CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-986 & 22-072

CHEMISTRY REVIEW(S)

NDA 21-986

SPRYCEL™ (dasatinib) Tablets

(for chronic myelogenous leukemia)

and

NDA 22-072

SPRYCEL™ (dasatinib) Tablets

(for Ph+ acute lymphoblastic leukemia)

Bristol-Myers Squibb

William C. Timmer, Ph.D.: Drug Substance
Drug Product
Labeling

Ying Wang, Ph.D.: Manufacturing Science

Division of Pre-market Assessment and Manufactuirng Science, Office of New Drug Quality Assessment

Reviewed for the Division of Division of Drug Oncology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-986

2. REVIEW: #1

3. REVIEW DATE: 14 February 2006

4. REVIEWERS: William C. Timmer, Ph.D.: Drug Substance/Product; Labeling
Ying Wang, Ph.D.: Manufacturing Science: Sections P.2.3 and P.3.1 through P.3.5

5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE
IND 66,971	20 March 2003

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 21-986 N(000)	28 December 2005
NDA 21-986 N(000) BL	22 March 2006
NDA 21-986 N(000) BC	25 April 2006
NDA 21-986 N(000) BC	02 May 2006

7. NAME & ADDRESS OF APPLICANT:

NAME:	Bristol-Myers Squibb
ADDRESS:	5 Research Parkway, Wallinford, CT, 06492
REPRESENTATIVE:	Marie-Laure Papi, Pharm. D.
TELEPHONE:	203-677-3830

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	Sprycel
NON-PROPRIETARY NAME (USAN)	Dasatinib
CODE NAME/ NUMBER (ONDC ONLY)	N / A
CHEMISTRY TYPE / SUBMISSION PRIORITY	1 / P

9. LEGAL BASIS FOR SUBMISSION: 505(b)1

10. PHARMACOL. CATEGORY: Anti-leukemic

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 20 mg, 50 mg, 70 mg

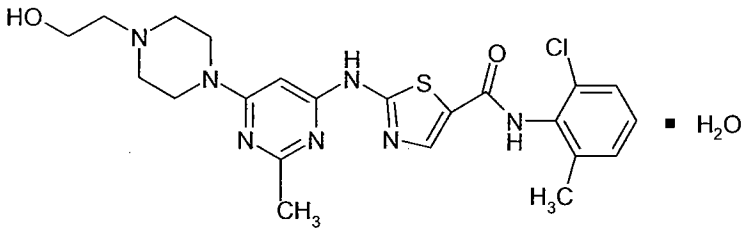
13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: _x_ R_x ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



CAS Name: *N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate

Molecular Formula: $C_{22}H_{26}ClN_7O_2S \cdot H_2O$
Formula Weight: Anhydrate: 488.01 g/mol Monohydate: 506.02 g/m

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
	IV			1	2	08-May-06
	III			4	—	N/A
	III			4	—	N/A
	III			4	—	N/A
	III			4	—	N/A
	III			4	—	N/A
	III			4	—	N/A
	III			4	—	N/A

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	66, 971	BMS-354825

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	05-JUN-06	J. DAmbrogio
Pharm/Tox	Approvable		H. Saber-Mahloogi, Ph.D.
OBCP	Approvable		A. Men, Pharm.D.
LNC	N/A	N/A	N/A
Methods Validation	*To be initiated.*	----	----
ODS DMETS	*Sprycel* Not Acceptable	12-MAY-06	Todd Bridges, R.Ph.----
EA	Acceptable; CE granted.	20-MAR-06	W.C. Timmer, Ph.D.
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-986

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Division of Oncology Drug Products administratively split the application into two NDAs, NDA 21-986 for CML and NDA 22-072 for Philadelphia positive ALL, but the CMC aspects remained the same for them. All outstanding CMC issues have been resolved and all manufacturing and testing sites were deemed acceptable for cGMP compliance by the Office of Compliance. The NDAs are recommended for approval from CMC standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The sponsor Bristol-Myers Squibb was submitted a CMC Information Request Letter on or about 23-MAY-06. The issues address in the IR letter do not represent NDA approvability issues. Effective the date of this review, BMS has not responded to the IR letter.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

The drug substance is the new chemical entity dasatinib (BMS-354825).

