CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-350

CHEMISTRY REVIEW(S)

Onglyza
(saxagliptin) tablets
NDA 22-350

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

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

Indication: Saxagliptin is an orally active reversible dipeptidyl peptidase-IV (DPP-IV) inhibitor proposed for the treatment of type 2 diabetes.

Presentation: Onglyza (saxagliptin) tablets are film coated tablets containing 2.5 mg or 5 mg, ——— . Both strengths will be available in 30 count (95 ml) and 500 count (200 ml) white opaque ——————— bottles with desiccant. The 5 mg tablets will be additionally available in aluminum/ aluminum blisters. b(4)

EER Status: Acceptable, 26-FEB-09

Consults: Methods Validation – Revalidation by Agency was not requested
EA – Categorical exclusion granted under 21 CFR §25.31(c)

Original Submission: 30-JUN-08

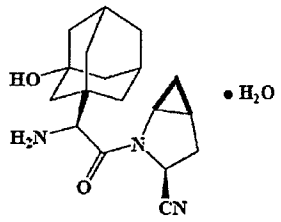
Post-Approval Agreements: None

Background for CMC Section of Application

The CMC portion of this NDA was submitted as part of the ONDQA CMC Pilot Program to explore science and risk based approaches to assuring product quality. A Comprehensive Quality Overall Summary was provided in Module 2 and an expanded pharmaceutical development section was submitted in Module 3, Section P.2. The applicant applied several Quality by Design (QbD) principles in the pharmaceutical development and manufacturing approaches.

Drug Substance:

The drug substance for Onglyza is saxagliptin in ——— monohydrate form. The formal chemical name is (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo [3.3.1.13,7]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate. The molecular structure is provided as follows: b(4)



The molecular formula is: $C_{18}H_{25}N_3O_2 \cdot H_2O$ with a calculated molecular weight of 333.43. Saxagliptin has been chemically and structurally characterized using:

b(4)

Saxagliptin drug substance will be manufactured at the BMS facility in Swords, Ireland using a commercial process from starting materials.

The NDA contained expanded information for the synthesis and process development of saxagliptin, using Quality by Design approaches. The approach included identification the critical quality attributes of the drug substance, identification of critical and "key" process parameters, and the implementation of process controls for producing drug substance of the desired quality. Several statistically designed experiments (DoEs) were utilized in the drug substance process development. The application included a design space for drug substance, allowing for increased flexibility for manufacturing. Drug substance quality is assured through manufacturing process controls combined with conventional end-product testing, including appearance, color, identification, and assay and impurities/degradants by High Performance Liquid Chromatography (HPLC). b(4)

Based on the 32-month primary stability data for saxagliptin drug substance from Process C and the 12-month primary stability data for saxagliptin drug substance from Process D stored at 5°C (±3°C), a period for the drug substance is granted with the following label statements: b(4)

b(4)

Conclusion: Drug substance is satisfactory

Drug product

Onglyza (saxagliptin) tablets is an immediate release tablet, with the following description:

- 2.5 mg tablet, containing 2.79 mg saxagliptin hydrochloride (anhydrous): round, biconvex yellow tablet printed with "2.5" on one side and "4214" on the other side, with a tablet weight of 236mg
- 5 mg tablet, containing 5.58 mg saxagliptin hydrochloride (anhydrous): round, biconvex pink tablet printed with "5' on one side and "4215" on the other side, with a tablet weight of 239 mg

Based on tablet dimension measurements, saxagliptin film coated tablets, 2.5 mg, and saxagliptin film coated tablets, 5 mg, are expected to have an average thickness of 4.2 mm and average diameter of 8.2 mm. b(4)

The saxagliptin film coated tablets contain the following excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium state, yellow (2.5 mg), pink (5 mg tablet), b(4) No novel excipients are used in the manufacture of saxagliptin film coated tablets. The drug loading for both strengths is relatively low at less than

The drug product is manufactured by a coating process in a

b(4)

b(4)

The enhanced pharmaceutical development provided in the application included use of risk assessment and DoEs to evaluate the criticality of process parameters and support development of the control strategy and design space. In addition, experimental data was leveraged to develop a mechanistic model of the coating operation used to predict process performance. Drug product quality is assured through manufacturing process controls combined with conventional end-product

testing, including identification, dissolution, water content, uniformity of dosage units, and assay and impurities/degradants by HPLC. b(4)

Saxagliptin film coated tablets will be packaged and marketed as 30 and 90 count in 95 mL and 500 count in 200 mL white, opaque, bottles, with a two piece child resistant closure having an aluminum foil induction seal. Each bottle contains a cotton coil and one 2g pouch containing silica gel (desiccant) and activated carbon. 5 mg saxagliptin film coated tablets will also be packaged and marketed in aluminum/aluminum (alu/alu) blisters. b(4)

Based on provided stability data, the 2.5 mg strength saxagliptin tablets are granted a 36 month stability period for 30 and 90 count bottles containing desiccant. The 5 mg strength saxagliptin tablets are granted a 36 month stability period for 30, 90 and 500 count bottles containing desiccant, and 36 month stability period when stored in aluminum/aluminum blisters. Both the 2.5 mg and 5 mg strengths contain the following labeling statement: "Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Conclusion: Drug product is satisfactory.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested.

The application includes design space for both drug product and drug substance.

A comparability protocol for extensive changes that could be made with reduced reporting requirements was originally submitted in the application but was later withdrawn. The applicant expressed interest in submitting a revised version of the comparability protocol as a supplement at a later date following additional discussion and clarification from the Agency.

Overall Conclusion: From a CMC perspective, the application is recommended for **approval.**

Christine M. V. Moore, Ph.D.
Acting Director, DPA I/ONDQA

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/s/

Christine Moore
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CHEMIST

Overall Summary of Quality

NDA 22-350

Onglyza (saxagliptin) IR tablets

Bristol-Myers Squibb (BMS)

ONDQA CMC Pilot Program Application

CMC Quality Review Team

Sharmista Chatterjee, Ph.D.

John C. Hill, Ph.D.

Prafull K. Shiromani, Ph.D.

Suong T. Tran, Ph.D.

I. Overview

This Overall Summary of Quality is intended to provide a synopsis of the review teams' thoughts, deliberations and decisions associated with the CMC review of NDA 22-350, Onglyza (saxagliptin) IR tablets. The intent is to capture the teams' thoughts to facilitate future CMC supplement review and ONDQA discussions about regulatory submissions containing Quality by Design (QbD) information. This application was submitted as part of ONDQAs' CMC Pilot Program, published in the Federal Register (Vol. 70, No.134, July 14, 2005).

Initial evaluation of this NDA and the decision as to its fileability was conducted by the PAL assigned to this project, Su Tran. This Initial Qiality Assessment (IQA) review is filed in DFS/DARRTS[1].

In this initial assessment, several critical CMC deficiencies were identified and communicated to the applicant in the filing memo. The timely responses to these deficiencies provided critical CMC information to facilitate the full CMC evaluation of this NDA.

The team review process for this specific pilot program application consisted of several independent reviews from each of the team members. These reviews were filed within the regulatory review timelines mandated under the Good Review Management Principles guidance. Each of these reviews focus on specific aspects of the CMC review, specific to the area of expertise of the individual reviewer. These reviews have been entered into DFS/DARRTS[2,3,4]:

Each of these reviews resulted in several CMC deficiencies which were communicated to the applicant. The evaluations of the responses to these deficiencies have also been entered into DFS/DARRTS[5,6,7].

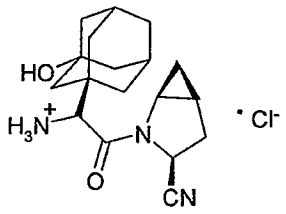
The current document summarizes the pertinent issues discussed in the six individual reviews filed in DFS/DARRTS.

