

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-465

CHEMISTRY REVIEW(S)

Memorandum

To: NDA 22-465
From: Sarah Pope Miksinski, Ph.D.
Date: 10/15/2009
Re: Final CMC recommendation for NDA 22-465

NDA 22-465 was initially submitted on 18-DEC-2008 and was granted a standard review by the Agency. Chemistry Review #1 (dated 07-OCT-2009) recommended approval of NDA 22-465 pending the receipt of an overall acceptable recommendation from the Office of Compliance.

Reference is also made to the ONDQA Division Director's Memo dated 08-OCT-2009, which provides supporting CMC language for a post-marketing commitment (PMC) proposed by the clinical division. While the final PMC language for the action letter is still being negotiated by the Applicant and the clinical division, the supporting CMC language for the PMC (as specified in the Division Director's Memo) will not change as a result of these negotiations.

This memo serves to update the determination of approvability for NDA 22-465 from a Chemistry, Manufacturing and Controls standpoint. The Office of Compliance issued an overall acceptable recommendation for this application on 09-OCT-2009. Accordingly, approval of NDA 22-465 is now recommended.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22465	ORIG-1	GLAXO WELLCOME MANUFACTURING PTE LTD DBA GLAXOSMITHKLIN E	VOTRIENT TABLETS

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/s/

Sarah Pope Miksinski
10/15/2009

ONDQA Division Director's Memo
NDA 22-465, VOTRIENT (pazopanib) 200 mg and 400 mg Tablets
Date: 08-OCT-2009

Introduction

VOTRIENT (pazopanib) tablets 200 mg and 400 mg are indicated for the treatment of advanced renal cell carcinoma. The CMC portions of the submission included QbD elements for the drug substance and drug product. This necessitated a team review which included several ONDQA Chemists, ONDQA Biopharm Staff, Biostatistics, and ONDQA Project Management. **ONDQA recommends approval of this NDA pending an acceptable overall recommendation from the Office of Compliance in the EES database.**

Administrative

The original submission of this 505(b)(1) NDA was received 18-DEC-2008 from GlaxoSmithKline, Singapore. During the review cycle of the QbD team-reviewed NDA, a total of eight CMC amendments were reviewed between 16-FEB-2009 and 25-SEP-2009.

The NDA is supported by IND 65,747. During the review cycle, the Medical Division saw a need for a 100 mg strength to cover dose reduction in the event of liver enzyme elevations. The applicant agreed to a post marketing commitment (PMC) which will be conveyed in the action letter as follows:

Develop a 100 mg dosage form (tablet) to allow for proper dose reductions when Votrient™ (Pazopanib) liver enzyme elevations occur. The 100 mg tablet strength should be sufficiently distinguishable from the 200 mg and 400 mg tablets. (b) (4)



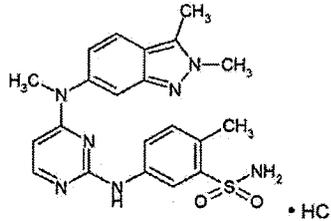
Also, the overall recommendation from OC is pending in EES as of this writing; COB 08-OCT-2009.

This NDA is recommended for approval from a Chemistry, Manufacturing and Controls standpoint, pending the receipt of an overall acceptable recommendation from the Office of Compliance.

Drug Substance (pazopanib hydrochloride)

The API is pazopanib hydrochloride. Despite having three basic nitrogens (with pKa's of 2.1, 6.4, and 10.2), it is a poorly soluble BCS Class-II drug substance. Pazopanib is a synthetic new molecular entity drug substance. It is (b) (4) for use in the drug product. A retest period of (b) (4); is acceptable for the (b) (4) drug substance.

Structural Formula



Molecular Formula

$C_{21}H_{23}N_7O_2S \cdot HCl$

Molecular Weight

473.99 g/mol (GW786034B,
hydrochloride salt)

437.53 g/mol (GW786034X, free base)

Drug Product (VOTRIENT) tablets 200 mg and 400 mg.

The drug product tablets are film coated and the declared tablet strengths correspond to the neutral species (base) as per the USP salt nomenclature policy; USP <1121>. Excipients include microcrystalline cellulose, sodium starch glycolate, povidone, and magnesium stearate. The tablets are packaged in (b) (4) bottles with child-resistant (b) (4) closures.

The applicant used a QbD approach to drug product development. During the review cycle, the applicant tightened their dissolution specification to Q (b) (4) in 30 minutes in response to cited deficiencies. However, the actual drug product dissolution performance is variable and drug product batch failures may result. (b) (4)

Of note during the review, it was seen that as tablet density becomes very low, or porosity very high, dissolution performance deteriorates. This is consistent with a neutrally buoyant tablet or a floating tablet. This was not addressed by the applicant or in the primary review.

The tablets are recommended to be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). An 18-month expiry period is recommended to be approved.

