add this topic to the agenda for discussion at that meeting.

There were no unresolved issues or action items.

Christy Cottrell
Consumer Safety Officer

Concurrence Chair:

Michael Brave, M.D.
Clinical Reviewer

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/s/

Christy Cottrell
8/29/2005 12:12:27 PM

Michael Brave
8/29/2005 12:23:22 PM

MINUTES OF TELECONFERENCE

DATE: June 15, 2005 **TIME:** 1:00 pm **LOCATION:** Conference Room I

IND/NDA: IND 66,971

Meeting Request Submission Date: 04-19-05

FDA Response Date: 05-03-05

Briefing Document Submission Date: 04-19-05

Additional Submission Dates: 05-04-05

DRUG: BMS-354825

SPONSOR/APPLICANT: Bristol-Myers Squibb Company

TYPE of MEETING:

1. CMC End-of-Phase 2 meeting
2. Proposed Indication: CML

FDA PARTICIPANTS:

Dr. Nallaperumal Chidambaram, Chemistry Team Leader
Dr. Xiao Hong Chen, Chemistry Reviewer
Dr. Brian Booth, Clinical Pharmacology Team Leader (pre-meeting only)
Dr. Angela Men, Clinical Pharmacology Reviewer
Dr. John Simmons, Director, DNDCI (pre-meeting only)
Dr. June Komura, Visiting Scientist (industry telecon only)
Christy Cottrell, Consumer Safety Officer

INDUSTRY PARTICIPANTS:

Dr. Claudia Arana, Manager, Biopharmaceutics R&D
Dr. Zihui (Julia) Gao, Principal Scientist, Biopharmaceutics R&D
Mary Moran, Manufacturing Technology Mgr., Technical Operations
Denise Perniciaro, Assoc. Director, Global Regulatory Sciences –

CMC

Dr. Michael Randazzo, Principal Scientist, Process R&D
Elizabeth Yamashita, Group Dir., Global Regulatory Sciences – CMC
Joel Young, Group Leader, Analytical R&D

BACKGROUND:

Prior meetings include an End-of-Phase 1 meeting held on December 15, 2004, and a meeting held on April 22, 2005, with management from the Office of Pharmaceutical Science to discuss utilizing BMS-354825 in the Agency's New Review Paradigm. The sponsor's minutes from the April 22, 2005, meeting were submitted as serial number 118 to IND 66,971, as part of the background material for this meeting.

At the time of this meeting, the CMC development of BMS-354825 and processes is in advanced stages with scale-up and transfer to the proposed commercial sites in progress.

This meeting was requested to reach agreement on designation of drug substance starting materials, dissolution methodology and the long term stability study plan for the initial NDA.

The Division's draft responses were sent to the sponsor on June 7, 2005.

MEETING/TELECON OBJECTIVES:

To reach agreement on the following:

- Designation of API starting materials
- Drug product dissolution method
- Long Term Stability Study plan to support NDA filing
- Executed Batch Records and Analytical Methods Validation Package
- Biowaiver Plan for the 70 mg strength tablet

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Designation of Active Pharmaceutical Ingredient (API) Starting Materials

1. An overview of the BMS-354825 API synthesis is provided in the drug substance section of this submission. BMS has designated _____ as starting materials _____ based on the guidelines provided in both the FDA "Guideline for Submitting Supporting documentation in Drug Applications for the Manufacture of Drug Substances, February 1987 and ICH Guideline Q7A, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients", August 2001.

_____ BMS requests that the Agency confirm agreement that _____ qualify as starting materials, or to provide guidance on what additional evidence would be required to support the starting material status.

FDA RESPONSE:

- We agree that _____ can be considered as starting materials for the synthesis of the BMS-354825 API. However, _____ cannot be considered as a starting material when the following factors are considered:

- We may be willing to consider _____ as a negotiated starting material, which means that you should source from the approved vendor(s), the synthesis route should be clearly defined and it should have tight specifications. If you would like to change the supplier for this starting material or if the vendor decides to change the route of synthesis, you need to submit a CMC supplement for the proposed change.

Discussion: The sponsor acknowledged that _____ can be considered as starting materials and the agency may be willing to accept _____ as a negotiated starting material. The sponsor asked if changes could be submitted in an annual report. The Division asked the sponsor to clarify what types of changes they were referring to and the sponsor replied that they meant a new site or a change in schematic, synthesis, or a new vendor. The Division responded that a new route of synthesis could form new impurities, so it can not be submitted in an annual report. The Division suggested that the sponsor submit a correspondence to the Division prior to submitting the supplement, outlining the changes proposed and ask whether it would qualify as CBE-0, CBE-30 or whether the changes would require a prior approval supplement. The sponsor stated that they will closely follow BACPAC-1 and the changes guidance and will follow-up with the reviewer and project manager.

The sponsor asked if a change in vendor but with the same chemistry could be submitted in an annual report. The Division stated that it would need to get back to the sponsor and noted that "negotiated" starting material is a different situation than a normal starting material so BACPAC may not apply.

Drug Product Dissolution Method

2. While the Agency accepts that the dissolution method is discriminating for the BMS-354825 50 and _____ tablet strengths, there is concern that the dissolution method is not discriminating for the 20 mg tablet strength. BMS-354825 tablets are manufactured from a common _____ and a single dissolution method is desired as a manufacturing control for all potential tablet strengths.

Additional data are presented to demonstrate the discriminating power of the method for batches of 20 mg strength tablets that are 1) _____ and 2) manufactured without _____. BMS requests Agency agreement that this method has demonstrated sufficient discriminating power for the 20 mg tablet strength.

FDA RESPONSE:

- The method appears to have the power to discriminate 20 mg strength tablets. The determination of the acceptability of the method will be made during the NDA review.