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

[1] Initial Quality Assessment: Su Tran (chem.IQA/filing,27-AUG-2008)
[2] Drug substance CMC/QbD review: Prafull Shiromani (CMC Review 1, 28-OCT-2008)
[3] Drug product CMC/QbD review: Sharmista Chatterjee (Drug Product QbD Review, 24-NOV-2008)
[4] Overall CMC review: John Hill (CMC Review #1 for NDA 22-350, 08-DEC-2008)
[5] Drug substance CMC/QbD review: Prafull Shiromani (CMC Review 2, 23-MAR-2009)
[6] Drug product CMC/QbD review: Sharmista Chatterjee (Drug Product QbD Review, 23-MAR-2009)
[7] Overall CMC review: John Hill (Review, 23-MAR-2009)

Drug Product

Saxagliptin film-coated tablets, 2.5 mg and 5 mg [redacted] will be manufactured at the BMS facility in Mount Vernon, Indiana. Saxagliptin film coated tablets, 2.5 mg and 5 mg strength [redacted], have been developed for commercializationThe active in the drug product is the hydrochloride salt form of the drug substance. The structure for this salt form is provided as follows. b(4)



Molecular Formula: $C_{18}H_{25}N_3O_2$ * HCl

Molecular Weight: 351.87

Since subjecting saxagliptin to common pharmaceutical operations such as [redacted] b(4)

b(4)

b(4)

Based on tablet dimension measurements, saxagliptin film coated tablets, 2.5 mg, and saxagliptin film coated tablets, 5 mg, are expected to have an average thickness of 4.2 mm and average diameter of 8.2 mm.

The saxagliptin film coated tablets contain the following excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium state, [redacted] yellow (2.5 mg), [redacted] pink (5 mg tablet), [redacted] No novel excipients are used in the manufacture of saxagliptin film coated tablets. Due to the [redacted] system, traditional excipient compatibility studies were not performed for the saxagliptin drug substance, it was addressed through saxagliptin stability studies. b(4)

The two strengths will be differentiated by color and printing on the tablets.

- 2.5 mg tablet, containing 2.79 mg saxagliptin hydrochloride (anhydrous): Round, bi-convex yellow tablet printed with "2.5" and "4214"
- 5 mg tablet, containing 5.58 mg saxagliptin hydrochloride (anhydrous): Round, bi-convex pink tablet printed with "5' and "4215"

Saxagliptin film coated tablets will be packaged and marketed as 30 and 90 count in 95 mL and 500 count in 200 mL white, opaque, [redacted] bottles, with a two piece child resistant closure having an aluminum foil induction seal. Each bottle contains a cotton coil and one 2g pouch containing silica gel (desiccant) and activated carbon. 5 mg saxagliptin film coated tablets will also be packaged and marketed in aluminum/aluminum (alu/Alu) blisters. b(4)

The quality of the drug product is assessed by visual and [redacted] High Performance Liquid Chromatography [redacted]-HPLC) methods and assured by Quality by Design (QbD) principles. b(4)

Saxagliptin is a highly potent, selective, reversible, and competitive dipeptidyl peptidase-4 (DPP4) inhibitor. DPP4 is the enzyme primarily responsible for the inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Incretin hormones are gastrointestinal hormones that increase insulin secretion in response to enteral stimulation. These hormones contribute to the control of postprandial glucose excursions in a glucose dependent manner, mitigating the risk of hypoglycemia. In addition to enhancing postprandial insulin release, GLP-1 also reduces glucagon release from the pancreatic α-cells, thereby reducing hepatic glucose production. This effect is also glucose-dependent, such that when plasma glucose is normal or low, the counter-regulatory response of glucagon release is not impaired.

Saxagliptin is intended to improve glycemic control for patients with T2DM:

- as monotherapy as an adjunct to diet and exercise;

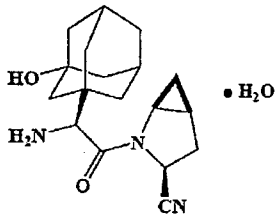
- in combination with metformin, a thiazolidinedione (TZD), or a sulfonylurea (SU)when the single agent alone, with diet and exercise does not provide adequate glycemic control; and
- as initial combination with metformin, as an adjunct to diet and exercise, when treatment with dual saxagliptin and metformin therapy is appropriate.

The proposed usual clinical dose is 5 mg once daily. The recommended dose is 2.5 mg once daily in subjects with moderate or severe renal impairment, and end-stage renal disease requiring hemodialysis.

Drug substance

Saxagliptin drug substance will be manufactured at the BMS facility in Swords, Ireland using a [redacted] step commercial process from [redacted] starting materials. The [redacted] is used in the manufacture of saxagliptin tablets. b(4)

The Drug substance is saxagliptin. The formal chemical name is (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo [3.3.1.13,7]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate. The molecular structure is provided as follows:



The molecular formula is: $C_{18}H_{25}N_3O_2 \cdot H_2O$ with a calculated molecular weight of 333.43.

Saxapliptin has been chemically and structurally characterized using: [redacted] b(4)

Saxagliptin drug substance is manufactured using a [redacted] step commercial process from [redacted] starting materials. The [redacted] is used in the manufacture of saxagliptin tablets. b(4)

Based on the 32-month primary stability data for saxagliptin drug substance from Process C and the 12-month primary stability data for saxagliptin drug substance from Process D stored at 5°C (±3°C), a period for the drug substance is granted with the following label statements: b(4)

b(4)

III. Background

The Quality section of the NDA was submitted as part of the FDA's CMC Pilot Program. On June 9, 2006 BMS requested acceptance into the Agency's CMC pilot program. BMS met with the Agency on August 14, 2006, to outline the saxagliptin QbD program and was accepted into the program on September 5, 2006. In the meeting minutes, FDA indicated BMS should submit a comprehensive Quality Overall Summary (QOS) and an expanded Pharmaceutical Development Section. BMS met with the Agency on April 26, 2007 to further discuss BMS's progress in the saxagliptin QbD development program. FDA agreed to BMS's proposed NDA content, which would include a comprehensive QOS and an expanded Section 3.2.P.2 "Pharmaceutical Development."

The FDA provided the following in response dated November 18, 2005 to a CMC-specific End of Phase II Briefing Document, submitted August 22, 2005 (IND 63,634,Serial No. 0085):

- The starting materials would be acceptable provided appropriate technical information as outlined in the Agency's reply is provided.
- Acceptance of the drug substance long term stability protocol.
- The Agency suggested the utilization of protocols to address changes to vendors, manufacturing processes, impurity profiles and acceptance specifications for starting materials, as well as changes to the manufacturing process and acceptance specifications for bulk drug substance.
- Acceptance of the proposed dissolution methodology which utilizes USP Apparatus II at 50 RPM in 0.1 N HCl.
- The Agency recommended modifying the drug product long term stability protocol for bottles, and accepted the proposed bracketing for blisters. The agency recommended modifying the proposed matrix to include testing each lot at the final time point.

BMS submitted additional information on April 12, 2007 (IND 63,634 Serial No. 0189) on the proposed starting materials, along with information about the proposed commercial drug substance manufacturing process and our proposal to utilize data from both Process C and Process D to determine the drug substance re-test period. Also, BMS requested comments on a proposed change to the dissolution method approved during

review of the End of Phase II briefing document. The Agency's response received via electronic mail on May 3, 2007 and May 11, 2007 indicated the following:

- The proposal to base the retest period on long-term stability data obtained on both Process C and D was acceptable
- The proposed modification to the dissolution method was acceptable
- The Agency had no objection to the information provided on starting materials.
- The Agency requested BMS address the possibility of low levels of the [redacted] in the drug substance.
- Discuss in the NDA observations regarding the behavior of saxagliptin tablets during dissolution testing.

b(4)

b(4)

BMS submitted Pre-NDA CMC questions to the Agency on December 27, 2007 (IND 63,634 Serial No. 0238). A response to these questions was received via electronic mail on February 15, 2008. The FDA had no comments on BMS' plan to submit 18- and 24-month LTSS data during the NDA review provided it was submitted no later than 6 months after submission of the NDA. In addition, the Agency indicated that it would not be able to review a Post-Approval Management Plan as outlined by BMS, but that BMS had the option of submitting one or more comparability protocols permissible under the current draft guidance. As a result of these responses, BMS submitted a Comparability Protocol as part of the saxagliptin NDA.