Rik Lostritto, Director, ONDQA Division III, DPAMS

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NDA-22465	ORIG-1	GLAXO WELLCOME MANUFACTURING PTE LTD DBA GLAXOSMITHKLIN E	VOTRIENT TABLETS

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/s/

RICHARD T LOSTRITTO
10/08/2009

NDA 22-465

**VOTRIENT (pazopanib)
200 mg and 400 mg Tablets**

**Glaxo Wellcome Manufacturing Pte Ltd d/b/a
GlaxoSmithKline**

**Sharmista Chatterjee
Bogdan Kurtyka
Brian Rogers**

CMC Reviewers

**Office of New Drug Quality Assessment
Division of Premarketing Assessment III & Manufacturing Science
Branch VI**

**CMC REVIEW OF NDA 22-465
For the Division of Drug Oncology Products (HFD-150)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 22-465
2. REVIEW #: 1
3. REVIEW DATE: 06-OCT-2009
4. REVIEWERS: Sharmista Chatterjee, Bogdan Kurtyka, and Brian Rogers
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	18-DEC-2008
Amendment (BC)	16-FEB-2009
Amendment (BC)	11-MAR-2009
Amendment (BC)	24-JUN-2009
Amendment (BC)	17-JUL-2009
Amendment (BC)	31-JUL-2009
Amendment (BC)	18-AUG-2009
Amendment (BC)	14-SEP-2009
Amendment (BC)	16-SEP-2009
Amendment (BC)	25-SEP-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Glaxo Wellcome Manufacturing Pte Ltd d/b/a
GlaxoSmithKline

Address: 1 Pioneer Sector 1
Jurong, Singapore, 628413

Representative: Ellen Cutler, Senior Director, Regulatory Affairs,
Oncology
GlaxoSmithKline
1250 South Collegeville Road, PO Box 5089
Collegeville, PA 19426-0989

Telephone: 610-917-6823

FAX: 610-917-5772

CMC Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: VOTRIENT Tablets
Non-Proprietary Name: pazopanib 200 mg and 400 mg tablets

b) Code Name/#: GW786034

c) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-tumor

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 200 mg and 400 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

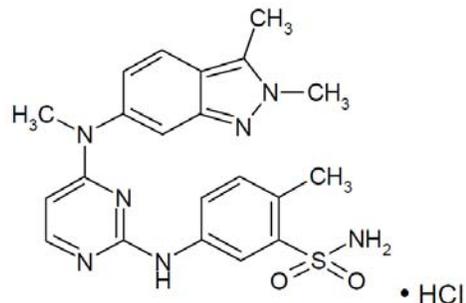
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

CMC Review Data Sheet

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

Structural Formula**Molecular Formula**C₂₁H₂₃N₇O₂S • HCl**Molecular Weight**473.99 g/mol (GW786034B,
hydrochloride salt)

437.53 g/mol (GW786034X, free base)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	4	(b) (4)	(b) (4)	4			Composition and specifications provided in application
	4	(b) (4)	(b) (4)	4			Composition and specifications provided in application
	3	(b) (4)	(b) (4)	4			
	3	(b) (4)	(b) (4)	4			
	3	(b) (4)	(b) (4)	4			
	3	(b) (4)	(b) (4)	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

CMC Review Data Sheet

- 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	65,747	Pazopanib

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	See body of text	9/30/09	Meiyu Shen
EES	No Overall Recommendation has been provided by OC as of the date of this review.		Inspection results for Glaxo in Ware, UK (FEI 3003262904) is still pending as of the date of this review.
Pharm/Tox	N/A		
Biopharm	Dissolution method is acceptable as modified (Q= (b) at 30 min). <div style="background-color: gray; width: 100px; height: 20px; margin-top: 5px;">(b) (4)</div>	9/18/09	John Duan
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS			
EA	Categorical exclusion (see review)		
Microbiology	N/A		

Executive Summary Section

The CMC Review for NDA 22-465

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA# 22-465 is recommended for approval from a Chemistry, Manufacturing and Controls standpoint, pending the receipt of an overall acceptable recommendation from the Office of Compliance.

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

II. Summary of CMC Assessments

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

(1) Drug Substance

Pazopanib hydrochloride is a new molecular entity of Biopharmaceutics Classification System (BCS) Class 2 (poor solubility, high permeability) and a crystalline solid. Its solubility in pH 1.1 is 0.65 mg/mL. The conjugate acids of the basic nitrogens have the following acidity constants: $pK_a - pK_1 = 2.1$ (indazole), $pK_2 = 6.4$ (pyrimidine), $pK_3 = 10.2$ (sulfonamide).

(b) (4)

(b) (4)

(b) (4) pazopanib hydrochloride drug substance is manufactured by Glaxo Wellcome Manufacturing Pte. Limited, Jurong, Singapore. (b) (4)

The applicant has used a Quality by Design (QbD) approach and risk management to increase their understanding of the process and drug substance properties. A number of Critical Quality Attributes (CQAs) were identified. These are: *Identity by IR, Chloride Identity, Crystalline Form, Content by HPLC, Drug-related Impurities* (including named impurities and genotoxic

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impurities content), *Residue on Ignition*, *Particle Size*, *Residual Solvents*, *Water Content* by Karl Fischer, *Description*, *Pd Content*, and *Heavy Metals*.

These CQA are mainly controlled by controlling starting material attributes, intermediate attributes (e.g. specifications of GW786034B (b) (4) and (b) (4) quality process parameters, and by following the manufacturing process. A risk based method (e.g. failure mode and effects analysis (FMEA)) was used to identify the Quality Critical Process Parameters (QCPPs), Quality Process Parameters (QPPs), CQAs and Quality Attributes (QAs) for the pazopanib hydrochloride manufacturing process. The inputs to the FMEA were knowledge gained through the work to develop the impurity fate map, spiking and purging studies, the Design of Experiments (DOE) work to establish potential QCPPs/QPPs, one factor at a time experiments to establish parameter proven acceptable ranges, and 6 years of plant experience preparing over (b) (4) batches of pazopanib hydrochloride in 3 plants throughout the GSK network. It was concluded from this risk assessment that there are no QCPP but a few QPP in the drug substance (DS) manufacturing process. Stages 1 and 2 had no QPP, the few were only present in stages 3 and 4. All the QPP were scale invariant. A combination of multivariate DOE and univariate experimentation was used to determine the Proven acceptable Ranges (PAR) for the variables. The risks for combining univariate and multivariate experimentation were found to be minimal, on the basis of outcome from the robustness study. For this study, all the process parameters were all set at the lower limit of the PARs to create a worst-case scenario for impurity purging. Neither new impurities nor elevated levels of known impurities were detected. This data demonstrated that multivariate interactions will not lead to elevated levels of impurities.