Long Term Stability Study Plan to Support NDA Filing

3. BMS has initiated a Long Term Stability Study (LTSS) for API and drug product to support planned NDA filing for BMS-354825 tablets based on the guidelines provided in ICH Guideline Q1A (R2), "Stability Testing of New Drug Substances and Products", February 2003. As both BMS-354825 drug substance and drug products exhibit satisfactory stability profiles, BMS proposes to submit the following primary long term stability study (LTSS) and supporting data in the initial NDA:

Drug Substance- primary LTSS data for batches and supporting stability data for

Drug Product- primary LTSS data for batches of each tablet strength (20, 50 mg) and supporting stability data consisting of from the Phase II/commercial formulation (of 20 and tablet strengths) and from the Phase I formulation (of the 5 and 50 mg tablet strengths).

BMS requests Agency concurrence with the plan or to provide feedback regarding any additional information that may be required.

FDA RESPONSE:

- In general, we expect stability data for both drug substance and drug product in the NDA submission. We consider your proposal to submit LTSS for both drug substance and drug product as minimal. However, we are willing to accept your submission with primary stability data and a one time update of the stability data during NDA review. Please note that shelf life and/or retest date will be determined based primarily on real time primary stability data.

Discussion: The sponsor explained that the LTSS protocol includes 3 strengths (20, 50 and and the commercial strengths will be 20, 50, and 70 mg. The sponsor further stated that they plan to submit drug substance stability data as well as of LT supportive stability data on the proposed commercial formulation and supportive data on the 20 and ng strengths (ref. page 56 of the background document). The sponsor explained that they are requesting a retest date for drug substance of and a shelf-life for drug product of The Division stated that this is a review issue but noted the sponsor's concerns regarding the 70 mg shelf-life since the 70 mg is bracketed between the 20 and mg. The Division said that it will take into consideration the supportive data when shelf life is determined. The division also noted that how much weight supportive data will carry will be dependent on formulation, and any process changes that may have occurred between supportive stability and primary stability batches as well as quality of data. The Division further elaborated that it will mainly rely on primary stability data, but will consider the supportive data.

The Division asked how different the IND formulation is from the commercial formulation. The sponsor replied that the magnesium stearate in IND formulation is — and in the commercial formulation is —. The Division inquired whether there was an impact on — or dissolution and the sponsor said no. The Division stated that in the NDA, the sponsor should clearly indicate the differences between the IND and commercial formulations in a tabular format. The sponsor agreed.

The sponsor asked if it would be acceptable to submit a request for extension of shelf-life post-approval in the annual report and the Division said yes provided stability data is from the approved stability protocol.

Executed Batch Records and Analytical Methods Validation Package

- 4. Based on experience, executed batch records and the Analytical Methods Validation package (for submission to the FDA Testing Laboratory(ies)) have not had an impact on the review or approval of an NDA. To focus the review on critical aspects, BMS proposes to not include executed batch records or the Analytical Methods Validation Package in the initial NDA submission for BMS-354825. BMS would be prepared to submit the Analytical Methods Validation Package upon receipt of request from the FDA Testing Laboratory (ies). Does the Agency agree with this proposal?**

FDA RESPONSE:

- Executed batch records should be provided in the NDA submission according to 21 CFR 314.50(d)(1)(ii)(b). Although you may not have received any comments regarding executed batch records, they are useful when we evaluate manufacturing process and controls for the product. Your proposal not to include analytical methods validation package (for submission to the FDA Testing Laboratory) in the initial NDA submission is acceptable. This package can be submitted later after the Agency's evaluation and approval of the regulatory specifications.

Discussion: Regarding the batch records, the sponsor stated that in the NDA, they propose to submit — for 1 commercial strength and noted that 20, 50, and — have the same — and are identical except for —. The sponsor feels that — would be representative of all the other strengths. The Division said that the sponsor will need to submit — records for the extremes, i.e., 20 mg and 70 mg, and that the others should be readily available. The sponsor noted that the 70 mg batch record is not from the LTSS and asked if they could submit the batch records for — instead so it would be from the LTSS. The Division agreed but reminded the sponsor the batch records for the other strengths should be available as requested.

Biowaiver Plan

5. BMS intends to market three strengths of BMS-354825 tablets (20, 50 and 70 mg). To date, BMS-354825 20 and 50 mg tablets have been used in clinical studies. Based on 1) the fact that all of the tablet strengths are manufactured from a common —
2) similarity of the dissolution profiles, and 3) linear PK results across the dose range studied in Phase 1 multiple ascending dose studies in patients, we intend to request a waiver of bioequivalence studies for the 70 mg strength tablet. The approach is in accordance with:

FDA Guidance for Dissolution Testing of Immediate Release Solid Oral Dosage Forms (Aug-97)

FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (2003) which recommends that for an NDA, biowaiver of a higher strength will be determined to be appropriate based on 1) clinical safety and/or efficacy studies including data on the dose and the desirability of the higher strength, 2) linear elimination kinetics over the therapeutic dose range, 3) the higher strength being proportionally similar to the lower strength, and 4) the same dissolution procedures being used for both strengths and similar dissolution results obtained.

Does the Agency agree with the plan or have any comments?

FDA RESPONSE:

- This plan is acceptable.

There were no unresolved issues. The teleconference concluded at 1:30 pm.

ACTION ITEMS:

- Division to see if a change in vendor but with same chemistry is allowed to be submitted in the annual report. Dr. Chidambaram to follow-up.

Christy Cottrell
Consumer Safety Officer

Concurrence Chair:

Nallaperumal Chidambaram, Ph.D.
Chemistry Team Leader

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

/s/

Christy Cottrell
7/15/05 03:40:47 PM

Nallaperumal Chidambaram
7/15/05 06:22:51 PM