BMS submitted the NDA on June 30, 2008. Some of the issues identified in the Initial Quality Assessment[1] were:

- Lack of characterization information on saxagliptin hydrochloride, the active ingredient form in the drug product
- Different dosage strengths having [redacted]
- Lack of information [redacted]
- [redacted] not being proposed as a Critical Quality Attribute in the drug product manufacture [redacted]
- Use of [redacted] Understanding and Design Space" studies
- Lack of Dissolution in the drug product specification

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b(4)

These and other issues identified in the IQA were addressed in subsequent reviews[2,3,4] and adequately resolved.

IV. Assessment of Implementation of Quality by Design

As part of the pilot program, BMS was expected to include in this NDA an expanded Pharmaceutical Development section and critical CMC information that appropriately demonstrate product knowledge and process understanding of the drug substance and drug product using QbD principles and science-based approaches. In addition, a more

comprehensive Quality Overall Summary (cQOS) summarizing all critical CMC elements, along with an evaluation and assessment of those elements was expected.

These sections have been included in NDA 22-350. As part of the pilot program, the expanded pharmaceutical sections for both the drug substance and drug product have been independently assessed as part of ONDQA's team review philosophy. Several deficiency letters have been communicated to BMS and their responses have been received and evaluated.

The six reviews filed in DFS for this application [2,3,4,5,6,7] reflect the teams' evaluation of the overall quality of the CMC data provided. Each review reflects the strengths and expertise of the individual team members. While these evaluations have been filed independently, significant team discussions about the adequacy of the CMC data submitted have provided a unifying focus to the review process. The result is an in-depth evaluation of the overall QbD data (both drug substance and drug product) which BMS has provided in support of this application and the applicability of these data to aspects of the general chemistry and stability of saxagliptin.

After thorough evaluation of the quality data presented in this NDA, it is clear that BMS has demonstrated an understanding and implementation of aspects of QbD. The review process has also identified areas in which BMS would benefit from further exploration, development and refinement of their design space.

In general, the positive aspects of this QbD application have been identified as:

- The depth of specific information describing the control of the starting materials [redacted] and the manufacturing of the drug substance (DS). This information includes acceptable rationale for proven acceptable ranges (PARs) of reaction parameters and determination of the criticality of these parameters[1, pages 3-9, 12, 18, 20]. b(4)

- The implementation of suitable in-process PAT controls, e.g. [redacted] (above reference: page 10).

- The implementation of QbD during development of the DS manufacturing process, facilitating the identification of critical and key process parameters. Critical Quality Attributes have also been identified (above reference: pages 45, 46, 52).

- The establishment of proven acceptable ranges (PARs) and normal operating ranges (NORs) to ensure consistent quality and yield of the DS. It is noteworthy that the NORs for the manufacture of the drug substance are within the experimental range studied in the DOE for the drug substance. All the experiments performed in this DOE produced high-quality drug substance thus, substantiating these NORs, i.e. the Design Space (above reference: pages 54,57).

- Rationale for selection of formulation variables e.g. coating thickness, choice of coating material, ratio of drug substance to [redacted] in the coating suspension, pH of coating suspension[3]. b(4)

- Presentation of scientific rationale for designating various drug product (DP) quality attributes as critical[3].

- Implementation of a scientific, top down risk assessment methodology as per ICH Q9, e.g. use of [redacted] diagrams, to determine operations that were critical to drug product quality. Once the critical operation was identified, risk assessment methodology was again used to determine the critical sub steps. The critical sub steps were then examined in detail using a combination of risk assessment and DOE based experimentation[3]. b(4)

- Following a step by step rationale approach to determine DP manufacturing design space for critical variables at pilot scale based on DOE data and then scale to commercial scale[3].

- Use of [redacted] approach to leverage understanding gained from experimentation related to DP manufacturing and use it to limit future trial and error type experiments[3]. b(4)

- Presenting a rationale approach to use the [redacted] model to select a new operating range within/outside the design space[3].

Points where BMS would benefit from further exploration and development include:

- Provide a clear thesis/rationale for why they decided to submit the additional QbD, DoE and expanded manufacturing data in the application and what their expectations were (what regulatory actions or relief were they seeking)

- The mathematical model and associated statistical analyses for the DOE associated with the manufacture of saxagliptin were not presented/explained adequately in the original submission[2]. Preferably, these data should be presented in a systematic manner, with a few appropriate concise tables, e.g. i) Independent (X) and Dependent (Y) variables for the particular DOE; ii) Experimental range-statistical and corresponding physical units of Xs; iii) Yates Algorithm - the value of Xs for each experimental batch - with the whole set of experimental batches manufactured in a random order so as minimize experimental error; iv) Table of Y- values for each batch with mean and SD; v). Mathematical model/equation generated by the computer from the input raw Ys' data in the form: [redacted] b(4)

  Correlation coefficients (R^2) - to determine the fit of each Y to the computer generated model; vii) Optimum Formulation - through computer search techniques (feasibility and grid searches); viii) Validation

experiment and it's data to confirm predictive power of the predictor equation; xi) Determination of critical Ys, i.e. Model Reduction/Refinement, by Principal Component Analysis or comparison of each regression coefficient with the standard error; x) Contour and Response Surface Plots, (in all fairness, this deficiency is not restricted to this BMS NDA, but to a few recent NDAs with QbD elements; this should be resolved, eventually, as the QbD paradigm becomes the norm in drug product development).

- Provide data justifying criticality analysis of excipients, i.e. to show if any variation in excipient properties would impact CQA of finished product. For example no data was presented to show if lot to lot variation in amounts [redacted] would have an impact on quality of drug product. This information was provided as a response to an information request letter[6, response to comment #4, pg 6.] b(4)

- Lumping several variables to assess probability (P), severity (S) and risk (R) while performing risk assessment for DP manufacturing process variables. Individual effects are thus masked. Upon communicating this deficiency to the sponsor, they agreed to follow the suggested approach for future submissions[6, response to comment #2, pg 13)].

- Lack of assurance of the controls in place to ensure content uniformity of finished drug product, especially for movements outside the target operating conditions within the design space, at commercial scale[6, Summary, pg2)].

- Some gaps identified in not evaluating interaction of design spaces. For example, sponsor did not evaluate interaction of PAR of nozzle parameter with variation in equipment design. They agreed to add appropriate manufacturing controls in the batch record in terms of nozzle dimensions[6, response to comments #2 and 8, pg 13, 18)].

- Lack of data presented in the original submission to show how proven acceptable ranges for critical coating process variables were scaled from pilot to commercial scale, for example no scale up correlations were presented. This was provided later in response to an information request letter[6, response to comment #14, pg 25)].