(b) (4)

The form (i.e. hydrochloride salt form) was verified by measuring the chloride levels in all the batches and were consistently found to be the chloride form.

Initially the applicant proposes to use the 3 batch validation scheme for DS manufacturing, however, their current intent is to implement Continuous Verification approach throughout the life cycle of the product.

Batch analysis data are provided for three drug substance production-scale batches manufactured using the commercial process at the commercial site, and tested by the proposed commercial methods, except the particle size distribution. (b) (4)

(b) (4) To bridge the data between the primary stability/clinical batches and future measurements with a different PSD analytical method (also for the purpose of justifying their proposed PSD acceptance criteria), the applicant provided three separate conversion correlations

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for X_{10} , X_{50} and X_{90} from the two particle size methods since they utilize different instrument platforms. **Analysis of the correlations showed the R^2 values for the linear regression lines were unacceptable.** (b) (4)

(b) (4) PSD data from the clinical batches have been provided to support (b) (4) drug substance PSD acceptance criteria.

A comparability protocol has been provided to add an alternative drug substance (b) (4) site. The comparability protocol is considered acceptable

To support requested control on the X_{90} particle size of the (b) (4) drug substance, GSK provided data from clinical lots of (b) (4) drug substance. The applicant has adopted the supported acceptance criterion of (b) (4) for X_{90} . The (b) (4) particle size method has been validated to provide the controls for this measurement. The use of the (b) (4) method in this instance does not justify its use for other purposes in this application.

The retest date of the (b) (4) substance is (b) (4).

Twelve months of primary stability data are provided for three production-scale batches of (b) (4) drug substance and one batch of (b) (4) drug substance. The drug substance is chemically stable.

The applicant has proposed a (b) (4) retest period for the (b) (4) drug substance when stored up to 30°C (86°F). This is acceptable.

(2) Drug Product

Pazopanib Tablets, 200 mg and 400 mg are film-coated IR oral tablets. The two strengths contain 216.7 mg and 433.4 mg pazopanib hydrochloride, respectively, which are equivalent to 200 mg and 400 mg pazopanib (free base), respectively.

Excipients in the tablet core are: microcrystalline cellulose, sodium starch glycolate, povidone, and magnesium stearate.

Pazopanib Tablets, 200 mg are modified capsule-shaped, gray film-coated tablets, one side plain and the opposite side debossed with an identifying code of 'GS JT'.

Pazopanib Tablets, 400 mg are modified capsule-shaped, yellow film-coated tablets, one side plain and the opposite side debossed with an identifying code of 'GS UHL'.

The tablets are manufactured at Glaxo Operations UK Limited, Priory Street, Ware, Hertfordshire SG12 0DJ, United Kingdom. Primary packaging of tablets will be performed by either Glaxo Operations UK Limited, Priory Street, Ware, Hertfordshire SG12 0DJ, United Kingdom or GlaxoSmithKline Inc, 1011 North Arendell Avenue, Zebulon, North Carolina 27597, USA.

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The commercial packages for Pazopanib Tablets, 200 mg are white (b) (4) bottles with child resistant (b) (4) closures containing 30 and 90 tablets. The commercial packages for Pazopanib Tablets, 400 mg are white (b) (4) bottles with child resistant (b) (4) closures containing 30 and 60 tablets, respectively.

The applicant has used a QbD approach and risk management tools to improve understanding to apply appropriate control strategies to drug product manufacture. Medium to high risk attributes were particle size distribution, identity, form, and level of impurities owing to their impact on the Drug Product CQAs and the secondary drug product manufacturing process. The drug product manufacturing process was selected on the basis of prior experience and knowledge about the drug substance characteristics. The manufacturing process (b) (4)

The CQA identified for the drug product are: description, identification, content, drug related impurities content, uniformity of dosage units and dissolution. QbD approach for drug product development was implemented by the following process:

1. Optimal ranges of the excipients were selected on the basis of a DOE. (b) (4)
2. Initial risk assessment was performed using techniques such as Failure Mode Effects Analysis (FMEA) and BRITEST (Best Route Innovation Technology Evaluation and Selection Techniques) to identify manufacturing process parameters and attributes that may have the greatest impact on product quality.
3. Identified parameters were then investigated experimentally by statistical Design of Experiments (DOE), to evaluate the significance of their impact. DOEs were carried out both at pilot and commercial scale.
4. On the basis of risk analysis and DOE data, the identified parameters were then designated as QCPP or QPP. Similarly, attributes were designated as CQA or QA.
5. It was identified during early development the two critical unit operations are (b) (4). A statistically based DOE was thus carried out at commercial scale considering parameters from both (b) (4) steps. On the basis this DOE data, initially a design space was proposed as a multivariate relationship between the three QCPP (b) (4). However, upon feedback from the agency to

Executive Summary Section

the applicant about the inappropriateness of the proposed dissolution acceptance criteria, the multivariate design space was withdrawn and instead linear PARs (Proven Acceptable Range) were proposed for the three QCPP (b) (4). The proposed PARs were independently evaluated by the Statistician (refer to the review by Meiyu Shen dated 9/30/09). As indicated in the review by Meiyu, on using an acceptance criteria of (b) (4) at 30 minutes and considering individual tablet dissolution (not mean) will result in a design space as: (b) (4)

(b) (4) It is noted that these ranges, are slightly tighter than those proposed by the applicant in the amendment dated September 16, 2009 (b) (4)

(b) (4). However, given the limitations of associated measuring devices, it may not be feasible to exactly implement the ranges proposed by the statistician.