Dasatinib has the molecular formula $C_{22}H_{26}ClN_7O_2S \cdot H_2O$, and molecular weight of 506.02 g/mol for the monohydrate. It is a crystalline white powder that

, it typically melts at ~ 285 °C.

The structure of dasatinib was derived from its synthesis and
analyses ( ), and was confirmed by a
data.

For the most part, dasatinib is insoluble in water and polar organic solvents; however, the aqueous solubility is pH dependent. Dasatinib is considered a low solubility compound in the Biopharmaceutical Classification System (BCS). Therefore, dissolution of dasatinib can potentially be rate-limiting step for absorption.

The manufacturing process consists of a [redacted]. The in-process controls established for [redacted] are based on development experience.

For each starting material used in the synthesis of dasatinib, all impurities observed at levels of ≥ [redacted] wt have been characterized. The fate of these starting material impurities during downstream processing has been established, and the impact on the impurity profile of the final intermediate and drug substance is understood and appropriately controlled.

No impurities in the starting materials have been carried over intact into the drug substance. Impurities that react in the manufacturing process to generate corresponding downstream impurities, which can be carried over into drug substance, are controlled by specifications to ensure the quality of dasatinib.

Dasatinib DS is packaged in [redacted]

[redacted] of stability data were included in the submission; an update during the review cycle brought the total stability data submitted to [redacted] Analysis of all of the stability data revealed:

- The drug substance is stable when stored at long-term or intermediate conditions when stored in [redacted]
- The drug substance is not sensitive to light.
- The analytical data from all three batches placed on long-term stability show similar stability profiles.
- The data support a retest period of at least [redacted] when stored in [redacted]

Based on the evaluation of all stability data, *viz.*, [redacted] data at long-term and intermediate storage conditions, six-month accelerated data, and [redacted] supportive stability data, the following label statement is supported:

"Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]."

Drug Product

The drug product is Sprycel (dasatinib) Tablets.

Dasatinib tablets were developed for commercialization in strengths of 20 mg, 50 mg, and 70 mg. A — mg tablet was manufactured and used in developmental studies; however, this strength will not be marketed. The container closure systems are made of equivalent materials to those used in stability studies and are supported by the stability studies.

All excipients used in the manufacture of the tablets are compendial. The excipients are lactose monohydrate (—), microcrystalline cellulose (and/or tableting aid), hydroxypropyl cellulose (—), croscarmellose sodium ( ) and magnesium stearate (—). The levels of HPC, CCS, and magnesium stearate are commonly used and BMS has demonstrated that their selected combination provides appropriate processing characteristics (*e.g.*, —) and tablet properties (*e.g.*, — dissolution). Dasatinib tablets are film coated with — White.

Dasatinib tablets will be packaged into a 95 cc bottle (60, count)

Dasatinib has low aqueous solubility and high permeability, and is classified as a BCS Class II compound; hence, dissolution is the rate limiting step to absorption.

— In this case, the drug *substance* accounts for — w/w of the tablet weight, so the — can clearly affect processing attributes.

BMS performed studies with various dasatinib particle sizes with D[90] ranging from — Particle size had no impact on *in-vitro* tablet dissolution and content uniformity. In addition, — were unaffected at acceptable — s, irrespective of the drug substance particle size.

The manufacturing process for the drug product uses — All three strength tablets (20, 50, and 70 mg) are manufactured from the same common — The process parameters for — at long-term stability, clinical, and scale up batch scales have produced tablets with acceptable — dissolution properties for over — batches.