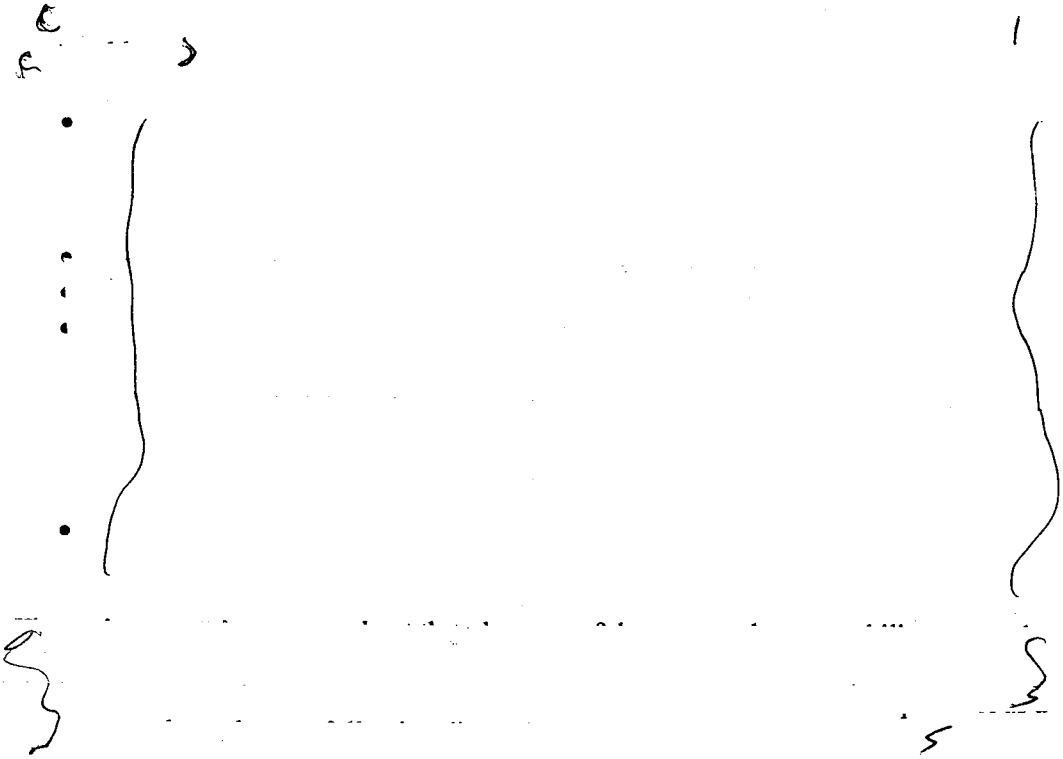
- Minimal information was provided in the original submission about the in-process assay that is performed after at least [redacted]. Note, this in process step is performed only at commercial scale, [redacted] b(4)
Similar in process step was not deemed necessary at pilot scale. Adequate information was provided about this assay in response to IR letters[6, response to comment #16, 17, 18 pg 28, 32-34)].

It is opined that if this was well understood and controlled at all scales, such an in process step would not have been required at commercial scale. Having said that,

the in process step would give additional assurance that the final product would meet the criterion for assay.

- Lack of assurance in the original submission about procedures for handling movements within design space at commercial scale. In addition, some critical manufacturing procedures and controls including the design space table were not included in the P.3 section. These omissions were corrected subsequently via amendments to the NDA, in response to IR letters[6, response to comments #3, 4, 5, 6, 11, 15 pg 13-16, 19, 26-28).

- Insufficient information presented in the original submission for the DOE's that were used for formulation and manufacturing process development (e.g. statistical analysis of the DOE data). These omissions were corrected subsequently via response to IR letters[6, response to comments #6, 21 pg 8, 36 respectively).



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b(4)

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b(4)

V. Notes for future inspections and Supplement Reviews

1.) The applicant executed a statistically designed set of experiments (DOE) to test and verify the ranges proposed for key and critical process parameters of the process. The primary purpose of the DOE was to confirm that the critical impurity was adequately controlled. Indeed, all experiments, covering the extreme values of

the parameters studied, produced drug substance with [redacted] below the reporting limit of the HPLC method. None of the main effects were significant, as determined by appropriate statistical tests, and hence, it was assumed that the associated [redacted] were insignificant. The applicant found that the quality of the drug substance in each of these experiments was indistinguishable from the quality of the drug substance produced at commercial manufacturing scale. Based on the DOE results and the alignment between the DOE and commercial manufacturing batch quality, BMS believes that the design space proposed for the drug substance manufacture has been substantiated; to which this reviewer concurs. Accordingly, movement within the design space requires no agency notification during routine commercial manufacturing[5]. b(4)

2.) One interesting feature in the developmental report for the saxagliptin drug product

b(4)

3.) A lingering concern is the issue of demonstration of adequate tablet content uniformity when moving outside the target operating condition but within the design space for active coating of tablets [redacted] To be noted that this is a relatively low dose drug (<2.5%) and USP<905> is currently followed to demonstrate content uniformity. The concern is based in part on the fact that it is noted that there is an increase in [redacted] when moving outside the target operating condition (refer table 13.1 in amendment # 17 to the NDA dated January 21, 2009)[3]. It is recommended to evaluate the sponsor's quality system to ensure that it includes appropriate sampling to assure content uniformity when moving outside the target operating condition but within the design space at commercial scale. b(4)

4.) If the opportunity arises, participation by an ONDQA reviewer in any inspection to support a Prior Approval Supplement dealing with modification of the approved

design space is recommended. Onsite inspection by the reviewer would be beneficial to the investigator to understand the various approaches to QbD.

5.) In the NDA application, BMS did not include dissolution as a regulatory requirement for final drug product release or stability. In order to attain approval of their application, BMS has agreed to include a regulatory test for dissolution for release and stability. The Agency indicated that we were open to discussions about alternative tests for dissolution/bioavailability in the future.[7]. The upshot of this action is that there will be further interactions/meetings with the applicant to explore alternative method(s) to evaluate dissolution. Such discussions will require participation by ONDQAs' Biopharm review staff.

6.) The stability data for the saxagliptin 2.5 mg coated tablet packaged in blisters [redacted] demonstrate that this packaging is not as robust as the Alu/Alu blister or the [redacted] bottle configuration. The stability data demonstrate that there is a humidity and temperature affect on overall impurity profile; elevations in either lead to the drug product failing to pass the proposed stability specification[4]. In the 74 day filing letter (12-SEP-2008), BMS was asked to Clarify whether the 2.5 mg tablets will be packaged in blisters because this packaging is not in the proposed labeling even though this packaging is listed for this dosage strength in the Container Closure and Stability sections of the NDA. In their response dated 15-OCT-2008, BMS states that they plan to launch the 2.5 mg tablets in bottles. Subsequently, blister packs might be added for hospital unit doses and physician samples[4 7]. Potentially, there will be a CMC supplement in the future requesting review and [redacted] In such a case, the impact of the proposed blister material (moisture permeability, etc.) will be an important review consideration.

b(4)

b(4)

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/s/

John C. Hill
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Suong Tran
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Prafull Shiromani
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Sharmista Chatterjee
4/3/2009 12:06:22 PM
CHEMIST

Christine Moore
4/3/2009 12:17:12 PM
CHEMIST

NDA 22-350
Review #2 (Section 3.2.P.2)

Onglyza Tablets

Bristol-Myers Squibb Company

Sharmista Chatterjee, Ph.D.

Member of CMC Review Team

Office of New Drug Quality Assessment

SUMMARY

This is a follow up to the Drug product QbD review dated November 24, 2008 . As indicated in the November 24th review, many comments were sent to the firm on December 1, 2008 upon evaluation of the Pharmaceutical Development (P.2) section of the NDA. Responses were received on January 21, 2009. Upon evaluation of these responses, some were found to be still inadequate and an additional Information Request letter was sent to the firm on February 25, 2009 and responses were received on March 12, 2009. The current review documents an evaluation of all these responses.

It is noted that the sponsor has implemented some aspects of the QbD paradigm for drug product development. These can be summarized as: b(4)

- Provided adequate rationale for selection of formulation variables e.g. coating thickness, choice of coating material, ratio of drug substance to [redacted] in the coating suspension, pH of coating suspension.

- Evaluated the impact of excipient lot to lot variability ([redacted]) on drug product attribute (i.e. level of degradant [redacted] b(4)

- Presented adequate scientific rationale for designating various drug product (DP) quality attributes as critical

- Implemented a scientific, top down risk assessment methodology as per ICH Q9, e.g. use of [redacted] diagrams, to determine operations that were critical to drug product quality.

- Followed a step by step rational approach to determine drug product manufacturing design space for critical variables at pilot scale and then scaled these to commercial scale. In the original submission adequate scale up procedures was not presented but was provided upon request.

- Used a mechanistic modeling approach to leverage understanding gained from experimentation related to drug product coating (i.e. [redacted] and proposed a pathway to use this model to limit future trial and error type experimentation. b(4)

- Though many manufacturing details as well as design space tables were not included in the P.3 section in the original submission, these were corrected upon the recommendation of the CMC review team.