6. -In addition, on the basis of developmental studies, PARs were proposed for the QPP: (b) (4)
Analysis of the commercial scale DOE data also showed that (b) (4). Thus, these attributes were designated as Quality Attributes (QA) (as defined).
7. Drug product design space was defined in terms of PAR for the QCPP, QPP and QA. It is indicated that changes to these parameters post approval, would be managed via guidelines concurrent with ICH Q8 and Q8(R) guidelines.
8. Several Process Analytical Technology (PAT) tools were used as apart of the control strategy to monitor in-process attributes, (b) (4)

In order to understand the impact of particle size, developmental batches were manufactured with three different lots of DS, whose particle size was deliberately varied. (b) (4)

(b) (4). No significant impact of particle size on dissolution was observed as shown by the dissolution profile data. Additionally, a review by the Bio-pharmaceutics reviewer (refer review by John Duan dated September 18, 2009) of 57 batches using 28 lots of drug substances, showed that drug substance particle size had no significant effect on dissolution.

The following controls were proposed to be used during manufacturing:

(b) (4)

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[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED]

[REDACTED] and the product will be released by measuring dissolution via traditional methods.

The applicant proposes to use [REDACTED] (b) (4)
[REDACTED] (b) (4)
The assay method was originally submitted independently, but in later amendments it was merged into a comparability protocol for tablet assay.

The original application included limited information on (b) (4) methods. More information was requested and provided in application amendments. The review found all (b) (4) methods acceptable and confirmed that they were properly designed, developed, and validated.

In addition the application includes a Comparability Protocol for tablet assay. In the protocol GSK proposes to implement at-line (b) (4) testing for content and discontinue end-product HPLC

Executive Summary Section

via a CBE-30 supplement based on assessment according to the protocol. This includes the completion of a parallel testing exercise (simultaneous end product testing using HPLC method and at-line testing using (b) (4) method) for content on 30 commercial scale batches.

The Comparability Protocol describes control strategy for content, assay (b) (4) method development and validation, method application including sampling plan, 30 batch parallel testing protocol and acceptance criteria, and the model maintenance.

During the review, all proposed elements of the Comparability Protocol were found acceptable, including scope of data to be submitted and the reporting category.

The particle size test method used for all development work, including DOE for drug substance (b) (4)

There is an inadequate correlation between the (b) (4) and the (b) (4) PSD methods. The uncertainty related to the particle size analytical methods was mitigated by obtaining (b) (4) data from the clinical trials lots of drug substance – acceptance criteria for release of the (b) (4) drug substance were derived from these measurements. The (b) (4) method will be approved to provide control on the particle size (X_{90}) for the (b) (4) drug substance.

For the drug product, GSK proposes to use continuous verification to ensure product quality rather than following a conventional validation approach.

Twelve months stability data are provided for three primary NDA stability batches manufactured at the proposed commercial scale at the proposed commercial manufacturing site, Ware, UK. The batches of Pazopanib Tablets, 200 mg and 400 mg are identical to those proposed for marketing and were packed in the proposed market pack.

The results of the accelerated and long-term stability studies demonstrate acceptable drug product chemical and physical stability when stored for up to 12 months at 25°C/60% RH, or for up to 6 months at 40°C/75% RH.

The applicant proposes a shelf life of (b) (4) when stored at 25°C (77°F); excursions permitted 15 to 30°C (59 to 86°F) [See USP Controlled Room Temperature]. The current extent of the data do not support this length of expiry. The approved expiration dating period will be 18 months at the proposed storage conditions, based on the 12 months of long-term and 6 months accelerated data.

A biopharmaceutics consult was submitted and was addressed in the review by John Duan dated 9/18/09. In the original submission, the applicant had proposed a dissolution acceptance criteria of Q (b) (4) at 45 minutes. Upon discussions with the agency at the face to face meeting on July 1, 2009, they proposed to revise it as Q = (b) (4) at 45 minutes. However, upon review of individual tablet dissolution data for 91 batches by John Duan, the proposed acceptance criteria was found

Executive Summary Section

to be unacceptable and the applicant was recommended to revise the acceptance criteria as indicated below. The summary of comments from the biopharmaceutics review are as:

1. *The proposed dissolution method is adequate. However, the proposed dissolution acceptance criteria for pazopanib tablets are not acceptable and are recommended as shown below.*

$Q = \frac{(b)}{(A)}$ at 30 minutes using the following conditions.

Apparatus: USP Apparatus 2
Volume: 900 mL
Medium: 50 mM sodium acetate buffer, pH 4.5, containing 0.75% SDS
Agitation: Paddle speed of 75 rpm.
Analysis: UV at 270 nm with a background correction at 400 nm.
Temperature: 37 °C.

2. *The acceptance criteria in the DOE for defining the design space in the dissolution comparability protocol are not appropriate and withdrawal of the protocol is recommended.*
3. *The applicant is recommended to further identify the sources of the observed large variability in dissolution.*

Per the September 16, 2009 amendment to the NDA, the applicant agreed to tighten the specification to $Q \frac{(b)}{(4)}$ at 30 minutes. (b) (4)

and indicated that the product would be released instead by measuring dissolution by the approved traditional method.

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

Pazopanib tablets are available in 200 mg and 400 mg strengths. The tablets are orally administered and no unusual preparation of dose prior to administration is required. The tablets are recommended to be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). The tablets have a proposed expiration dating period of (b) (4) when stored under recommended conditions. An 18-month expiry at the proposed storage conditions will be granted based on the provided stability data.