The — assay has been demonstrated to be robust; it is used for ID, assay, and impurities/degradants for dasatinib tablets. The — method is stability indicating for dasatinib and is used at both drug product release and in the stability protocol.

Regarding the individual specifications, no impurities or degradants specific to the current drug product formulations were observed in dasatinib tablets. In addition, the dissolution specification of ≥ (Q) in 30 minutes was proposed based on — long term stability data.

As previously noted, the —mg tablet strength, not requested for approval, was used as part of the bracketing for long-term stability program. A bracketing design was also used to bracket intermediate bottle fill sizes between — and — count fill sizes.

The long-term stability studies monitored the physico-chemical characteristics and microbiological integrity of the drug product. Dasatinib tablets, 20 mg, 50 mg and 150 mg, packaged in — count and — count — bottles (show little or no change in stability after —— A photostability study indicated that the product does not need to be protected from light.

A 24-month expiry period is supported by the long term stability data for dasatinib tablets for all commercial strengths (20 mg, 50 mg and 70 mg) and package presentations (— bottles. — when stored at room temperature as stated below..

> Storage at 25°C (77°F); excursions permitted
> between 15°-30°C (59°-86°F)
> [See USP Controlled Room Temperature]

B. Description of How the Drug Product is Intended to be Used

Dasatinib BMS-354825 is a novel small-molecule tyrosine kinase inhibitor indicated for the treatment of chronic myelogenous leukemia (CML). CML arises from the excessive production of abnormal stem cells in the bone marrow which eventually suppress the production of normal white blood cells. CML usually has three identifiable phases: the chronic phase, which is typically benign and lasts for an average three to five years, the accelerated phase and the blast-crisis phase.

The vast majority of patients with CML have a genetic mutation called the Philadelphia (Ph+) chromosome, which is due to reciprocal translocation between the long arms of chromosomes 9 and 22. This leads to the creation of a *bcr-abl* fusion gene that encodes the production of the bcr-abl protein, a tyrosine kinase

that influences cell growth, differentiation and survival. Because the bcr-abl fusion protein is almost never seen outside leukemia cells, it presents an attractive therapeutic target and has been successfully exploited in the development of new treatments for CML.

At present there are several treatment options for patients with CML; they include conventional cytotoxic chemotherapy, interferon-alpha, allogeneic stem-cell transplant (the only potentially curative therapy) and the current gold standard, imatinib mesylate.

Imatinib mesylate (Gleevec), also small-molecule tyrosine kinase inhibitor, competitively inhibits bcr-abl tyrosine kinase activity. By blocking the effects of the bcr-abl fusion protein, imatinib helps destroy leukaemic cells. It is currently indicated as a first-line treatment in patients with chronic Philadelphia-positive-chromosome CML as well as those who initially present in the accelerated or blast cell crisis phase.

Although most patients with CML initially respond to treatment with imatinib, cases of imatinib resistance are increasingly being reported. There is a need for a drug that can override imatinib resistance in patients with CML, especially in those who progress to the accelerated and blast-crisis phase.

Dasatinib is a potent inhibitor of multiple kinases, including bcr-abl and src kinases along with other oncogenic kinases. Overexpression or activation of these kinases play critical roles in the etiology of various cancer types and in malignant characteristics such as unregulated proliferation and metastasis.

Dasatinib is active *in vitro* and *in vivo* in nonclinical models of CML representing variants of both imatinib-sensitive and imatinib-resistant diseases. Nonclinical studies in leukemic cell lines representing variants of imatinib mesylate sensitive and resistant disease show that dasatinib can overcome imatinib resistance resulting from bcr-abl overexpression, bcr-abl kinase domain mutations, activation of alternate signaling pathways involving the src family kinases, and multi-drug resistance gene overexpression.

Dasatinib was effective in subjects with all phases of CML and Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL), resulting in lasting hematologic and cytogenetic responses.