- No indication were provided in the original submission as to how the firm would handle movements within and outside the design space. It was clarified in the March 12, 2009 amendment to the NDA, that the manufacturing sites would have access to the design

space tables and for movements outside the design space, appropriate regulatory filing mechanisms would be pursued.

A remaining concern of this reviewer is the issue of demonstration of adequate tablet content uniformity when moving outside the target operating condition but within the design space for active coating of tablets in the [redacted] To be noted that this is a low dose drug (<2.5%) and USP<905> is currently followed to demonstrate content uniformity. The concern is based on the fact that it is noted that there is an increase in [redacted] when moving outside the target operating condition (refer table 13.1 in amendment # 17 to the NDA dated January 21, 2009). It is opined that relaying these concerns about additional monitoring to the sponsor is outside the purview of this review, since it borders in the area of GMP. Instead, this reviewer has captured these concerns as 'Notes for Future Inspection and Supplement Reviews'. b(4)

P.2 Pharmaceutical Development

P.2.1 Components of the Drug Product

Acceptable, see Drug Product QbD review dated November 24, 2008.

P.2.1.1 Drug Substance

Acceptable, see Drug Product QbD review dated November 24, 2008.

P.2.1.2 Excipients

Acceptable, see Drug Product QbD review dated November 24, 2008.

P.2.2 Drug Product

P.2.2.1 Formulation Development

See background information and initial evaluation in Review dated November 24, 2008 . Find below an evaluation of response to comments pertaining to this section that were sent to the sponsor. It is to be noted that all initial comments addressed in this review were sent to the sponsor on December 1, 2008 and responses were received on January 21, 2009 (Sequence #17).

Comments to Sponsor and Response:

(1) It is noted that the selection of the drug substance to coating material ratio for each tablet strength is based [redacted] b(4)

34 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 3

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/s/

Sharmista Chatterjee
3/23/2009 12:02:23 PM
CHEMIST

Christine Moore
3/25/2009 03:57:23 PM
CHEMIST

NDA 22-350

Review #2 - 3.2.S.2

Onglyza (Saxagliptin)
2.5 & 5 mg Tablets

Bristol-Myers Squibb

Prafull K. Shiromani Ph.D.
Division of Pre-Marketing Assessment 1
Office of New Quality Assessment

28 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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

/s/

Prafull Shiromani
3/23/2009 02:17:04 PM
CHEMIST

Christine Moore
3/25/2009 03:55:09 PM
CHEMIST

NDA 22-350

Onglyza
(saxagliptin)

Bristol-Myers Squibb

John C. Hill, Ph.D.
ONDQA/DPMA-1 and DMEP (HFD-510)

Chemistry Review #2

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-350

2. REVIEW #2

3. REVIEW DATE: 19-MAR-2009

4. REVIEWER: John C. Hill, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 63634	08-NOV-2001
22-350 –000 N-document	30-JUN-2008
BC (partial response to 74 day filing memo)	15-OCT-2008
BZ (partial response to 74 day filing memo)	24-OCT-2008
BZ (partial response to 74 day filing memo)	03-NOV-2008
BZ (partial response to 74 day filing memo)	19-NOV-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
BC (Partial Response to CMC Defeciencies)	12-MAR-2009
BC (Partial Response to CMC Defeciencies)	26-FEB-2009
BC (Partial Response to CMC Defeciencies)	03-FEB-2009
BC (24 month stability data update)	24-DEC-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Bristol-Myers Squibb Company
Address:	P.O. Box 4000 Princeton, NJ 08543-4000
Representative:	Pamela J. Smith, M.D., Group Director, GRS
Telephone:	609-252-5228

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Onglyza
b) Non-Proprietary Name (USAN): Saxagliptin
c) Code Name/# (ONDC only): BMS-477118
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Dipeptidyl peptidase 4 (DPP4) inhibitors, Anti-Diabetic

11. DOSAGE FORM: Immedeiate Release Tablet

12. STRENGTH/POTENCY: 2.5 mg and 5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_ Rx ___OTC

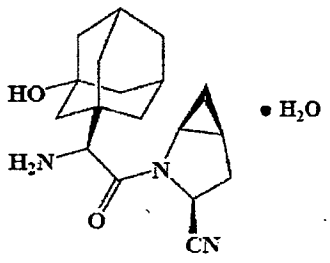
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

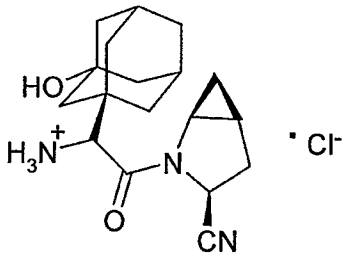
Chemical Name: (1S,3S,5S)-2-[(2S)-2-Amino-2-(3-hydroxylricyclo[3.3.1.13,7] dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate

Molecular Formula: $C_{18}H_{25}N_3O_2 * H_2O$



Molecular Weight: 333.43 (315.41 anhydrous)

Note: The active in the drug product is the hydrochloride salt form of the drug substance. The structure for this salt form is provided as follows.



Molecular Formula: $C_{18}H_{25}N_3O_2$ * HCl

Molecular Weight: 351.87

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	IV	[redacted]	[redacted]	4	Adequate	16-MAR-2009 04-MAR-2009 23-SEP-2008	LOA: 22-AUG-2008
[redacted]	IV	[redacted]	[redacted]	4	Adequate	16-MAR-2009 04-MAR-2009 23-SEP-2008	LOA: 22-OCT-2007
[redacted]	III	[redacted]	[redacted]	4	Adequate	12-MAR-2009	LOA: 18-JUN-2007
[redacted]	III	[redacted]	[redacted]	4	Adequate	*	LOA: 20-

b(4)

b(4)

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Chemistry Review Data Sheet

						FEB-2008
	III		4	Adequate	*	LOA: 18-OCT-2007
	III		4	Adequate	*	LOA 25-OCT-2007
	III		4	Adequate	*	LOA: 25-OCT-2007
	III		4	Adequate	*	LOA: 25-OCT-2007
	III		4	Adequate	*	LOA: 27-SEP-2007

b(4)

b(4)

b(4)

[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)

* Review not needed in accordance with review policy for container-closure systems for solid oral dosage forms.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63,634	Use of BMS-477181 (an orally active, reversible DPP4 inhibitor) in the treatment of type 2 diabetes

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	26-FEB-2009	S. Ferguson
Pharm/Tox	NA		
Biopharm	NA		
LNC			
Methods Validation	Not required		
OPDRA		24-NOV-2008	John Hill
EA	Acceptable	08-DEC-2008	John Hill
Microbiology	NA		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-350

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application can be APPROVED from a CMC viewpoint.

Based on the provided stability data, the 2.5 mg strength saxagliptin tablets are granted:

A 36 month expiry period when stored as 30-count and 90-count in 95-mL induction sealed bottles, containing [redacted] b(4)

with the following label statement: "Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]."

Based on the provided stability data, the 5 mg strength saxagliptin tablets are granted:

A 36 month expiry period when stored as 30-count and 90-count in 95-mL induction sealed bottles, containing [redacted] desiccant and as 500-count in 200-mL induction sealed bottles containing [redacted] desiccant; or b(4)

A 36 month expiry period when stored in Alu/Alu blisters;

with the following label statement: "Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]."

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

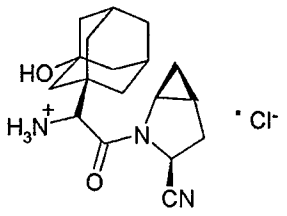
None

II. Summary of Chemistry Assessments

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

Drug Product

Saxagliptin film coated tablets, 2.5 mg and 5 mg strengths [redacted], have been developed for commercialization. The active in the drug product is the hydrochloride salt form of the drug substance. The structure for this salt form is provided as follows. b(4)



Executive Summary Section

Molecular Formula: $C_{18}H_{25}N_3O_2 * HCl$

Molecular Weight: 351.87

Saxagliptin film coated tablets are manufactured by a [redacted] active coating process. [redacted] b(4)

[redacted] b(4)

Based on tablet dimension measurements, saxagliptin film coated tablets, 2.5 mg, and saxagliptin film coated tablets, 5 mg, are expected to have an average thickness of 4.2 mm and average diameter of 8.2 mm.