C. Basis for Approvability or Not-Approval Recommendation

The application is currently recommended for approval from a Chemistry, Manufacturing and Controls standpoint pending receipt of an overall acceptable recommendation from the Office of Compliance.

This recommendation is based upon the acceptable identity, strength, quality, and purity of the drug product. There are weaknesses in the application, particularly in the lack of data pertaining to the source of the batch-to-batch dissolution variability. These are not a critical factor in the

Executive Summary Section

decision for approvability since the applicant has agreed to an acceptably tight dissolution specification on release [REDACTED] (b) (4)

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Sharmista Chatterjee, CMC Reviewer

Bogdan Kurtyka, CMC Reviewer

Brian Rogers, CMC Reviewer

B. Endorsement Block:

(See appended electronic signature page)

Terrance Ocheltree, Pharmaceutical Assessment Lead, Branch V, ONDQA

Sarah Pope Miksinski, Branch Chief, Branch V, ONDQA

Rik Lostritto, Division Director, DPAMS, ONDQA

C. CC Block: entered electronically in DFS

236 Pages Withheld as b(4) Trade Secret/
Confidential

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22465	ORIG-1	GLAXO WELLCOME MANUFACTURING PTE LTD DBA GLAXOSMITHKLIN E	VOTRIENT TABLETS

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/s/

BRIAN D ROGERS
10/06/2009

SHARMISTA CHATTERJEE
10/06/2009

TERRANCE W OCHELTREE
10/06/2009

RICHARD T LOSTRITTO on behalf of Sarah Pope Miksinski
10/07/2009

RICHARD T LOSTRITTO
10/07/2009

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22465

Applicant: GSK

Stamp Date: 19DEC2008

Drug Name: Pazopanib

NDA/BLA Type:

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		Sites and statement were submitted prior to submission of the NDA
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases and at the pre-NDA meetings been included?		X	
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the methods validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?			Not applicable

IS THE CMC SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Terrance Ocheltree, Ph.D., R.Ph.

05FEB2009

Acting Pharmaceutical Assessment Lead

Date

Sarah Pope, Ph.D.

05FEB2009

Branch Chief

Date

File name: 5_Chemical Manufacturing Controls (CMC) Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

Terrance Ocheltree
2/9/2009 10:24:41 AM
CHEMIST

Richard Lostritto
2/9/2009 05:12:55 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:	22-465
Applicant:	GlaxoSmithKline.
Stamp date:	19 DEC 2008
PDUFA Date:	19 OCT 2009
Proposed Trade Name:	VOTRIENT™
Established Name:	Pazopanib
Laboratory Code:	Not applicable
Dosage Form:	Tablet, Immediate Release (200 and 400 mg)
Route of Administration:	Oral
Indication:	Treatment of patients with advanced renal cell carcinoma (RCC).

Pharmaceutical Assessment Lead: Terrance Ocheltree, R.Ph., Ph.D.

	YES	NO
ONDQA Fileability:	<u>√</u>	—
Draft Comments for 74-Day Letter:	<u>√</u>	—

Summary, Critical Issues and Comments

A. Summaries

Background Summary

NDA 22-465 was submitted by GlaxoSmithKline (GSK) for VOTRIENT™ (pazopanib), an immediate release tablet for oral administration containing either 200 mg or 400 mg of pazopanib free base (GW786034X) as the hydrochloride salt (GW786034B). Pazopanib is a new molecular entity and is submitted for review pursuant to Section 505(b)(1) of the Food, Drug and Cosmetic Act. Reference is made to one active Investigational New Drug application, IND 65,747.

Five drug development related meetings were conducted during the development program. CMC comments were issued in the Applicant's 17-Feb-2006, CMC specific End-of-Phase 1/Pre-Phase 3 meeting, 21-May-2007 Request for Special Protocol Assessment: Stability, 23-Aug-2007 Follow-up End-of-Phase 1/Pre-Phase 3 meeting – CMC Specific Meeting, 13-JUN-2008 CMC specific pre-NDA Quality by Design meeting, and 4-Nov-2008 Type C face-to face meeting to discuss CMC Continuous Verification proposal. Minutes for these meetings should be examined by the reviewer.

A Comparability Protocol and a proposal to use a continuous verification approach have been submitted in module 3.2.R and require review. The Comparability Protocol is for the registration of additional site(s) for (b) (4) of the drug substance by submitting the change and supporting data in an Annual Report when specific criteria are met. The proposal to use a continuous verification approach states that continuous verification will be used to validate the manufacturing process for pazopanib drug product, rather than the conventional three batch approach. The use of continuous verification was discussed with the Office of New Drug Quality Assessment (ONDQA) and the Office of Compliance (OC). The minutes of this 4-Nov-2008 Type C meeting should be reviewed by the reviewer when considering this proposal and a summary should be conveyed to the Investigators involved in the Pre-Approval Inspection (PAI) of the drug product manufacturing site, if applicable.

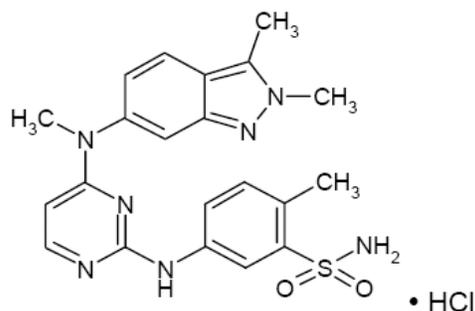
Letters of Authorization are presented for four Type III (b) (4) and one Type IV (b) (4) Drug Master Files (DMFs).