Dasatinib is proposed for the treatment of adults with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib. Dasatinib is also proposed for the treatment of adults with Ph+ ALL and lymphoid blast CML with resistance or intolerance to prior therapy.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, BMS has submitted sufficient and appropriate information to support the approval of the drug product. The physical and chemical characteristics, impurity profile, and stability for dasatinib drug substance and dasatinib tablets has been adequately demonstrated in this submission. The acceptance criteria are appropriate to ensure the identity, strength, quality, potency, and purity of both the drug substance and the finished drug product. The criteria are also adequate to assure consistent quality so as to eliminate batch-to-batch variations. In particular, the — assay provides an acceptable degree of separation of dasatinib from its impurities. Based on analysis of the stability data, the approved shelf life for Sprycel (dasatinib) Tablets, 20 mg, 50 mg, and 70 mg tablets is 24 months at room temperature.

III. Administrative

A. Reviewer's Signature

/s/ William C. Timmer, Ph.D.

/s/ Ying Wang, Ph.D.

B. Endorsement Block

Ravi S. Harapanhalli, Ph.D.,
Branch Chief, DPAMS, ONDQA
(electronically signed in the DFS)

C. CC Block

204 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 1

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/s/

William Timmer
6/27/2006 04:13:39 PM
CHEMIST

Ying Wang
6/27/2006 04:16:31 PM
CHEMIST

Ravi Harapanhalli
6/27/2006 04:31:08 PM
CHEMIST
Firm should respond to the IR letter dated 5/24/06 in a new correspondence to the NDA (Not an approability issue).

CMC Branch Chief Memo: NDA 21-986 and NDA 22-072:
Ravi S. Harapanhalli, Ph.D.
Chief, Branch V, DPAMS, ONDQA
June 27, 2006

Background:

The proposed indications are for the treatment of chronic myeloid leukemia and PH + acute lymphoblastic leukemia. The Division of Oncology Drug Products administratively split the application into two NDAs, NDA 21-986 for CML and NDA 22-072 for Philadelphia positive ALL, but the CMC aspects remained the same for them.

The NDA was submitted on 28-DEC-2005 with a PDUFA date of 28-OCT-2006 and Sarah Pope's initial quality assessment was signed off into the DFS on 10-FEB-2006. Since the NDA contained significant portion of the drug substance synthesis and manufacturing information and — — process controls it was recommended for team review. Bill Timmer and Ying Wang reviewed the NDA together. All critical issues pertaining to approvability were resolved through information request letter. Additional stability update was also reviewed in support of proposed expiration dating period of 24 months. The primary review was signed off into the DFS on 27-JUN-2006.

Overall recommendation:

All outstanding CMC issues have been resolved and all manufacturing and testing sites were deemed acceptable for cGMP compliance by the Office of Compliance. The NDAs are recommended for approval from CMC standpoint.

Pending issues (Not related to approvability):

1. BMS should submit responses to the IR letter dated 23-MAY-2006.

The CMC questions pertained to the justification for the upper limit of ~ in the in-process LOD specification for —, a justification for the use of non-specific LOD method for — and the listing of test in the section on controls of critical steps and intermediates. Additionally, a clarification is needed for the use of —. We requested the PM to include a reminder in the action letter indicating that the firm should respond to these outstanding questions in a new correspondence to the NDA. However, upon discussion with the medical team, the PM informed us that such statements will not be included in the action letter

and that the PM will pursue with the firm to submit the pending information to the NDA.

2. BMS should revise their container and carton labels to include parenthesis around the established name "Dasatinib."
   In discussion with the Project manager today, we realized that the firm has already made the final printed labels without the parenthesis around the established name. We requested the firm to revise it at the next printing schedule.