The saxagliptin film coated tablets contain the following excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium state, [redacted] yellow (2.5 mg), [redacted] pink (5 mg tablet), [redacted] No novel excipients are used in the manufacture of saxagliptin film coated tablets. b(4)

The two strengths will be differentiated by color and printing on the tablets.

- 2.5 mg tablet, containing 2.79 mg saxagliptin hydrochloride (anhydrous): Round, bi-convex yellow tablet printed with "2.5" and "4214"
- 5 mg tablet, containing 5.58 mg saxagliptin hydrochloride (anhydrous): Round, bi-convex pink tablet printed with "5' and "4214"

Saxagliptin film coated tablets will be packaged and marketed as 30 and 90 count in 95 mL and 500 count in 200 mL white, opaque [redacted] bottles, with a two piece child resistant closure having an aluminum foil induction seal. Each bottle contains a cotton coil and one 2g pouch containing silica gel (desiccant) and activated carbon. 5 mg saxagliptin film coated tablets will also be packaged and marketed in aluminum/aluminum (alu/Alu) blisters.

The quality of the drug product is assessed by visual and [redacted] High Performance Liquid Chromatography (HPLC) methods and assured by Quality by Design (QbD) principles.

Based on the provided stability data, the 2.5 mg strength saxagliptin tablets are granted:

> A 36 month stability period is granted for saxagliptin stored in 30-count and 90-count in 95-mL induction sealed bottles, containing [redacted] desiccant;

with the following label statement: "Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]."

Based on the provided stability data, the 5 mg strength saxagliptin tablets are granted:

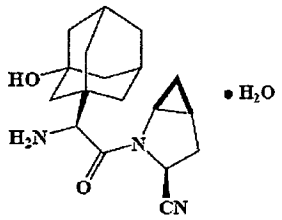
A 36 month stability period is when stored as 30-count and 90-count in 95-mL induction sealed bottles, containing desiccant and as 500-count in 200-mL induction sealed bottles containing desiccant; or

A 36 month expiry period when stored in Alu/Alu blisters;

with the following label statement: "Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]."

Drug substance

The Drug substance is saxagliptin. The formal chemical name is (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo [3.3.1.13,7]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate. The molecular structure is provided as follows:



The molecular formula is: $C_{18}H_{25}N_3O_2 \cdot H_2O$ with a calculated molecular weight of 333.43.

Saxapliptin has been chemically and structurally characterized using:

b(4)

Saxagliptin drug substance is manufactured using a commercial process from starting materials. The form is used in the manufacture of saxagliptin tablets.

b(4)

Based on the 32-month primary stability data for saxagliptin drug substance from Process C and the 12-month primary stability data for saxagliptin drug substance from Process D stored at 5°C (±3°C), a period for the drug substance is granted with the following label statements:

b(4)

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

Saxagliptin is an orally active reversible dipeptidyl peptidase-IV (DPP-IV) inhibitor proposed for the treatment of type 2 diabetes mellitus. Bristol-Myers Squibb (BMS) plans to market 2.5 and 5 mg film coated tablets for oral administration of saxagliptin.

b(4)

C. Basis for Approvability or Not-Approval Recommendation

This NDA has been reviewed and is recommended for APPROVAL from a CMC viewpoint. This recommendation is based on the supporting developmental manufacturing and formulation data, supporting QbD and DoE data, chemical characterization, available stability data, and acceptable responses to the CMC Qualitry Deficiency Comments.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:	Same date as draft review
ChemistryTeamLeaderName/Date:	Same date as draft review

C. CC Block

27 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry-1

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/s/

John C. Hill
3/23/2009 02:12:42 PM
CHEMIST

Christine Moore
3/25/2009 04:00:02 PM
CHEMIST

NDA 22-350

Onglyza Tablets

Bristol-Myers Squibb Company

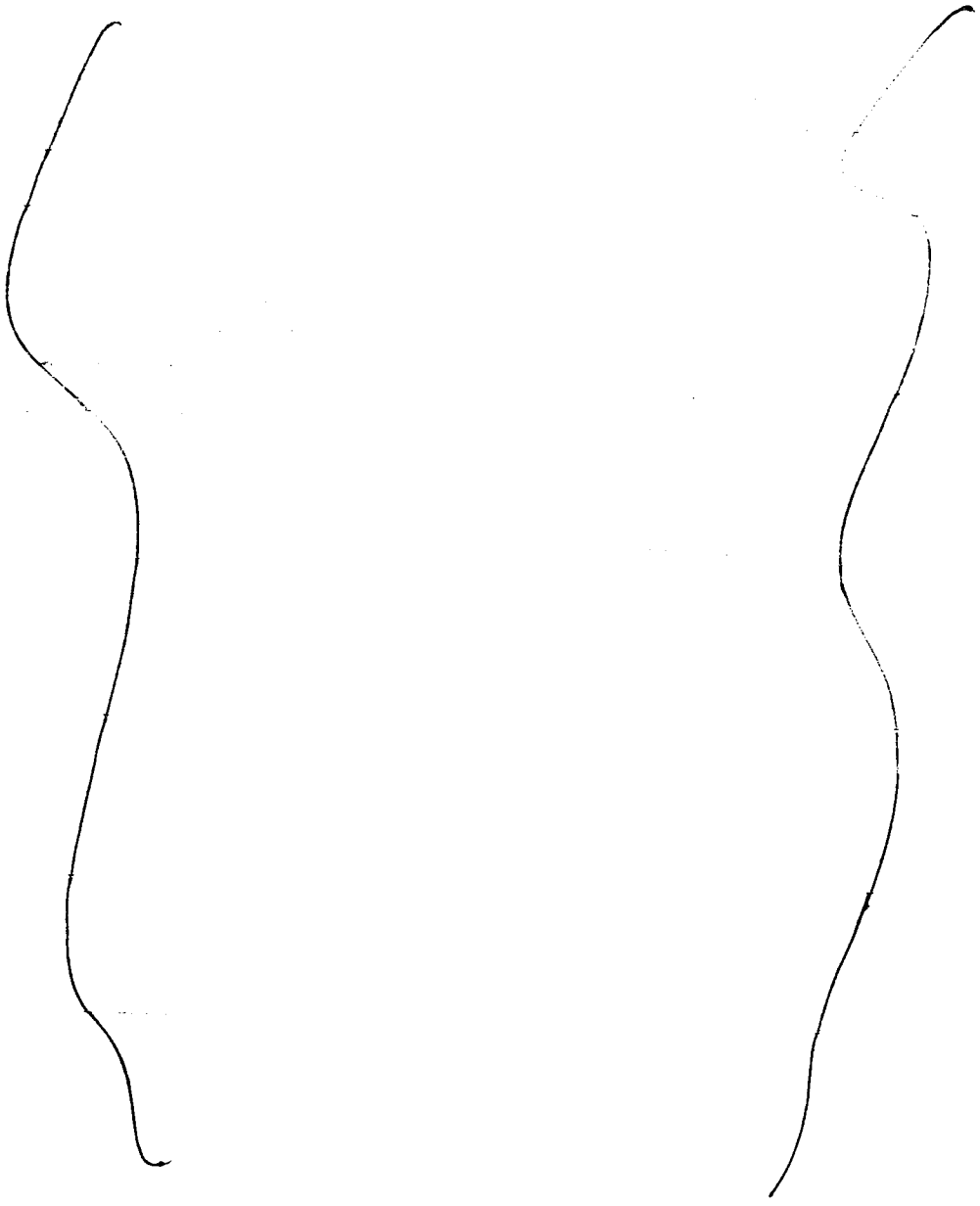
Sharmista Chatterjee, Ph.D.