Pazopanib was developed using a Quality by Design (QbD) approach, identified by GSK as "Design for Manufacture" (DFM). The DFM process, which includes risk analysis and management, was utilized to determine the design space and control strategy for the drug substance and drug product. A glossary of terms and descriptions used by GSK for QbD is provided in m2.3. Quality Overall Summary Introduction.

Drug Substance Summary

Pazopanib hydrochloride is a white to slightly yellow crystalline solid, (b) (4)
(b) (4)

The chemical structure of pazopanib hydrochloride is below.



Pazopanib hydrochloride (MW= 473.99 g/mol)

A retest period of (b) (4) is proposed for the (b) (4) drug substance when stored under prescribed conditions. However, only (b) (4) of stability data have been submitted.

Drug Product Summary

The drug product is an immediate release tablet, containing either 200 mg or 400 mg of pazopanib (free base), equivalent to 216.7 mg and 433.4 mg pazopanib hydrochloride, respectively. Each film-coated tablet contains microcrystalline cellulose, sodium starch glycolate, povidone, and magnesium stearate. The tablets are produced using a conventional manufacturing process utilizing (b) (4)

The QbD approach and risk management tools are reported to enhance understanding so that appropriate control strategies can be applied to the manufacturing process. In Module 3.P.3.3, GSK proposes to use real-time-release for the drug product. This is not reflected in the proposed drug product specifications.

A (b) (4) expiration dating period is proposed for the drug product when stored at 25°C (77°F); excursions permitted 15 to 30°C (59 to 86°F). However, only 12 months of stability data have been submitted.

B. Preliminary Review, Comments and Recommendations

Drug Substance Section

The Chemistry, Manufacturing and Controls information for pazopanib hydrochloride is fully contained within NDA 22-465.

A QbD approach was utilized to develop and optimize the manufacturing process for pazopanib hydrochloride. The Critical Quality Attributes (CQAs) and Quality Attributes (QAs) were identified for the production of a drug substance suitable for formulation into the desired drug product. The Drug Substance CQAs are identity by IR, chloride identity, crystalline form, content by HPLC, drug-related impurities (including named impurities and genotoxic impurities content), residue on ignition, particle size, residual solvents, water content by Karl Fischer, description, Pd content, and heavy metals.

The (b) (4) pazopanib hydrochloride drug substance is manufactured by:
Glaxo Wellcome Manufacturing Pte
Limited, 1 Pioneer Sector 1
Jurong, Singapore 628413

The pazopanib hydrochloride is (b) (4) by:
(b) (4)
(b) (4)

Release testing of the commercial pazopanib hydrochloride (b) (4) is performed at:
Glaxo Operations UK Limited (trading as Glaxo Wellcome Operations)
Priory Street
Ware
Hertfordshire SG12 0DJ
United Kingdom

A (b) (4) has been used to prepare all the drug substance used in clinical trials, the drug product primary stability batches, and the drug product validation batches. (b) (4)

The following control strategies are proposed by on the use of a QbD approach and risk management tools:

- Starting material specifications.
- Quality attributes for intermediates.
- Quality Process Parameters (QPPs) for all (b) (4)

- (b) (4)
- Drug substance specification based on CQAs.

Drug Product Section

Pazopanib tablet is an immediate release tablet, containing either 200 mg or 400 mg of pazopanib (free base), equivalent to 216.7 mg and 433.4 mg pazopanib hydrochloride, respectively. The tablets are distinguished by size, color and debossing. The tablets are produced using a

conventional manufacturing process involving [REDACTED] (b) (4)

A risk-based, QbD approach was applied for the development of pazopanib tablets using methodologies such as FMEA and BRITEST and statistical DOEs to identify risk and improve overall product understanding. Particle size was identified as a drug substance CQA based on the BCS Classification (Class 2) of pazopanib hydrochloride. The drug product manufacturing process involves [REDACTED] (b) (4)

[REDACTED] QCPPs/QPPs and CQAs/QAs have been identified for the manufacturing process and drug product.

Typical end-product testing is proposed for the release of the finished pazopanib tablet. A thorough evaluation should be performed, especially with consideration of any genotoxic impurities from the drug substance. [REDACTED] (b) (4)

The proposed commercial package for pazopanib tablets, 200 mg are opaque, white [REDACTED] (b) (4) bottles filled with either 30 or 90 tablets. The proposed commercial package for pazopanib tablets, 400 mg are opaque, white [REDACTED] (b) (4) bottles filled with 30 and 60 tablets, respectively. Letters of Authorization are provided in Module 1.

The Agency agreed to accept 9 month stability data in the NDA, followed by a 12 month stability update to be submitted at least 3 months prior to the PDUFA action goal date (see FDA Response NDA Stability Proposal 18-Jun-2007). However, since the 12 month stability has been submitted in the NDA, the reviewer will need to determine if this previous agreement allows for additional stability data to be submitted during the review cycle.

C. **Critical issues for review and recommendation**

General Comments

- a. The reviewers are encouraged to have open and frequent discussions (as necessary) with the applicant related to the QbD approach used to develop the drug substance and drug product.
- b. The reviewers are encouraged to be involved (either through participation or other means of communication) in any PAI that may occur related to the drug substance or drug product.