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

/s/

Ravi Harapanhalli
6/27/2006 05:07:54 PM
CHEMIST

Firm should submit responses to the IR letter dated 05/24/06 (Not related to approvability)

ONDQA Division Director's Memo

NDA 21-986 and NDA 22-072
Sprycel® (dasatinib) Tablets 20 mg, 50 mg, and 70 mg
Date: June 26, 2006

Introduction

All three strengths of to-be-marketed Sprycel® (desatinib) Tablets are supplied as white tablets which are differentiated on the basis of tablet shape, size and debossed markings as follows; 20 mg (round, BMS/527), 50 mg (oval BMS/528), and 70 mg (round BMS/524). The tablets are packaged in — bottles of 60, and count (60 count only for 70 mg tablets) with —

Administrative

The corresponding IND for these two applications is 66,971. The Division of Oncology Drug products administratively split this application into two NDAs as follows: NDA 21-986 for CML and NDA 22-072 for Philadelphia positive ALL. These NDAs are priority (1P) new molecular entity submissions and are identical in their CMC aspects.

All inspection activities were completed and found to be acceptable 05-JUN-2006. In a memo dated 12-MAY-2006, ODS DMETS recommended that the proposed trade name of Sprycel be rejected. The full ODS DMETS review is pending as of this writing.

For the CMC review; a team approach was implemented with Dr. Ying Wang contributing the Manufacturing Science portion of the final review. Overall, **ONDQA is recommending an approval (AP) action** based on resolution of all CMC deficiencies which are captured in Dr. Timmer's Review.

Drug Substance

Dasatinib is a crystalline white powder which is synthesized — The to-be-marketed form is the monohydrate with a retest period of — for the final API). Solubility is pH dependent and in physiological fluids it is influenced by two weakly basic nitrogens with pKas of 3.1 and 6.8 respectively (e.g., 18 **mg**/mL at pH 2.6, 8 **ug**/mL at pH 6, and <1 **ug**/mL at pH 7.4). There is third weakly acidic pKa of 10.9 which will not dissociate to any appreciable extent in physiological fluids. The solubility of dasatinib in ethanol is 3.4 mg/mL.

Dasatinib is a BCS Class-II substance (low solubility / high permeability); thus the rate of absorption may be strongly influenced by the dissolution rate.

There was an issue with proposed starting material [redacted] from EOP2. The sponsor provided adequate justification in the NDA to include it as an acceptable starting material.

Drug Product

The drug product tablets are to-be-marketed in three strengths (20 mg, 50 mg, and 70 mg) as described in the Introduction to this memo. The tablets are film coated, immediate release, and all strengths utilize the same proportional formulation containing the following excipents; dasatinib (API), lactose monohydrate [redacted], microcrystalline cellulose [redacted], hydroxypropyl cellulose [redacted], croscarmellose sodium [redacted], magnesium stearate [redacted], and [redacted] White (film coat).

The applicant adequately characterized the dissolution performance with respect to changes in composition and manufacturing process. The drug product exhibited adequate performance on stability (including dissolution behavior) to warrant an approval of a 24 month expiry period in all packaging configurations.

Summary of CMC Issues:

There are no outstanding CMC issues.

Rik Lostritto, Ph.D., Director
ONDQA, Division-III

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/s/

Richard Lostritto
6/26/2006 04:42:13 PM
CHEMIST

Initial Quality Assessment
Branch V
Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment

OND Division:	Division of Drug Oncology Products
NDA:	21-986
Applicant:	Bristol-Meyers Squibb Company
Stamp date:	28-DEC-2005
PDUFA Date:	28-OCT-2006
Proposed Trade Name:	Sprycel™
Established Name:	Dasatinib
Laboratory Code:	BMS-534825-03
Dosage Form:	Tablets
Route of Administration:	Oral
Indication:	Treatment of chronic myeloid leukemia and PH+ acute lymphoblastic leukemia

Pharmaceutical Assessment Lead: Sarah C. Pope, Ph.D.

	YES	NO
ONDQA Fileability:	√	___
Draft Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summaries

Background Summary

NDA 21-986 has been submitted for Sprycel (dasatinib) Tablets, intended for treatment of chronic myeloid leukemia and PH+ acute lymphoblastic leukemia. Dasatinib was granted fast-track status on 25-JAN-2005. In a letter dated 05-DEC-2005, the Agency accepted the Sponsor's proposal for submission of NDA 21-986 as a rolling submission. The current CMC section is the second and final portion of this rolling submission. The NDA was officially submitted on 28-DEC-2005.

Dasatinib was studied under IND 66,971, which has been active at the Agency since 04-MAR-2003. A CMC-specific EOP2 meeting was held on 15-JUN-2005, and two pre-NDA meetings were held on 07-JUL-2005 and 27-OCT-2005. Official meeting minutes are filed under IND 66,971.

Drug Substance Summary

Dasatinib is a New Molecular Entity. It is a crystalline white powder and is insoluble in water The structure of BMS-354825 is presented below (Figure 1). Three ionization constants have been identified for BMS-354825 in aqueous solution (Table I). BMS-354825 is not soluble in water (0.008 mg/mL at 24°C ± 1°C).

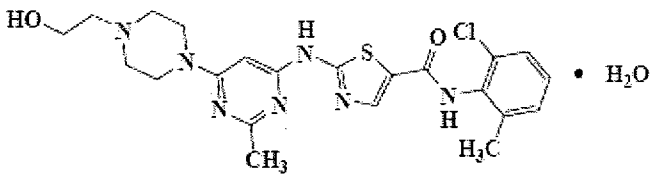

Figure 1. BMS-354825
N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)
-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-
thiazolecarboxamide, monohydrate
$C_{22}H_{28}ClN_7O_3S$
MW = 506.02 mg/mmol

Table I. Acid dissociation constants for BMS-354825

Ionization Constant	Description
3.1	Cyclic nitrogen
6.8	Cyclic nitrogen
10.9	Hydroxyl

BMS-354825 is synthesized using conventional

Packaging, labeling, and testing
Bristol-Meyers Squibb Company
1 Squibb Drive
New Brunswick, NJ 08903

The amount of submitted stability data for the drug product is based on agreements reached at the 15-JUN-2005 EOP2 meeting. The Sponsor has provided long term [redacted] and accelerated [redacted] stability testing results for three batches of drug product per dosage strength (for the 20- and 50-mg tablets), manufactured via the proposed commercial process. The 20 mg batches were manufactured at commercial scale, while the 50 mg batches were manufactured at pilot scale. The Sponsor has proposed a bracketing scheme for the drug product, and no stability data for the 70-mg tablet is provided. The 70-mg tablet is bracketed by the two lower and one higher [redacted] mg) dosage strengths. While the [redacted] mg tablet is not proposed for approval, the related pilot-scale stability data have been provided to support the bracketing scheme.

Dasatinib tablets will be marketed in two packaging configurations, including [redacted] bottles with child-resistant closures [redacted] Complete Drug Master File references have been provided for these proposed packaging components. Stability samples were packaged in each of the proposed marketing configurations.

The Sponsor has proposed an [redacted] expiration dating period for the drug product.

B. Critical issues for review and recommendation

Drug Substance

a. Previous (EOP2) negotiations have resulted in the Sponsor's proposal of [redacted] starting materials: [redacted]. The Agency confirmed acceptance of [redacted], as starting materials in a 15-JUN-2005 meeting. However, the Agency did not confirm acceptance of [redacted] as a starting material, based on [redacted]. As outlined in the official EOP2 meeting minutes, the Sponsor was advised that [redacted] would potentially be an acceptable starting material, pending further negotiation and additional information provided in the NDA.

Several issues remain active for this specific issue. The acceptability of [redacted] as a confirmed starting material has not been established and therefore, this should be reviewed and addressed as soon as possible. Specific reference (see meeting minutes dated 15-JUN-2005) was made to a potential "change control" agreement, including appropriate post-approval submission filing status for starting material changes. Due to the significant impact of the starting material designation, this is of critical concern for drug substance manufacture.

b. The Sponsor has submitted minimal stability data for the drug substance. As agreed in the 15-JUN-2005 EOP2 meeting, additional stability data should be submitted via a timely update to the pending NDA.

c. The Sponsor has proposed [redacted] process parameters for dasatinib synthesis. [redacted]. The [redacted] has also been proposed as a critical process parameter.

d. Quality and change control strategies for the proposed starting material — have been provided in Section 3.2.S.2.3.1. The manufacturing sites for the proposed starting material — —) have not been entered into the Establishment Evaluation System. If this proposed starting material —) is not determined to be acceptable, additional correspondence with the Office of Compliance will be required.

e. The use of a —

f. Three synthetic processes (A-C) are referenced in the pending NDA. The described process evolution may be critical to the resulting impurity profiles and impurity development data, as well as to the purity of the proposed commercial drug substance. Process differences have been outlined in Table 3.2.S.2.6.T01.

g. Due to dasatinib's status as a New Molecular Entity, the provided characterization and impurity identification data are critical to the proposed identity of the drug substance and resulting impurity profile.

h. As specified in the 15-JUN-2005 meeting minutes, a separate methods validation package has not been included and will be provided after approval of the regulatory specifications.

i. The low aqueous solubility and high permeability of dasatinib implicate tablet dissolution as rate-limiting for absorption. The potential impact of — on dissolution should be assessed during the primary review.

Drug Product

a. As specified in the 15-JUN-2005 meeting minutes, the Sponsor has requested a biowaiver for the 70-mg tablet. The acceptability of this approach should be confirmed with the appropriate Clinical Pharmacology reviewer.

b. — have been proposed as critical process controls (Section 3.2.P.3.4). The pertinent development data and justification are located in the Pharmaceutical Development section.

c. The classification of dasatinib as a low-solubility, high-permeability (Class 2) compound implicates the proposed specification for dissolution as a critical quality attribute. The acceptability of the proposed acceptance criterion should be confirmed, and the proposed method should be sufficiently discriminatory to confirm the quality for each dosage strength of the drug product. Pertinent information/discussions are outlined in the 15-JUN-2005 meeting minutes.

d. The manufacturing process used to manufacture primary stability batches should be confirmed as representative of that proposed for commercial supplies.

C. Comments for 74-day Letter:

1. 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.

D. Recommendation for fileability: Fileable

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		Requested 03-FEB-2006.
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?		√	Data have been provided but without analysis. Additional data should be provided in a timely update.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?		√	Methods validation data is included, but the MV package will be submitted post-approval.
15	Is a separate microbiological section included?		√	Solid oral dosage form – not necessary.
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)		 √ √ √ √ √	Microbiology **Pharm/Tox** Biopharm **Statistics (stability)** OCP/CDRH/CBER LNC DMETS/ODS **EER**

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LOA Included
			Yes
			Yes
			Yes
			Yes
			Yes
			Yes
			Yes

Recommendation for Team Review:

This NDA includes a significant portion of drug substance synthesis and manufacturing information. The drug product is a conventional solid-oral dosage form. However, dasatinib is a new molecular entity, and critical quality attributes of the drug product will include the resulting impurity profiles for both release and stability.

The team review approach is recommended for this NDA, based on the complete information provided in the document, which will allow multiple reviewers with varied expertise to assess different sections. Additionally, the team approach will facilitate a careful review of the interaction between the proposed synthetic strategy for the drug substance and the overall quality (including impurity profiles) of the proposed drug product.

Sarah C. Pope, Ph.D. — 10-FEB-2006
Pharmaceutical Assessment Lead — Date

Ravi Harapanhalli, Ph.D. — 10-FEB-2006
Branch Chief — Date

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/s/

Sarah Pope
2/10/2006 05:28:28 PM
CHEMIST

Ravi Harapanhalli
2/10/2006 06:04:26 PM
CHEMIST