Member of CMC Review Team

Office of New Drug Quality Assessment

P.2 Pharmaceutical Development

P.2.1 Components of the Drug Product



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(b)(4)

(b)(4)

42 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 4

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/s/

Sharmista Chatterjee
11/24/2008 05:36:54 PM
CHEMIST

Blair Fraser
11/25/2008 04:06:24 AM
CHEMIST

NDA 22-350

Onglyza
(saxagliptin)

Bristol-Myers Squibb

John C. Hill, Ph.D.
ONDQA/DPMA-1 and DMEP (HFD-510)

Chemistry Review #1

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-350

2. REVIEW #1

3. REVIEW DATE: 24-Nov-2008

4. REVIEWER: John C. Hill, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 63634	08-NOV-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
22-350 –000 N-document	30-JUN-2008
BC (partial response to 74 day filing memo)	15-OCT-2008
BZ (partial response to 74 day filing memo)	24-OCT-2008
BZ (partial response to 74 day filing memo)	03-NOV-2008
BZ (partial response to 74 day filing memo)	19-NOV-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Bristol-Myers Squibb Company
Address:	P.O. Box 4000 Princeton, NJ 08543-4000
Representative:	Pamela J. Smith, M.D., Group Director, GRS
Telephone:	609-252-5228

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Onglyza

Chemistry Review Data Sheet

b) Non-Proprietary Name (USAN): Saxagliptin
c) Code Name/# (ONDC only): BMS-477118
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Dipeptidyl peptidase 4 (DPP4) inhibitors, Anti-Diabetic

11. DOSAGE FORM: Immedeiate Release Tablet

12. STRENGTH/POTENCY: 2.5 mg and 5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

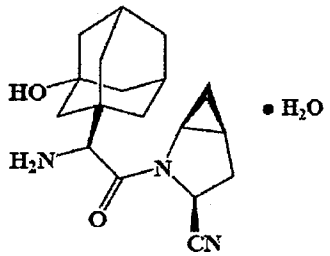
__X__Not a SPOTS product

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

Chemical Name: (1S,3S,5S)-2-[(2S)-2-Amino-2-(3-hydroxylricyclo[3.3.1.13,7] dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate

Molecular Formula: $C_{18}H_{25}N_3O_2 * H_2O$

Molecular Weight: 333.43 (315.41 anhydrous)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	IV			4	Adequate		LOA: 22-AUG-2008
	IV			4	Adequate		LOA: 22-OCT-2007
	III			4	Adequate		LOA: 18-JUN-2007
	III			4	Adequate		LOA: 20-FEB-2008
	III			4	Adequate		LOA: 18-OCT-2007
	III			4	Adequate		LOA 25-OCT-2007
	III			4	Adequate		LOA: 25-OCT-2007

b(4)

b(4)

b(4)

Chemistry Review Data Sheet

[redacted]	III	[redacted]	[redacted]	4	Adequate		LOA: 25-OCT-2007
	III			4	Adequate		LOA: 27-SEP-2007

b(4)

[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	63,634	Use of BMS-477181 (an orally active, reversible DPP4 inhibitor) in the treatment of type 2 diabetes

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending		
Pharm/Tox	NA		
Biopharm	NA		
LNC			
Methods Validation	Pending		
OPDRA		24-NOV-2008	John Hill
EA	Pending		
Microbiology	NA		

OGD:

CONSULTS/ CMC	RECOMMENDATION	DATE	REVIEWER

Chemistry Review Data Sheet

RELATED REVIEWS			
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-350

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is approvable pending resolution of the following CMC Deficiencies:

- Adequate responses to Quality by Design (QbD) deficiencies,
- Adequate responses to Chemistry, Manufacturing and Control deficiencies,
- Full and meaningful pre-approval inspection of all manufacturing facilities.

Based on the provided stability data, the 2.5 mg strength saxagliptin tablets are granted:

A month stability period when stored as 30-count and 90-count in 95-mL induction sealed bottles, containing [redacted] b(4)

with the following label statement: "Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]."

Based on the provided stability data, the 5 mg strength saxagliptin tablets are granted:

A month stability period when stored as 30-count and 90-count in 95-mL induction sealed bottles, containing [redacted] desiccant and as 500-count in 200-mL induction sealed bottles containing [redacted] desiccant; or b(4)

A month expiry period when stored in Alu/Alu blisters;

with the following label statement: "Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]."

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

The Included comparability protocol is not acceptable for the following reasons:

[redacted] b(4)

II. Summary of Chemistry Assessments

Executive Summary Section

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

Drug Product

Saxagliptin film coated tablets, 2.5 mg and 5 mg strengths [redacted], have been developed for commercialization. Saxagliptin film coated tablets are manufactured by a [redacted] b(4)

[redacted] b(4)

Based on tablet dimension measurements, saxagliptin film coated tablets, 2.5 mg, and saxagliptin film coated tablets, 5 mg, are expected to have an average thickness of 4.2 mm and average diameter of 8.2 mm. b(4)

The saxagliptin film coated tablets contain the following excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium state. [redacted] yellow (2.5 mg), [redacted] pink (5 mg tablet), [redacted] No novel excipients are used in the manufacture of saxagliptin film coated tablets. b(4)

The two strengths will be differentiated by color and printing on the tablets.

2.5 mg tablet: Round, bi-convex yellow tablet
5 mg tablet: Round, bi-convex pink tablet

The exact printing for each tablet strength has yet to be determined.

Saxagliptin film coated tablets will be packaged and marketed as 30 and 90 count in 95 mL and 500 count in 200 mL white, opaque, [redacted] bottles, with a two piece child resistant closure having an aluminum foil induction seal. Each bottle contains a cotton coil and one 2g pouch containing silica gel (desiccant) and activated carbon. 5 mg saxagliptin film coated tablets will also be packaged and marketed in aluminum/aluminum (alu/Alu) blisters. b(4)

The quality of the drug product is assessed by visual and [redacted] High Performance Liquid Chromatography [redacted] -HPLC) methods and assured by Quality by Design (QbD) principles.

Based on the provided stability data, the 2.5 mg strength saxagliptin tablets are granted:

A [redacted] month stability period is granted for saxagliptin stored in 30-count and 90-count in 95-mL induction sealed [redacted] bottles, containing [redacted] desiccant; b(4)

with the following label statement: "Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]."

Based on the provided stability data, the 5 mg strength saxagliptin tablets are granted:

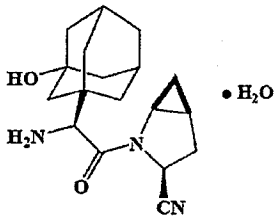
A [redacted] month stability period is when stored as 30-count and 90-count in 95-mL induction sealed [redacted] bottles, containing [redacted] desiccant and as 500-count in 200-mL induction sealed HDPE bottles containing [redacted] desiccant; or b(4)

A [redacted] month expiry period when stored in Alu/Alu blisters;

with the following label statement: "Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]."

Drug substance

The Drug substance is saxagliptin. The formal chemical name is (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo [3.3.1.13,7]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate. The molecular structure is provided as follows:



The molecular formula is: $C_{18}H_{25}N_3O_2 \cdot H_2O$ with a calculated molecular weight of 333.43.

Saxagliptin has been chemically and structurally characterized using: [redacted] b(4)

Saxagliptin drug substance is manufactured using a [redacted] commercial process from [redacted] starting materials. The [redacted] is used in the manufacture of saxagliptin tablets.

Based on the 32-month primary stability data for saxagliptin drug substance from Process C and the 12-month primary stability data for saxagliptin drug substance from Process D stored at 5°C (±3°C), a [redacted] period for the drug substance is granted with the following label statements: b(4)

- [redacted]
- [redacted]

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

Saxagliptin is an orally active reversible dipeptidyl peptidase-IV (DPP-IV) inhibitor proposed for the treatment of type 2 diabetes mellitus. Bristol-Myers Squibb (BMS) plans to market 2.5 and 5 mg film coated tablets [redacted] for oral administration of saxagliptin.

b(4)

C. Basis for Approvability or Not-Approval Recommendation

This NDA is not-approvable. The following outstanding CMC review issues must be adequately addressed by the applicant:

- Adequate responses to Quality by Design (QbD) deficiencies,
- Adequate responses to Chemistry, Manufacturing and Control deficiencies,
- Full and meaningful pre-approval inspection of all manufacturing facilities.