Drug Substance

- a. The acceptability of the starting materials should be determined early in the review. (b) (4)
[REDACTED]
- b. The identification and evaluation of QCPPs or QPPs should be evaluated based upon scientific rationale, demonstrated process understanding, and risk management.
- c. The formation, specifications (lack of), and control of the genotoxic or potential genotoxic impurities, (b) (4)
[REDACTED] should be evaluated with close attention being paid to any risk management strategy proposed by the applicant.
- d. Drug substance specifications and justifications should be evaluated for appropriateness based upon the scientific knowledge demonstrated in the NDA.
- e. Only 12 months of stability data are presented in the NDA based on an agreement from the Agency (see FDA Response NDA Stability Proposal 18-Jun-2007). However, GSK proposes a (b) (4) retest date.
- f. The Agency agreed to accept 9 month stability data in the NDA, followed by a 12 month stability update to be submitted at least 3 months prior to the PDUFA action goal date (see FDA Response NDA Stability Proposal 18-Jun-2007). However, since the 12 month stability has been submitted in the NDA, the reviewer will need to determine if this agreement allows for additional stability data to be submitted during the review cycle.
- g. Because a QbD approach, including the use of risk management tools, was used to develop the drug substance, it is recommended that a reviewer participates in the Pre-Approval Inspection of the drug substance manufacturing site.

Drug Product

- a. The appropriateness of the QbD approach along with the identification and justification of CQAs, QAs, QCPP and QPPs should be evaluated along with proposed design spaces.
- b. Drug product specifications, including dissolution and the omission of Microbial Limit Tests, should be evaluated for appropriateness based on the QbD approach, process understanding, and justifications. The need for a Microbiology consult should be made early in the review cycle.
- c. The proposed sampling plan for release testing should be evaluated with respect to GSK's use of QbD, design spaces, and desire to implement continuous verification in lieu of conventional three batch validation.
- d. [REDACTED] (b) (4)

- e. QbD approach, design space, and the continuous verification should be evaluated based on the potential impact on product quality, safety, and efficacy.
- f. Based upon prior agreement, only 12 months of stability data are presented (see Module 3.2.P.8.1). However, GSK proposes (b) (4) expiry date.
- h. The selection and use of PAT should be evaluated for appropriateness and impact on the final product. The reviewers may wish to elicit assistance, either formally or informally, from other reviewers possessing a background that includes chemometric experience.
- i. GSK is proposing that since no QCPPs or QPPs were found via the risk assessment process, PARs for these parameters may be extended without regulatory action (see CMC specific pre-NDA meeting held on June 13, 2008).
- j. Because a QbD approach, including the use of risk management tools, was used to develop the drug product, design spaces are proposed for the manufacturing process, and GSK proposes to use continuous verification, it is recommended that a reviewer participates in the Pre-Approval Inspection of the drug product manufacturing site.

D. Comments for 74-day Letter:

Provide your stability data in SAS transport or Excel files, and include statistical analysis for of all stability-indicating quality attributes.

E. 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 <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
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?	√		
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?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √	√ √ √ √ √	Microbiology Pharm/Tox Biopharm Statistics (stability) CDRH LNC DMETS/ODS EER

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

Description	DMF Holder	DMF Type	DMF Number	Location of Letter of Authorization
-------------	------------	----------	------------	-------------------------------------



(b) (4)

Recommendation for Team Review:

This NDA includes a Quality-by-Design (QbD) approach, identified as Designed for Manufacture (DFM), a Comparability Protocol for additional sites to perform (b) (4) of the drug substance, and a proposal for continuous validation in lieu of conventional three batch validation.

A team review approach is recommended for this NDA due to the use of QbD principles and the proposed continuous verification plan.

Terrance Ocheltree, R.Ph., Ph.D.
Acting Pharmaceutical Assessment Lead

5-FEB-2009
Date

Sarah C. Pope, Ph.D.
Acting Branch Chief

5-FEB-2009
Date

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

/s/

Terrance Ocheltree
2/9/2009 10:23:55 AM
CHEMIST

Richard Lostritto
2/9/2009 05:12:04 PM
CHEMIST

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application:	NDA 22465/000	Action Goal:	
Str Date:	19-DEC-2008	District Goal:	20-AUG-2009
Regulatory:	19-OCT-2009		
Applicant:	GLAXO WELLCOME MFG 5 MOORE DR RESEARCH TRIANGLE PARK, NC 27709	Brand Name:	VOTRIENT TABLETS
		Estab. Name:	
		Generic Name:	PAZOPANIB TABLET
Priority:	1	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	150		001; TABLET; PAZOPANIB HYDROCHLORIDE; EQ 200MG BASE 002; TABLET; PAZOPANIB HYDROCHLORIDE; EQ 400MG BASE
Application Comment:	APPLICATION IS FOR 200 MG AND 400 MG PAZOPANIB HYDROCHLORIDE IR TABLETS FOR TREATMENT OF PATIENTS WITH ADVANCED RENAL CELL CARCINOMA (on 13-JAN-2009 by B. ROGERS () 301-796-1742)		
FDA Contacts:	K. ROBERTSON	Project Manager	301-796-1441
	B. ROGERS	Review Chemist	301-796-1742
	S. POPE	Team Leader	301-796-1436
Overall Recommendation:	ACCEPTABLE	on 09-OCT-2009	by E. JOHNSON (HFD-320) 301-796-3334

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 9610411 FEI: 3003262904
GLAXO OPERATIONS UK LIMITED
PRIORY STREET
WARE, HERTFORDSHIRE, , UNITED KINGDOM

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER

Estab. Comment: SITE IS RESPONSIBLE FOR DRUG PRODUCT MANUFACTURING; DRUG PRODUCT PRIMARY AND SECONDARY PACKAGING; DRUG PRODUCT QUALITY CONTROL TESTING AND RELEASE TESTING; AND (b) (4) BULK DRUG SUBSTANCE QUALITY CONTROL, RELEASE, AND STABILITY TESTING. PRIMARY CONTACT FOR SCHEDULING PAI INSPECTIONS AT GSK FACILITIES IS MS. DIANE SEVIGNY, GSK, RESEARCH TRIANGLE PARK, NC 919 483 8974. (on 14-JAN-2009 by B. ROGERS () 301-796-1742)
A (b) MAY BE ISSUED FOR THIS ESTABLISHMENT AND APPLICATION. PLEASE CONTACT COKI CRUZ OR TARA GOOEN WITH ANY QUESTIONS. (on 12-JUN-2009 by M. STOCK (HFD-320) 301-796-4753)

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	14-JAN-2009				ROGERSB
SUBMITTED TO DO	04-FEB-2009	Product Specific			ADAMSS
ASSIGNED INSPECTION TO IB	05-FEB-2009	Product Specific			JOHNSONE
INSPECTION SCHEDULED	12-AUG-2009		21-JUL-2009		IRIVERA
DO RECOMMENDATION LD REC NAI	09-OCT-2009			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	09-OCT-2009			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 9611205 FEI: 3002807079
GLAXO WELLCOME MANUFACTURING PTE LIMITED
2262
JURONG, SINGAPORE

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Estab. Comment: SITE RESPONSIBLE FOR (b) (4) D DRUG SUBSTANCE MANUFACTURING AND QUALITY CONTROL TESTING. PRIMARY CONTACT FOR SCHEDULING PAI INSPECTIONS AT GSK FACILITIES IS MS. DIANE SEVIGNY, GSK, RESEARCH TRIANGLE PARK, NC 919 483 8974. CHEMISTRY REVIEWER WISHES TO PARTICIPATE IN SITE INSPECTION. THIS APPLICATION CONTAINS SUBSTANTIAL QBD INFORMATION (b) (4) APPLICANT PLANS TO USE CONTINUOUS VERIFICATION FOR VALIDATION. (on 04-FEB-2009 by B. ROGERS () 301-796-1742)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	14-JAN-2009				ROGERSB
SUBMITTED TO DO	04-FEB-2009	Product Specific			ADAMSS
DO RECOMMENDATION	05-FEB-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	05-FEB-2009			ACCEPTABLE	ADAMSS

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 9610421 FEI:
GLAXOSMITHKLINE
HARMIRE ROAD
BARNARD CASTLE, COUNTY DURHAM, UNITED KINGDOM DL12 8DT

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE STABILITY TESTER

Estab. Comment: SITE IS RESPONSIBLE FOR (b) (4) DRUG SUBSTANCE STABILITY TESTING AND DRUG PRODUCT STABILITY TESTING. PRIMARY CONTACT FOR SCHEDULING PAI INSPECTIONS AT GSK FACILITIES IS MS. DIANE SEVIGNY, GSK, RESEARCH TRIANGLE PARK, NC 919 483 8974 (on 14-JAN-2009 by B. ROGERS () 301-796-1742)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	14-JAN-2009				ROGERSB
SUBMITTED TO DO	16-JAN-2009	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	05-FEB-2009	GMP Inspection			JOHNSONE
OC RECOMMENDATION	19-MAY-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 1033964 FEI: 1033964
GLAXOSMITHKLINE INC
1011 NORTH ARENDELL AVE
ZEBULON, NC 275971217

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

Estab. Comment: SITE RESPONSIBLE FOR PRIMARY AND SECONDARY PACKAGING OF DRUG PRODUCT, AND RESPONSIBLE FOR DRUG PRODUCT STABILITY TESTING. PRIMARY CONTACT FOR SCHEDULING PAI INSPECTIONS AT GSK FACILITIES IS MS. DIANE SEVIGNY, GSK, RESEARCH TRIANGLE PARK, NC 919 483 8974 (on 14-JAN-2009 by B. ROGERS () 301-796-1742)
SITE IS RESPONSIBLE FOR DRUG PRODUCT PRIMARY AND SECONDARY PACKAGING; AND DRUG PRODUCT STABILITY TESTING. PRIMARY CONTACT FOR SCHEDULING PAI INSPECTIONS AT GSK FACILITIES IS MS. DIANE SEVIGNY, GSK, RESEARCH TRIANGLE PARK, NC 919 483 8974 (on 14-JAN-2009 by B. ROGERS () 301-796-1742)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE
TABLETS, PROMPT RELEASE NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	14-JAN-2009				ROGERSB
SUBMITTED TO DO	22-JAN-2009	GMP Inspection			FERGUSONS
DO RECOMMENDATION	27-JAN-2009			ACCEPTABLE	MWOLESKE
A GMP INSPECTION WAS CONDUCTED 7/28-8/1/2008 AND WAS CLASSIFIED AS NO ACTION INDICATED. WHILE PROFILE CLASS CTL WAS NOT SPECIFICALLY LISTED, THIS FIRM IS A MANUFACTURER OF TABLETS AND IS CAPABLE OF TESTING TABLETS. PROFILE CLASSES COVERED INCLUDED (b) (4). THE DISTRICT'S COMMENDATION IS APPROVABLE.				BASED ON FILE REVIEW	
OC RECOMMENDATION	28-JAN-2009			ACCEPTABLE	FERGUSONS
				DISTRICT RECOMMENDATION	
OC RECOMMENDATION	28-JAN-2009			ACCEPTABLE	FERGUSONS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	14-JAN-2009				ROGERSB
OC RECOMMENDATION	14-JAN-2009			ACCEPTABLE	KIEL
				BASED ON PROFILE	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4)
 (b) (4)

FEI: (b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

Estab. Comment: (b) (4). (on 14-JAN-2009 by B. ROGERS () 301-796-1742)

Profile: (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	14-JAN-2009				ROGERSB
OC RECOMMENDATION	14-JAN-2009			ACCEPTABLE BASED ON PROFILE	KIEL