The proposed comparability protocol is unacceptable for the following reasons:

- (
-
-
-
-) b(4)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:	Same date as draft review
ChemistryTeamLeaderName/Date:	Same date as draft review

C. CC Block

193 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 5

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/s/

John C. Hill
12/8/2008 07:43:55 AM
CHEMIST

Blair Fraser
12/9/2008 05:29:56 AM
CHEMIST

NDA 22-350

3.2.S.2

Onglyza (Saxagliptin)
2.5 & 5 mg Tablets

Bristol-Myers Squibb

Prafull K. Shiromani Ph.D.
Division of Pre-Marketing Assessment 1
Office of New Quality Assessment

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S.2 Manufacture [name, manufacturer]

S.2.1 Manufacturers

Manufacturing, packaging, quality control testing, and release of saxagliptin drug substance are performed at the following Bristol-Myers Squibb facility:
Swords Laboratories
Watery Lane
Swords, County Dublin, Ireland

S.2.2 Description of Manufacturing Process and Process Controls

b(4)

75 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 6

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/s/

Prafull Shiromani
10/28/2008 05:04:14 PM
CHEMIST

Blair Fraser
10/29/2008 05:59:49 AM
CHEMIST
CMC Consult Review

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Division of Metabolism and Endocrinology Products

NDA:	**22-350**
Applicant:	Bristol-Myers Squibb Company
Stamp Date:	**30-JUN-2008**
PDUFA Date:	**30-APR-2009**
Proposed Proprietary Name:	Onglyza
Established Name:	Saxagliptin
Dosage form and strength:	Tablet, 2.5 mg or 5 mg (free base)
Route of Administration:	Oral
Indications:	Treatment of type 2 diabetes mellitus.
PAL:	Su (Suong) Tran, Branch II/DPA I/ONDQA
ONDQA Fileability:	**Yes**
Filing date:	**29-AUG-2008**
Comments for 74-Day Letter:	**Yes, on the last page.**

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm	*Not applicable.*
CDRH	*Not applicable.*
EA	Categorical exclusion request will be assessed by Primary Reviewer.
EES	EER was sent to Office of Compliance on 14-JUL-2008.
DMETS	*Labeling consult request will be sent as part of DMEP's request.*
Methods Validation	*Validation may be requested of FDA labs after test methods are finalized.*
Microbiology	*Not applicable.*
Pharm/Tox	*Not applicable.*

Summary:

[See the discussion in Critical Issues later in this review.]

This is an electronic NDA, filed as a 505(b)(1) application. The associated IND is IND 63634.

The drug substance saxagliptin (monohydrate) is a New Molecular Entity (NME) and is a small synthetic molecule. It is a reversible dipeptidyl peptidase-IV (DPP-IV) inhibitor for the treatment of type 2 diabetes mellitus. The product is an immediate release single-entity tablet available in two strengths: 2.5 mg and 5 mg [redacted] b(4)

Maximum daily dose is 5 mg [redacted] saxagliptin.

Route of administration	Oral
Dosage form	Immediate release tablet
Package type	Plastic bottles with desiccant and child-resistant closures, and blister packs. 5 mg: Bottles of 30-, 90-, and 500-count, and blisters of [redacted] b(4) 2.5 mg: Bottles of 30- and 90-count
Potency	2.5 mg and 5 mg [redacted]
Color	5 mg: pink 2.5 mg: yellow
Shape	Round, biconvex
Coating	Film coating
Size	*Unknown (comment to be sent in the 74-day letter)*
Scoring	None
Imprint codes	Blue ink printing 5 mg: "5" and "4215 2.5 mg: "2.5" and "4214"
Symbols	None

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Summary:

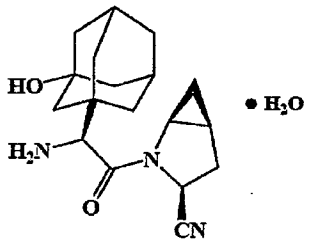
[See the discussion in Critical Issues later in this review.]

Drug substance:

Chemical Name (CAS):	(1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo-[3.3.1.1^{3,7}]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate
CAS Registry Number:	945667-22-1
Trade Name:	To be determined
Generic Name (USAN, INN):	Saxagliptin
Laboratory Code:	BMS-477118-11

Structure

Chemical Structure:



Molecular Formula:	$C_{18}H_{25}N_3O_2 \cdot H_2O$
Formula Weight:	333.43 (315.41 anhydrous)

42 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 7

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/s/

Suong Tran
8/27/2008 01:31:44 PM
CHEMIST

Revised as we discussed, comments already sent to PM
for the 74-day letter.

Blair Fraser
8/27/2008 02:18:20 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 22350/000	Action Goal:	
Stamp:	30-JUN-2008	District Goal:	01-MAR-2009
Regulatory Due:	31-JUL-2009	Brand Name:	SAXAGLIPTIN
Applicant:	BRISTOL MYERS SQUIBB	Estab. Name:	
	4000	Generic Name:	SAXAGLIPTIN
	PRINCETON, NJ 08543		
Priority:	1S	Dosage Form:	(TABLET)
Org Code:	510	Strength:	2.5 AND 5 MG FREE BASE

Application Comment:

Contacts:	R. HARTFORD	301-796-0331 , Project Manager
	S. TRAN	301-796-1764 , Team Leader

Overall Recommendation: ACCEPTABLE on 29-APR-2009by M. STOCK (HFD-320)301-796-4753

ACCEPTABLE on 26-FEB-2009by S. FERGUSON(HFD-322)301-796-3247

Establishment: CFN [redacted] FEI [redacted]

5 5 b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: TCM OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator

SUBMITTED TO OC	14-JUL-2008				TRANS
OC RECOMMENDATION	15-JUL-2008			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: CFN 1825662 FEI 1825662

BRISTOL MYERS SQUIBB CO

4601 HWY 62 E

MOUNT VERNON, IN 47620

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TCM OAI Status: NONE

b(4)

Estab. Comment: APPLICANT STATES THAT [redacted] WAS USED IN DEVELOPING THE DRUG PRODUCT MANUFACTURING PROCESS. (on 14-JUL-2008 by S. TRAN () 301-796-1764)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO OC	14-JUL-2008				TRANS
SUBMITTED TO DO	15-JUL-2008	PS			FERGUSONS
ASSIGNED INSPECTION T	15-JUL-2008	PS			PDOMINGO
ASSIGNED INSPECTION T	17-JUL-2008	PS			PDOMINGO
INSPECTION PERFORMED	28-JAN-2009		28-JAN-2009		PDOMINGO
DO RECOMMENDATION	26-FEB-2009			ACCEPTABLE INSPECTION	PDOMINGO
OC RECOMMENDATION	26-FEB-2009			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS
INSPECTION PERFORMED	16-MAR-2009				LARRY.AUSTI

AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED

INSPECTION PERFORMED	16-MAR-2009				LARRY.AUSTI

AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED

DO RECOMMENDATION	29-APR-2009			ACCEPTABLE INSPECTION	PDOMINGO

INSPECTION OF 1/20-29/09 WAS CLASSIFIED VAI. FIRM IS ACCEPTABLE.

OC RECOMMENDATION	29-APR-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

Establishment: CFN — FEI —

b(4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment: APPLICANT STATES THAT [redacted] b(4)

IN DEVELOPING THE DRUG SUBSTANCE MANUFACTURING PROCESS. (on 14-JUL-2008 by S. TRAN () 301-796-1764)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	14-JUL-2008				TRANS
OC RECOMMENDATION	14-JUL-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS