DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration
Rockville, MD 20857

NDA 22-465

INFORMATION REQUEST LETTER

GlaxoSmithKline
Attention: Ellen S. Cutler
Senior Director, US Regulatory Affairs
Oncology
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Ms. Cutler:

Please refer to your new drug application (NDA) submitted December 18, 2008, received December 19, 2008, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VOTRIENT™ (pazopanib hydrochloride) Tablet, 200 mg; 400 mg.

We also refer to your submission dated June 5, 2009, and the face-to-face Type C Chemistry, Manufacturing and Controls meeting held on July 1, 2009.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information requests. We request that you respond by July 31, 2009, in order to continue our evaluation of your NDA.

1. Please identify where the following information is located in the NDA, or provide it if not already included:

    a. The dissolution method development report with detailed dissolution data for different methods.
    b. The dissolution data for individual tablets at all time points for all batches tested so far.
    c. Detailed justification for the proposed dissolution specification (with raw data).

2. Provide the observations for individual tablets for DOE of dissolution models in SAS or Excel format.
3. Provide justification for using (b) (4) Provide any available data to show the relationship between (b) (4) Justify that there is no impact of other variables, e.g., (b) (4)
4. Provide the design space (i.e., response surface) in terms of:

(b) (4)

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Sarah Pope
7/13/2009 04:58:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration
Rockville, MD 20857

NDA 22-465

INFORMATION REQUEST LETTER

GlaxoSmithKline
Attention: Ellen S. Cutler
Senior Director, US Regulatory Affairs
Oncology
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Ms. Cutler:

Please refer to your new drug application (NDA) submitted December 18, 2008, received December 19, 2008, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VOTRIENT™ (pazopanib hydrochloride) Tablet, 200 mg; 400 mg.

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

1) In regards to the drug substance manufacturing process (m3.2.S.2.2), define the relationship between solvent volumes and reagent equivalents.

2) Under *Control of Materials, Summary*, the use of the word "may" makes the described testing optional. The statements related to the frequency of testing following a change in supplier and the frequency of periodic full supplier verification testing, should be revised to include a specific minimum number of batches to be tested upon a change in supplier (e.g., the first ten batches) and the frequency of periodic full supplier verification testing (e.g., at least one batch annually). The following statements exemplify our request:

> *When purchased from a new supplier, full testing of the materials (except hazardous reagents, gases and processing aids noted) will be performed on a minimum of the first ten batches until reliability of the supplier has been established. When purchased from an established supplier, the materials are subjected to a minimum of identification confirmation upon receipt and accepted on the supplier's certificate of analysis/conformity. Additionally, continued reliability of the established supplier will be monitored by testing of at least one batch annually to specification. The only exception to this is for hazardous reagents, gases, processing aids noted and materials that are highly reactive, where the act of sampling may compromise the quality of the material. In this instance the material is accepted on a certificate of analysis or conformity.*

Alternatively, specify risk-based criteria for the proposed sampling frequency applied to materials following any changes in supplier(s).

3) In footnote 2 in the *Specification for Pazopanib Hydrochloride*, the impurity (b) (4) is incorrectly listed as (b) (4) Resubmit your proposed specification for the drug substance with this correction implemented.

4) The proposed acceptance criteria for *related impurities content by HPLC* in the specification for intermediate (b) (4) are not reflective of the batch analysis data in Table 5 (m3.2.S.2.4) batch analysis data, and you

have not demonstrated the effect of the proposed impurity levels (as exemplified by your proposed acceptance criteria) on the drug substance quality. Show that you have a thorough understanding of the effect of the related impurity levels proposed in the specification for (b) (4) on the drug substance quality, or revise the acceptance criteria for *Related impurities content by HPLC* to the following to be consistent with the quality of the batches in Table 5:

(b) (4)

Additionally, provide a rationale for proposing acceptance criteria for impurities (b) (4) (b) (4) at values that are almost ten fold higher than those observed in results from DOE experiments for stages 1 and 2 (refer to DOE data provided in Tables 15 and 18).

5) The proposed acceptance criterion for level of (b) (4) in *Related impurities content by HPLC* in the (b) (4) are not reflective of the batch analysis data in Table 4 (m3.2.S.2.4), and you have not demonstrated the effect of the proposed impurity level (as exemplified by your proposed acceptance criterion) on the drug substance quality. Show that you have a thorough understanding of the effect of the levels of (b) (4) proposed in your specification on the drug substance quality, or revise the acceptance criterion for the level of (b) (4) and Total Related Impurities in (b) (4) in *Related impurities content by HPLC* to (b) (4), respectively, to be consistent with the levels seen in Table 4.

6) The proposed acceptance criterion for level of (b) (4) in *Drug-related impurities content by HPLC* in the specification for intermediate (b) (4) are not reflective of the batch analysis data in Table 5 (m3.2.S.2.4), and you have not demonstrated the effect of the proposed impurity levels (as exemplified by your proposed acceptance criteria) on the drug substance quality. Show that you understand the effect of the levels of (b) (4) proposed in your specification on the drug substance quality, or revise the acceptance criterion for the level of (b) (4) and Total drug-related impurities in (b) (4) (b) (4) respectively, to be consistent with the levels seen in Table 5.

7) (b) (4)

8) Insert controls for microbial limits and water (b) (4) content in the drug product specifications over the shelf-life of the product or provide appropriate justification for their absence.

9) Remove or revise the statement in section m3.2S.2.2 that states that changes outside the PAR for Quality Attributes and Quality Process Parameters would be made via an annual report; because, per ICH Q8 and Q8R guidance: "Movement out of the design space is considered to be a change and would normally initiate a post approval process".

10) Confirm that PAR (Proven Acceptable Ranges) given in tables 32 to 36, in section m3.2.S.2.6 define your design space. Alternately, provide a summary design space table. Confirm that the design space information will be available at the drug substance manufacturing site.

11) Address the following for section m3.2.S.2.6, Section 7:

    a) For stage 1, it is indicated for the reaction DOE (refer table 12) some interaction between parameters was observed and that prompted an execution of a response surface DOE. Indicate how these interactions are captured in specifying PAR for the parameters

    b) Indicate why impurity (b) (4) was not monitored as a response during DOE for (b) (4) even though this impurity is listed as a (b) (4) impurity in the impurity fate map.

    c) Provide a synopsis of the risk assessment performed for stages 2 and 3, that led to the selection of a narrow set of parameters for further evaluation via DOE.

    d) Clarify the reason for not monitoring the following impurities (b) (4) (b) (4) as responses in (b) (4) DOE. In addition, provide a rationale for not evaluating the impact of variation in (b) (4) volume (identified as a QPP) via the multivariate DOE for (b) (4)

    e) Indicate if impact of variables listed as QCPP in table 23 (for stage 4) were evaluated via any DOE. It is indicated that PAR for these variables were determined in a univariate manner. Elaborate and indicate how interactions between these variables were captured.

    f) Provide further details (e.g. process parameters) about the purging study referenced in Table 26. In addition, indicate if the impact of variation in process parameters were evaluated.

12) It is noted that PAR for some of the process parameters were determined in a univariate fashion. For example, for the impurities identified as potential CQA/QA for (b) (4) it is stated that "The response of these impurities to the parameters investigated in the DOE was defined in univariate experimentation". Provide data to show that multivariate interactions of process parameters would not result in elevated levels of impurities.

13) Clarify your approach to scale up PAR for process parameters determined via DOE's at laboratory scale for stages 1 through 4, to commercial scale. For example, it is noted that for the reaction DOE (b) (4) the range of reaction time evaluated at laboratory scale was (b) (4) However, a reaction time of (b) (4) was selected for pilot scale batches.

14) Provide details about the risk assessment that led to the determination that none of the parameters for stages 1 and 2 were QCPP or QPP, and thus not included in the design space.

15) Provide details about the FMEA process for (b) (4) ı. For example, what RPN number was chosen to determine criticality of variables and its relevancy.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Sarah Pope
6/11/2009 09:24:13 AM

From: Robertson, Kim
Sent: Wednesday, September 23, 2009 6:56 PM
To: 'ellen.s.cutler@gsk.com'
Subject: Reminder--NDA 22-465; Labeling and Analysis of Hy's Law Cases

Importance: High

Hello Ellen:

I just wanted to remind you to please submit to us by weeks end the following items:

- The VOTRIENT label with GSK comments incorporated
- An analysis of any cases of Hy's Law or more serious hepatic injury from your combination studies

Thank you,
Kim

Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Robertson, Kim
Sent: Thursday, September 24, 2009 7:13 PM
To: ellen.s.cutler@gsk.com
Subject: NDA 22-465; VOTRIENT-Information Request-Patients 152 & 300; Gastric Cancer

Importance: High

Hello Ellen:

Please see the following information request:

- We note that two patients in VEG105192 died due to gastric cancer, patients 152 and 300. Given the small number of patients and the limited observation period, we are concerned about these events. Please present your interpretation of these events. This should include the expected incidence of gastric cancer in this population and any pre-clinical data concerning tumor initiation or promotion with pazopanib. Please state whether secondary tumors have been observed with pazopanib (monotherapy and combination therapy) and if so, please provide detailed information. Please provide a timeline for your response.

Thank you,
Kim

Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845

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

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

/s/

KIM J ROBERTSON

09/30/2009

September 23 and September 24 Clinical IRs re: Analysis of Hy's Law Cases and Patient Info. re: Patients 152 & 300; Gastric Cancer

From: Robertson, Kim
Sent: Monday, September 21, 2009 2:00 PM
To: ellen.s.cutler@gsk.com
Subject: NDA 22-465 VOTRIENT

Hello Ellen:

The review team of your NDA for VOTRIENT is requesting the following information:

When is the actual time for the final OS analysis?

Thank you,
Kim

Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845

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

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

/s/

KIM J ROBERTSON

09/30/2009

Original Request Sent September 21, 2009; DARRTS Entry-September 30, 2009; NDA 22-465; VOTRIENT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-465

INFORMATION REQUEST

GlaxoSmithKline
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Attention: Ellen S. Cutler
Senior Director, US Regulatory Affairs
Oncology

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) dated December 18, 2008, received December 19, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (pazopanib hydrochloride) Tablet, 200 mg; 400 mg.

We have reviewed the referenced material and have the following request for information:

1. The Division of Drug Oncology Products is requesting that GlaxoSmithKline provide a complete copy of the medical record for Subject 912 in study VEG105192. This should include all medical documents from screening to study discontinuation as well as actual radiographic images.

If you have any questions, call Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

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

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

/s/

KIM J ROBERTSON
07/28/2009
24July09 Information Request Subject 912

ANTHONY J MURGO
07/28/2009
Signing for: Robert L. Justice, M.D., M.S.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-465

GlaxoSmithKline
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Attention: Ellen S. Cutler
Senior Director, US Regulatory Affairs
Oncology

Dear Ms. Cutler:

Please refer to your December 19, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Votrient® (pazopanib hydrochloride) Tablet, 200mg; 400mg, received December 19, 2008.

We also refer to our filing letter dated February 23, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is October 19, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 26, 2009.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

If you have any questions, call Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Robert Justice
6/12/2009 05:01:02 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-465

INFORMATION REQUEST LETTER

GlaxoSmithKline
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Attention: Ellen S. Cutler
Senior Director, US Regulatory Affairs
Oncology

Dear Ms. Cutler:

Please refer to your December 18, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Votrient (pazopanib) 200 mg and 400 mg Tablets.

The Division of Oncology Drug Products and the Division of Medication Error Prevention and Analysis (DMEPA) are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Division of Oncology:

1. For both VEG105192 and VEG 102616, the submitted datasets for protocol violations and/or deviations are limited to disagreements in eligibility criteria. Please submit datasets that include all protocol conduct violations and deviations identified during the studies.

2. In the study report of VEG102616, Attachment 5 (Comprehensive ECG Analysis Report) is blank. We only found numerous vertical lines on the top of each page. Please submit that part of the report.

3. For VEG102616, we could not locate the details of the independent radiology review process. Please submit the information.

Division of Medication Error Prevention and Analysis (DMEPA); Container Labeling:

1. Remove the green and orange blocks of color from the net quantity statement on the 200 mg and 400 mg tablet bottles, respectively. The color is the same on both bottle sizes of each strength tablet, and this does not help to distinguish the two different package sizes from each other. Additionally, it competes with the product strength which is blocked in the same color, thus detracting from this important information.

2. Remove the orange and green borders surrounding the green and orange boxes that surround the 200 mg and 400 mg strength, respectively. As currently designed, these color schemes for the 200 mg and 400 mg strength are opposites of each other, and can increase confusion between the two strengths when the products are stored side-by-side.

3. Increase the prominence of the established name (which includes dosage form). Ensure that the prominence of the established name is commensurate with the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

4. Remove the statement (b) (4) This statement is unnecessary since your product will be packaged with (b) (4) child resistant closures as specified in your NDA submission.
The inclusion of this statement is misleading and infers that the packaging does not contain the required safety closure.

If you have any questions, call Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Kim Robertson
6/1/2009 01:11:09 PM
01June09 Clinical Request and DMEPA Comments NDA 22-465

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, Maryland 20993

NDA 22-465

PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE

GlaxoSmithKline
ATTENTION: Ellen Cutler
Senior Director, Regulatory Affairs, Oncology
1250 South Collegeville Road
PO Box 5089
Collegeville, Pennsylvania 19428-0989

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) dated December 18, 2008, receipt date December 19, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for pazopanib hydrochloride tablets, 200 mg and 400 mg.

We also refer to your February 13, 2009, correspondence, received February 13, 2009, requesting review of your proposed proprietary name, Votrient. We have completed our review of the proposed proprietary name, Votrient, and have concluded that it is acceptable.

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

If **any** of the proposed product characteristics as stated in your February 13, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sandra Griffith, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

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

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

/s/

Robert Justice
5/7/2009 07:39:23 PM

Fax

DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Ms. Ellen S. Cutler	From: Kim J. Robertson
Fax:	Fax: 301-796-9845
Phone: (610) 910-6823	Phone: 301-796-1441
Pages, including cover sheet: 1	Date: 27 April 2009

Re: **New NDA 22-465 Votrient (pazopanib)—re: Clinical Information Requests**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

- Dear Ms. Cutler:

Please refer to your newly submitted NDA for Votrient (pazopanib); GW786034 Tablets submitted December 18, 2009, received December 19, 2009. The clinical reviewers of your NDA are requesting the following information:

- Would you please provide CRFs for all the patients who received pazopanib on study 105192?

Regards,

Kim J. Robertson
Consumer Safety Officer

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

/s/

Kim Robertson
4/27/2009 03:38:29 PM
CSO
27April09 Clinical Request for Information CRFs-'09

Fax
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Ellen S. Cutler, Senior Director	From: Kim J. Robertson
Fax: (610) 787-7062	Fax: 301-796-9845
Phone: (610) 787-3733	Phone: 301-796-1441
Pages, including cover sheet: 1	Date: 17 April 2009

Re: **Agency Statistical Feedback re: NDA 22-465 Votrient (pazopanib)**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

- Dear Ms. Cutler:

Below, please find our responses addressing your request for feedback outlined in your April 1, 2009 submission regarding NDA 22-465:

GSK's Request #2: Please confirm whether an additional analysis censoring these 20 subjects is still required.

FDA response: Please perform one additional PFS sensitivity analysis censoring those 20 subjects at the last assessment with document of no progression prior to their discontinuations.

GSK's Request #3: Please clarify what is required in the column of Table 2 for the log-rank test. Is it meant to test whether the distribution of the time to each assessment was equal between the two treatment arms? Can you please clarify what censoring scheme should be used in this table?

FDA response: Yes. It is meant to test whether the distribution of the time to each assessment was equal between the two treatment arms.

No censoring scheme is used in the log-rank test. For each analysis on time to scheduled assessment (1st, 2nd, 3rd, ...), patients who had actual assessments are included in the log rank test and will be considered as events.

Thank you,

Kim J. Robertson
Consumer Safety Officer

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

/s/

Kim Robertson
4/17/2009 05:34:11 PM
CSO
17April09 (02April09 Origin) Stat Feedback to GSK NDA 22-465

Fax

DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Ms. Ellen S. Cutler	From: Kim J. Robertson
Fax:	Fax: 301-796-9845
Phone: (610) 910-6823	Phone: 301-796-1441
Pages, including cover sheet: 1	Date: 10 April 2009

Re: **New NDA 22-465 Votrient (pazopanib)—re: Clinical Comments**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

- Dear Ms. Cutler:

Please refer to your newly submitted NDA for Votrient (pazopanib); GW786034 Tablets submitted December 18, 2009, received December 19, 2009. The review team has the following comments:

- Please state whether the errors in the AE.xpt dataset, communicated on April 2, 2009, will be corrected in the Safety Update. If you are not able to include a fully corrected dataset in the Safety Update, please explain why and provide a timeline for its submission. Please note that correction of these errors is essential to our verification of your data.

- We would like to examine updated information concerning laboratory LFT abnormalities. Please include an update of the lab.xpt dataset with the Safety Update. If you are not able to include this with the Safety Update, please explain why and provide a timeline for its submission.

If you should have any further questions/concerns, please don't hesitate to contact us.

Regards,

Kim J. Robertson
Consumer Safety Officer

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

/s/

Kim Robertson
4/10/2009 02:49:44 PM
CSO
10April09 Clinical Comments NDA 22-465 Pazopanib

Fax

DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Ms. Ellen S. Cutler	From: Kim J. Robertson
Fax:	Fax: 301-796-9845
Phone: (610) 910-6823	Phone: 301-796-1441
Pages, including cover sheet: 3	Date: 02 April 2009

Re: **New NDA 22-465 Votrient (pazopanib)—re: Clinical Information Comments/Requests & Timeline Communications**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

- Dear Ms. Cutler:

Please refer to your newly submitted NDA for Votrient (pazopanib); GW786034 Tablets submitted December 18, 2009, received December 19, 2009. The review team has identified the following issues for you to address:

For Study VEG105192, there were 112 narratives submitted; however, many of them have no corresponding CRFs in the submission. Please submit all CRFs based on the specified agreement in the pre-NDA meeting for Studies VEG105192 and VEG102616.

Your VEG105192 AE dataset should be examined carefully for its accuracy and reliability and resubmitted after clean up. After scrutinizing the 112 narratives and checking the described adverse reactions against those in the AE dataset, we noticed inaccurate grading of toxicity, incorrect coding dose interruption or discontinuation, and incorrect documentation of whether an adverse reaction led to study withdrawal. The information in the table below only serves as examples illustrating part of the problem.

Subject /Center ID	Narrative	CRF	Discrepancy in AE dataset
#601/24756	Submitted	Not found	AEWD-no (supposed to be Yes)
#129/24590	Submitted	Not found	Anemia Grade 2 (supposed to be Grade 3)
#519/29632	Submitted	Not found	Fistula Grade X (supposed to be Grade 3) AEWD-no (supposed to be Yes)
#804/30165	Submitted	Submitted	Decrease in LVEF (Grade 3) not listed
#1/25702	Submitted	Not found	AEACTRCD is 1 rather than 5 (multiple instances of this)
#121/24590	Submitted	Submitted	Dataset states IP permanently d/c'd (b) (6) IP CRF states IP taken 8-11 to 12-9-06 AE CRFs states IP withdrawn 12-8-06 and 10-1-06
#135/25134	Submitted	Submitted	Study conclusion CRF dated 10-26-06 and 7-20-07 (also #145) IP CRF states IP stopped 2-27-07 AE CRF states IP stopped 2-15-07
#351/25093	Submitted	Not found	The AE HTN, mentioned in the narrative and critical to her development of a TIA is not in the dataset.
#354/25093	Submitted	Not found	The narrative states proteinuria began on 12-19-07. In dataset, it began 1-8-08. Unclear if pt had nephrotic syndrome.
#129/24590	Submitted	Submitted	Non-serious AE CRF states IP withdrawn 12-15-06, c/w dataset; IP CRF state dose unchanged until 2-20-07
#159/34145	Submitted	Submitted	Narrative, SAE CRF state IP perm d/c'd due to anemia (b) (6). IP CRF states dose held 1-8-07 due to error in EKG reading. Prolonged QTc is deleted from the non-serious AE CRF and it is not in the dataset.
#160/24723	Submitted	Submitted	Narrative states dose reduced due to HTN, hemoptysis. This is c/w CRFs. Dataset has dose interrupted, not interrupted and reduced. IP CRF states IP held due to vomiting during interval 6-3 to 7-4-07. AE CRF and dataset record vomiting on 4-19-06, dose held.

We also urge you to check whether similar problems exist in the submitted data for the supporting studies (VEG102616 and VEG107769) and correct them as needed.

We have the following additional requests for information..

1) For patients who had a disagreement in assessment of disease progression between the IRC and investigators, please provide reasons for such differences.

2) For patients who had disease progression events based on both the IRC and investigator assessment, were there any disagreements in progression date? If so, please provide reasons for such disagreements and specify the extent of the difference between two progression dates.

3) We are unable to find a clearly stated rationale in the application to justify the applicability of foreign data to the U.S. population/practice of medicine in patients with renal cell carcinoma. Please provide one.

4) Please provide the dataset for 109693. Amendment 8 contains 109603.

Planned Dates for Important Review Milestones:

- NDAs Mid-Cycle Review: May 19, 2009
- AC/ODAC Meeting: Tentatively scheduled for September 15, 2009
- Proposed Transmitting Initial Labeling Comments: Anticipated to begin August, 2009 (could vary during the review cycle)
- PMCs/PMRs: In all probability; September, 2009 (could vary during the review cycle)

If you should have any further questions/concerns, please don't hesitate to contact us.

Regards,

Kim J. Robertson
Consumer Safety Officer

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

/s/

Kim Robertson
4/2/2009 07:15:13 PM
CSO
02April09 Clinical Requests/Comments Timeline Information NDA 22-465 Votrie

Fax
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Ellen S. Cutler, Senior Director	From: Kim J. Robertson
Fax: (610) 787-7062	Fax: 301-796-9845
Phone: (610) 787-3733	Phone: 301-796-1441
Pages, including cover sheet: 9	Date: 25 March 2009

Re: **Agency Statistical Request of information re: NDA 22-465 Votrient (pazopanib)- IND# 65,747**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

- Dear Ms. Cutler:

Below, please find the following Statistical requests for information regarding NDA 22-465:

Request #1:

Table 1 shows that the PFS censoring status for patients who discontinued due to reasons other than progressive disease were considered as PFS events in the final PFS analyses and the patients who discontinued due to progressive disease were censored, not considered as PFS events. Please provide detailed explanations for such PFS status (event/censored) classifications for each patient listed in Table 2.

Request #2:

Please perform a PFS analysis in which patients, who discontinued due to reasons other than progressive disease, are censored at the last assessment with document of no progression prior to the discontinuation.

Please provide a PFS dataset for such an analysis. The PFS dataset needs to include the discontinuation dates and the dates of the last assessment with document of no progression prior to the discontinuation for patients who discontinued due to reasons other than progressive disease were considered as PFS events in your submitted PFS analyses. Please also provide programs for the analysis and data creation.

Table 1:

TRT	PFSCFLCD	SDREAS	N
Pazopanib	1	Adverse Event	21
Pazopanib	0	Death	2
Pazopanib	0	Disease Progression	55
Pazopanib	1	Investor Decision	4
Pazopanib	1	Other, specify	2
Pazopanib	1	Subject decided to withdraw from the study	3
Placebo	1	Adverse Event	3
Placebo	0	Death	1
Placebo	0	Disease Progression	37
Placebo	1	Investor Decision	1
Placebo	1	Lost to follow up	1
Placebo	0	Other, specify	1

Datasets: onctte and stopdrug

Table 2:

USUBJID	TRTGRP	PFSCFL CD	PFSMO	SDREAS
VEG105192.0000003	Pazopanib	0	4.1725	Disease progression
VEG105192.0000024	Placebo	0	4.8953	Disease progression
VEG105192.0000064	Placebo	0	0.0329	Disease progression
VEG105192.0000071	Pazopanib	0	0.0329	Death
VEG105192.0000072	Placebo	0	0.0329	Disease progression
VEG105192.0000075	Placebo	0	0.0329	Death
VEG105192.0000077	Pazopanib	1	1.4127	Adverse event
VEG105192.0000085	Placebo	0	2.7926	Disease progression
VEG105192.0000086	Pazopanib	1	12.9117	Subject decided to withdraw from the study
VEG105192.0000091	Placebo	1	1.4127	Adverse event
VEG105192.0000110	Pazopanib	0	1.4127	Disease progression
VEG105192.0000111	Pazopanib	0	1.4127	Disease progression
VEG105192.0000113	Pazopanib	0	2.7926	Disease progression

Table 2:

USUBJID	TRTGRP	PFSCFL CD	PFSMO	SDREAS
VEG105192.0000117	Placebo	0	1.4127	Disease progression
VEG105192.0000119	Pazopanib	0	4.1725	Disease progression
VEG105192.0000121	Pazopanib	1	4.3696	Adverse event
VEG105192.0000123	Pazopanib	1	14.7515	Adverse event
VEG105192.0000126	Placebo	0	5.5524	Disease progression
VEG105192.0000127	Pazopanib	0	0.0329	Disease progression
VEG105192.0000129	Placebo	1	1.4127	Adverse event
VEG105192.0000130	Pazopanib	0	4.1725	Disease progression
VEG105192.0000135	Placebo	1	2.7926	Other, specify
VEG105192.0000137	Pazopanib	0	11.0719	Disease progression
VEG105192.0000141	Placebo	0	7.3922	Disease progression
VEG105192.0000144	Pazopanib	0	5.5524	Disease progression
VEG105192.0000151	Placebo	0	1.4127	Disease progression
VEG105192.0000158	Pazopanib	0	0.0329	Disease progression
VEG105192.0000159	Pazopanib	1	5.5524	Adverse event
VEG105192.0000160	Pazopanib	1	8.2136	Adverse event
VEG105192.0000166	Pazopanib	0	1.4127	Disease progression
VEG105192.0000175	Pazopanib	0	2.7926	Disease progression
VEG105192.0000180	Pazopanib	0	7.3922	Disease progression
VEG105192.0000182	Pazopanib	0	9.2320	Disease progression
VEG105192.0000186	Placebo	0	12.9117	Disease progression
VEG105192.0000189	Placebo	0	16.5914	Disease progression
VEG105192.0000203	Pazopanib	0	12.9117	Disease progression
VEG105192.0000205	Pazopanib	0	2.0041	Disease progression
VEG105192.0000212	Pazopanib	0	18.4312	Disease progression
VEG105192.0000224	Pazopanib	0	2.7926	Disease progression
VEG105192.0000226	Placebo	0	2.7926	Disease progression

Table 2:

USUBJID	TRTGRP	PFSCFL CD	PFSMO	SDREAS
VEG105192.0000230	Placebo	0	4.1725	Disease progression
VEG105192.0000235	Placebo	0	1.4127	Disease progression
VEG105192.0000236	Pazopanib	0	1.4127	Disease progression
VEG105192.0000238	Pazopanib	1	2.7926	Subject decided to withdraw from the study
VEG105192.0000242	Pazopanib	0	1.4127	Disease progression
VEG105192.0000247	Pazopanib	0	5.5524	Disease progression
VEG105192.0000251	Placebo	0	2.7926	Disease progression
VEG105192.0000256	Pazopanib	1	5.5524	Other, specify
VEG105192.0000300	Pazopanib	1	4.1725	Adverse event
VEG105192.0000311	Placebo	0	1.4127	Disease progression
VEG105192.0000320	Pazopanib	0	9.2320	Disease progression
VEG105192.0000323	Pazopanib	1	1.6756	Adverse event
VEG105192.0000335	Placebo	0	2.7926	Disease progression
VEG105192.0000342	Pazopanib	0	7.3922	Disease progression
VEG105192.0000346	Pazopanib	0	5.5524	Disease progression
VEG105192.0000349	Pazopanib	0	4.1725	Disease progression
VEG105192.0000351	Pazopanib	1	5.5524	Adverse event
VEG105192.0000354	Pazopanib	1	14.7515	Adverse event
VEG105192.0000355	Pazopanib	0	4.1725	Disease progression
VEG105192.0000381	Pazopanib	0	4.1725	Disease progression
VEG105192.0000386	Pazopanib	1	1.0513	Investigator decision
VEG105192.0000388	Pazopanib	1	1.6427	Investigator decision
VEG105192.0000390	Placebo	0	2.7926	Disease progression
VEG105192.0000398	Pazopanib	1	1.3799	Adverse event
VEG105192.0000410	Pazopanib	0	9.2320	Disease progression
VEG105192.0000412	Pazopanib	0	3.4825	Disease progression

Table 2:

USUBJID	TRTGRP	PFSCFL CD	PFSMO	SDREAS
VEG105192.0000422	Pazopanib	0	9.2320	Disease progression
VEG105192.0000441	Pazopanib	1	5.5524	Adverse event
VEG105192.0000463	Pazopanib	0	1.4127	Death
VEG105192.0000467	Placebo	0	5.5524	Disease progression
VEG105192.0000468	Pazopanib	0	9.2320	Disease progression
VEG105192.0000471	Placebo	0	1.4127	Disease progression
VEG105192.0000489	Pazopanib	0	4.1725	Disease progression
VEG105192.0000492	Pazopanib	0	7.3922	Disease progression
VEG105192.0000501	Placebo	0	4.1725	Disease progression
VEG105192.0000502	Pazopanib	0	16.5914	Disease progression
VEG105192.0000505	Pazopanib	0	11.0719	Disease progression
VEG105192.0000506	Pazopanib	0	11.0719	Disease progression
VEG105192.0000510	Placebo	0	2.7926	Disease progression
VEG105192.0000515	Pazopanib	0	5.5524	Disease progression
VEG105192.0000518	Pazopanib	0	4.1725	Disease progression
VEG105192.0000521	Placebo	0	7.3922	Disease progression
VEG105192.0000530	Placebo	1	2.2669	Investigator decision
VEG105192.0000531	Placebo	0	7.3922	Disease progression
VEG105192.0000532	Pazopanib	0	18.4312	Disease progression
VEG105192.0000585	Placebo	0	12.9117	Disease progression
VEG105192.0000587	Placebo	0	11.0719	Disease progression
VEG105192.0000589	Pazopanib	1	2.7926	Adverse event
VEG105192.0000601	Pazopanib	1	16.5914	Adverse event
VEG105192.0000607	Placebo	0	1.4127	Disease progression
VEG105192.0000630	Pazopanib	0	1.4127	Disease progression
VEG105192.0000638	Pazopanib	0	7.3922	Disease progression
VEG105192.0000639	Placebo	0	2.7926	Disease progression

Table 2:

USUBJID	TRTGRP	PFSCFL CD	PFSMO	SDREAS
VEG105192.0000649	Pazopanib	1	5.5524	Adverse event
VEG105192.0000650	Pazopanib	0	7.3922	Disease progression
VEG105192.0000651	Placebo	0	1.4127	Disease progression
VEG105192.0000654	Pazopanib	0	1.4127	Disease progression
VEG105192.0000705	Pazopanib	1	5.5524	Adverse event
VEG105192.0000708	Placebo	0	7.3922	Disease progression
VEG105192.0000726	Pazopanib	0	1.4127	Disease progression
VEG105192.0000749	Pazopanib	0	7.3922	Disease progression
VEG105192.0000757	Pazopanib	1	2.7926	Other, specify
VEG105192.0000758	Pazopanib	0	9.2320	Disease progression
VEG105192.0000759	Pazopanib	1	1.4127	Adverse event
VEG105192.0000782	Pazopanib	0	0.0329	Disease progression
VEG105192.0000792	Pazopanib	0	9.2320	Disease progression
VEG105192.0000819	Pazopanib	1	7.3922	Subject decided to withdraw from the study
VEG105192.0000828	Placebo	0	5.5524	Disease progression
VEG105192.0000833	Placebo	0	1.4127	Disease progression
VEG105192.0000888	Pazopanib	0	1.4127	Disease progression
VEG105192.0000896	Placebo	0	1.4127	Disease progression
VEG105192.0000907	Pazopanib	1	4.1725	Adverse event
VEG105192.0000911	Pazopanib	1	9.6263	Investigator decision
VEG105192.0000918	Placebo	1	1.4127	Lost to follow-up
VEG105192.0000924	Pazopanib	0	0.0329	Disease progression
VEG105192.0000940	Pazopanib	0	2.7926	Disease progression
VEG105192.0000941	Placebo	0	2.7926	Disease progression
VEG105192.0000947	Pazopanib	0	1.4127	Disease progression
VEG105192.0000954	Pazopanib	1	5.5524	Adverse event

Table 2:

USUBJID	TRTGRP	PFSCFL CD	PFSMO	SDREAS
VEG105192.0000975	Pazopanib	1	5.5524	Adverse event
VEG105192.0000976	Placebo	0	2.7926	Disease progression
VEG105192.0000980	Placebo	0	2.2669	Disease progression
VEG105192.0000981	Pazopanib	0	7.8850	Disease progression
VEG105192.0000986	Pazopanib	0	9.2320	Disease progression
VEG105192.0000987	Pazopanib	1	5.5524	Investigator decision
VEG105192.0000993	Pazopanib	0	7.3922	Disease progression
VEG105192.0000998	Pazopanib	1	1.5770	Adverse event
VEG105192.0001053	Pazopanib	1	2.7926	Adverse event
VEG105192.0001054	Placebo	1	1.4127	Adverse event
VEG105192.0001066	Placebo	0	2.7926	Disease progression
VEG105192.0001100	Placebo	0	0.0329	Disease progression

Request #3:

In the following table (Table 27 in the study report), the number 103 in 'Number (%) of Subjects, n' in the Investigator-Evaulated category is not replicable. Please show us how to confirm this number.

Table 27 Summary of Duration of Response (RECIST Criteria) by the IRC and Investigator (ITT Population)

	Independently-Evaluated Pazopanib (N=290)	Investigator-Evaluated Pazopanib (N=290)
Number (%) of Subjects, n	88	103
Duration of Response (weeks)		
1st Quartile (95% CI)	38.3 (25.7, 52.1)	29.9 (25.1, 36.4)
Median (95% CI)	58.7 (52.1, 68.1)	62.4 (42.0, 68.6)
3rd Quartile (95% CI)	82.1 (64.9, NC)	NC (67.7, NC)

Data Source: Table 7.41 and Table 7.42.
IRC: Independent review committee; NC: not calculable; RECIST: Response Evaluation Criteria in Solid Tumors.

In order to evaluate if the time of assessment influenced the PFS outcome, please provide the following information.

1. Time from randomization to each assessment, means and standard deviations:

Table 1. Mean and SD (in months) of Time to Assessment from Randomization

Time from randomization to	# (%)		Mean (SD)	
	Pazopanib N=	**Placebo N=**	**Pemetrexed N=**	**Placebo N=**
1st Assessment (cycle # ??)				
2nd Assessment (cycle # ??)				
3rd Assessment (cycle # ??)				
4th Assessment (cycle # ??)				
5th Assessment (cycle # ??)				
6th Assessment (cycle # ??)				
…				

2. Log-rank test to test if cumulative percentages were equal.

Table 2. Median (in months) of Time to Assessment and Log-rank Test

Time from randomization to Assessment	**Pazopanib N=**	**Placebo N=**	**Log-rank Test**
1st Assessment (cycle # ??)			
2nd Assessment (cycle # ??)			
3rd Assessment (cycle # ??)			
4th Assessment (cycle # ??)			

5th Assessment (cycle # ??)			
6th Assessment (cycle # ??)			
…			

3. Please provide datasets and programs for the analyses above.

Thank you,

Kim J. Robertson
Consumer Safety Officer

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

/s/

Kim Robertson
3/25/2009 11:24:11 AM
CSO
25March09 Statistical Requests for Information

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-465

GlaxoSmithKline
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Attention: Ellen S. Cutler
Senior Director, US Regulatory Affairs
Oncology

Dear Ms. Cutler:

Please refer to your new drug application (NDA) submitted December 18, 2008 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Votrient® (pazopanib hydrochloride) Tablet, 200mg; 400mg, received December 19, 2008.

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

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

2. The Integrated Summary of Safety included in your application did not include safety data from all of the pazopanib monotherapy studies. We communicated this concern to you on February 9, 2009. We have reviewed your response dated February 13, 2009. We are satisfied with your proposals as outlined; however, we have the following comments, as listed in the table below, concerning the proposed submission of additional data.

Study ID	Number of Patients in the Current ISS Dataset	Number of Patients Reported in the Overview of Pazopanib Clinical Program	Difference in the Number of Patients	Issues To Be Addressed in your Proposed Submission
VEG 20002	138	142	4	Ensure that all patients are included your submission
VEG 105290	0	35	N/A	Include all patients enrolled
VEG 105430	0	36 (41 in your response)	N/A	Include narratives of all SAEs.
VEG 105281	60	119	59	Ensure that all patients, at all doses, are included in your submission

Study ID	Number of Patients in the Current ISS Dataset	Number of Patients Reported in the Overview of Pazopanib Clinical Program	Difference in the Number of Patients	Issues To Be Addressed in your Proposed Submission
VEG 107200	0	22	N/A	Include all patients enrolled
VEG 109609	0	6 (15 in your response)	N/A	FDA notes that the study was terminated for reasons unrelated to safety and that no datasets will be submitted. Submit narratives for patient deaths, discontinuations and SAEs.
VEG 109693	0	11	N/A	Include all patients enrolled
Study NCI8063	n/a	(27 in your response)	N/A	FDA reviewers note that data from this study of patients with mild-moderate hepatic dysfunction will be available in July, 2009.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

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

If you have any questions, call Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Robert Justice
2/23/2009 05:20:02 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-465

NDA ACKNOWLEDGMENT

GlaxoSmithKline
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Attention: Ellen S. Cutler
Senior Director, US Regulatory Affairs
Oncology

Dear Ms. Cutler:

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

Name of Drug Product: Votrient® (pazopanib hydrochloride) Tablet, 200 mg; 400 mg

Review Priority Classification: Standard

Date of Application: December 19, 2008 (Submitted December 18, 2008)

Date of Receipt: December 19, 2008

Our Reference Number: NDA 22-465

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 17, 2009 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be October 19, 2009.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We acknowledge receipt of your request for a waiver of pediatric studies for this application and have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

If you have any questions, call Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Kim Robertson
2/20/2009 03:47:15 PM
Acknowledgement Letter Pazopanib NDA 22-465

From: ellen.s.cutler@gsk.com
Sent: Monday, February 09, 2009 1:29 PM
To: Skarupa, Lisa
Cc: Cross Jr, Frank H; Robertson, Kim
Subject: Re: Clinc Pharm Comments and Requests NDA 22465

Hello Lisa,
Just confirming that I have received your request and am targeting having a response to you by the end of the week.
Regards,
Ellen

Ellen Cutler
GlaxoSmithKline
Regulatory Affairs
610-917-6823

"Skarupa, Lisa" <Lisa.Skarupa@fda.hhs.gov>

09-Feb-2009 06:46

To ellen.s.cutler@gsk.com
cc "Cross Jr, Frank H" <frank.crossjr@fda.hhs.gov>, "Robertson, Kim" <kim.robertson@fda.hhs.gov>
Subject Clinc Pharm Comments and Requests NDA 22465

Good morning Ellen,

On behalf of Kim Robertson, I am forwarding to you the following Clin.Pharm. comments and requests for NDA 22465:
1. As discussed during the post-submission meeting, please submit available reports and datasets of pooled dose/exposure-response analyses regarding liver enzymes and hypertension from studies included in the population PK analysis (Studies MD1103367, VEG10003, VEG10006, VEG10005, VEG10007, VEG102616, VEG105192, and VEG20006)

2. If available, please submit data from completed or ongoing trials regarding mutations in genes associated to pazopanib mechanism of action that may affect pazopanib efficiency.

3. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Sincerely,
Lisa
Regulatory Project Manager

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

/s/

Kim Robertson
2/11/2009 01:45:56 PM
CSO
Feb 9 Response from Ellen re: Clinpharm Comments and Requests

Fax

DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Ms. Ellen S. Cutler	From; Kim J. Robertson
Fax: (610) 787-7062	Fax: 301-796-9845
Phone: (610) 917-6823	Phone: 301-796-1441
Pages, including cover sheet: 1	Date: 21 January 2009

Re: NDA 22-465: Pazopanib Presentation to CDER's Division of Oncology

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

- Dear Ms. Cutler:

Some time ago, the Center for Drug Evaluation and Research's Division of Drug Oncology Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last approximately one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Oncology Drug should approve their NDA/sNDA.

GlaxoSmithKline has been granted a Sponsor Presentation date of **Friday, January 30, 2009; 11:00AM-12:30PM**. You will need to report to 10903 New Hampshire Avenue, Silver Spring, MD, 20903; White Oak Building #22. Please arrive aprox. 30 mins. prior to your presentation time, so that all GSK attendees can be processed by our security staff.

Please note:

1. If any of the attendees to our meeting are non-US citizens, you will need to fill out the attached form for each person. Please e-mail the completed form(s) to me no later than **Friday, January 23, 2009**. Security may not allow the individual(s) in the building if the forms are not sent in time. The non-US citizens will need to show their Passport or other national identity source document (i.e. a document which allowed the immigration into the US) as identification when entering the building at FDA.

2. Only FDA owned equipment and computers can be used on FDA equipment. If you want to use your own laptop, you will have to bring your own projector. Sponsor supplied flash drives, thumb drives, or CDs are not allowed on FDA computers. If you want to use slides during our meeting, you must send me an e-mail with the slides, hand out paper copies of your slides, or use your own computer and projector.

Regards,

Kim J. Robertson
Consumer Safety Officer

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	GlaxoSmithKline
MEETING START DATE AND TIME	January 30, 2009 11:00AM
MEETING ENDING DATE AND TIME	January 30, 2009 12:30PM
PURPOSE OF MEETING	Sponsor Presentation
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	White Oak Facility Building 22, Conference Room 1419
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Kim Robertson Consumer Safety Officer

	Division of Drug Oncology Products, HFD-150 Building 22, Room 2123 301-796-1441
ESCORT INFORMATION (If different from Hosting Official)	Same

Please allow a minimum of ten (10) business days in submitting information for processing. Upon completion please email the form(s) to: OSO-FOREIGN VISIT (Global Address Book) For late notice visits and other questions please contact:

Sebastian Malvagna (301) 827-7035 Sebastian.Malvagna@fda.hhs.gov
Steven Russell (301) 827-7038Steven.Russell@fda.hhs.gov

January 21, 2009

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

/s/

Kim Robertson
1/21/2009 03:39:37 PM
CSO
21January09 Sponsor Presentation Information - Pazopanib NDA 22-465

MEMORANDUM OF TELECON

MEETING DATE:	September 14, 2009
TIME:	1500-1600 ET
LOCATION:	White Oak Building 22/Rm 1421
APPLICANT:	GlaxoSmithKline
APPLICATION:	NDA 22-465
DRUG NAME:	Votrient (Pazopanib) Tablets
TYPE OF MEETING:	Teleconference
MEETING CHAIR:	Richard Lostritto, Ph.D.
MEETING RECORDER:	Deborah Mesmer

FDA ATTENDEES:

Sarah C. Pope, Ph.D., Branch Chief
Terrance Ocheltree, Ph.D., R.Ph. Pharmaceutical Assessment Lead
Deborah Mesmer, M.S., Regulatory Health Project Manager-Quality
Sharmista Chatterjee, Ph.D., Review Chemist
Brian Rogers, Ph.D., Review Chemist
Richard T. Lostritto, Ph.D., Division Director
John Duan, Ph.D., Biopharmaceutics
Patrick J. Marroum, Ph.D., Expert BioPharmaceutics
Meiyu Shen, Ph.D., Mathematical Statistician
Yi Tsong, Ph.D., Supervisory Mathematical Statistician
Heather Payton, Pharmacy Intern

EXTERNAL CONSTITUENT ATTENDEES:

GSK

Manish Gupta, PhD, Manager, Pharmaceutical Development
Tom Wrzosek, Manager, Statistics & Programming
Choon Oh, PhD, Director, Product Development Group
Michael Wilkins, PhD, Director, Global Manufacturing & Supply
Susan Spooner, PhD, Assistant Director, CMC Regulatory Affairs
Sherry Watson, Director, CMC Regulatory Affairs
Chi Li, Project Owner, Global Manufacturing & Supply
Ted Chen, PhD, Manager, Analytical Sciences
Yan Sun, PhD, Investigator, Physical Properties
Dharmesh Bhanushali, PhD, Investigator, Synthetic Chemistry
Michael McGuire, PhD, Team Manager, Synthetic Chemistry
Matthew Henry, PhD, Investigator, Product Development Group
Jeffrey Brum, PhD, Manager, Physical Properties
Norma Collinsworth, Director, CMC Regulatory Affairs
Andrew Scott, PhD, Director, Pharmaceutical Sciences
Theodora Kourti, PhD, Director, Pharmaceutical Sciences

BACKGROUND:

FDA sent Biometrics and BioPharm Comments to GSK on September 10, 2009, for discussion at the teleconference meeting on September 14, 2009. This is a Quality by Design application.

MEETING OBJECTIVES:

To discuss review comments relating to dissolution criteria, comparability protocol, and design space

DISCUSSION POINTS AND AGREEMENTS REACHED:

FDA Comment 1: There is excessive variability in dissolution performance for the 91 lots of drug product data provided. Of these 91 lots, 17 % failed a pair wise comparison of dissolution profiles using the f2 metric. This suggests a failure of bioequivalence between lots. Tighten your dissolution specification so as to be commensurate with a level of quality which is less likely to release batches which are potentially bio-inequivalent (e.g., (b) (4)). Alternatively and at your discretion, you may perform a bioequivalence study with batches at the highest and lowest extremes of dissolution performance to support that your currently proposed specification will not release drug product batches which are bio-inequivalent.

Meeting Discussion: GSK acknowledged FDA comments and will accept the dissolution specification, of Q = (b) (4) FDA stated that if GSK shows in vivo bioequivalence, they can widen the specification.

(b) (4)

FDA Comment 3: There is better agreement between observed versus predicted using the mixed effect model when the predicted is greater than (b) dissolved. As you reevaluate the design space, we recommend that you use dissolution criteria that include a predicted value of at least (b) dissolved.

Meeting Discussion: See Discussion for Comment 4.

FDA Comment 4: We note that all two-way interactions, three-way interactions, and the quadratic terms are all statistically significant in determining the amount dissolved. Therefore, it is impossible to establish the design space as a simple rectangle in this case. The design space of work needs to be in a narrower range (e.g., 3500 ± 10%). The range in water content needs to be in a correspondingly smaller range as well.

Meeting Discussion for Comments 3 and 4: FDA stated that GSK should (b) (4) GSK should propose the new space in an amendment, which FDA noted will be a major amendment. This could result in a clock extension. GSK responded that they have performed this calculation and will try to submit an amendment by Wednesday, September 16, 2009. GSK expressed concern about a clock extension, FDA responded that FDA can't answer further until they see the submission. FDA requested that GSK re-work their design space and submit based on individual data. GSK suggested that they could withdraw the design space and submit in place only the proven acceptable ranges. FDA acknowledged that is one path. FDA stated further that they appreciate GSK's design space approach and would like to see GSK follow the QbD approach. It is GSK's choice, and it is a review issue. Either way, FDA can't say if both approaches wouldn't be major amendments. FDA encouraged GSK to continue the design space study. FDA emphasized that there could be other issues for the drug not discussed at this meeting.

FDA confirmed that GSK may remove their design space and submit post-approval, and again encouraged GSK to continue their QbD approach.

GSK requested a post-approval meeting with stats, chemistry, and biopharm to discuss design space.

GSK stated that they will consider options and will likely withdraw the design space and submit accepted ranges while pursuing the design space post-approval. GSK acknowledged that FDA can't guarantee the submission won't be a major amendment.

ACTION ITEMS:

GSK will amend their application by September 16, 2009.

GSK will request a post-approval meeting with stats, chemistry, and biopharm to discuss design space.

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

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

/s/

DEBORAH M MESMER
10/21/2009

MEMORANDUM OF TELECON

DATE: October 19, 2009

APPLICATION NUMBER: NDA 22-465; VOTRIENT™ (pazopanib hydrochloride) Tablets, 200 mg, 400 mg

BETWEEN:

Name: Ellen S. Cutler
Phone: (610) 917-6823
Representing: GlaxoSmithKline

AND

Name: Kim J. Robertson
Division of Drug Oncology Products, HFD-150

SUBJECT: Confirmation of sponsor receipt of action letter.

A copy of the official action letter was e-mailed to Ellen S. Cutler on October 19, 2009, at 5:31PM. On October 19, 2009, at 5:48PM, Ellen S. Cutler called to confirm the receipt of the action letter.

{See appended electronic signature page}

Kim J. Robertson
Project Manager

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

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

/s/

KIM J ROBERTSON
10/19/2009
T-con Confirmation of Sponsor Receipt of Votrient Approval Letter; NDA 22-465

FDA ATTENDEES:

Richard Pazdur, M.D., Office Director
Robert L. Justice, M.D., Division Director
Anthony Murgo, M.D., Division Associate Director
V. Ellen Maher, M.D., Clinical Team Leader
Yang-Min (Max) Ning, M.D., Clinical Reviewer
John Senior, M.D., Clinical Reviewer, Office of Surveillance and Epidemiology
Sharmista Chatterjee, Ph.D., CMC Reviewer
Brian Rogers, Ph.D., CMC Reviewer
Robeena Aziz, Ph.D., Pharmacology/Toxicology Reviewer
Whitney Helms, Ph.D., Pharmacology/Toxicology Reviewer
Elizabeth Donohoe, M.D., Clinical Reviewer, Office of Surveillance and Epidemiology
Bahru Habtemariam, Ph.D. Clinical Pharmacology Reviewer
Brian Booth, Ph.D., Clinical Pharmacology Director
Shenghui Tang, Ph.D., Acting Statistical Team Leader
Yu-Ling Chang, Ph.D., Statistical Reviewer
Sandra Griffith, Regulatory Project Manager, Office of Surveillance and Epidemiology
Kim Robertson, Consumer Safety Officer

GSK ATTENDEES:

Ben Suttle, Clinical Pharmacology
Christopher Abissi, Clinical Safety and Pharmacovigilance
Colin Spraggs, Pharmacogenomics
Ellen Cutler, Regulatory
Lauren McCann, Statistics
Lini Pandite, Clinical Development
Ohad Amit, Statistics
Paolo Paoletti, Oncology Development
Rafael Amado, Medicines Development Leader
Robert Watson, Regulatory
Vicki L Goodman, Clinical Development

NDA 22-465; Votrient (pazopanib) Tablets August 21, 2009
Adv. Renal Cell Carcinoma
Questions asked of FDA Prior to GSK's August 24 Sponsor Presentation

BACKGROUND:

GlaxoSmithKline has submitted an NDA for VOTRIENT (pazopanib) Tablets; indicated for the treatment of patients with advanced renal cell carcinoma. GlaxoSmithKline will be meeting with the FDA at the behest of the Oncology Division to discuss the hepatotoxicity of pazopanib and the possible use of a Medication Guide. These discussions are being held prior to the sponsor's August 24, 2009 presentation with the Agency and prior to the October 5, 2009 ODAC.

Specific Questions

1. Does the FDA agree with the conclusions provided in the Liver Safety Overview, specifically our conclusions regarding the Hy's Law cases, our assessment of the hepatic events, and the overall benefit risk conclusions?

FDA Response: The purpose of this meeting is for you to address the issue of hepatotoxicity with pazopanib. We will not be able to answer your questions until we have completed our review and the application has been discussed at ODAC.

2. Are there further analyses that would aid the review?

FDA Response: Please provide an analysis of any cases of Hy's Law or more serious hepatic injury from your combination studies.

Please provide a case narrative for patient #152 (VEG107769).

3. What level of detail with regard to the liver safety overview would be appropriate for presentation to the ODAC?

FDA Response: This is a serious safety issue which should be adequately addressed in your ODAC presentation.

4. Does the FDA agree that a Medication Guide may be the only component of the REMS?

FDA Response: See our response to Question #1.

5. Are there other areas of focus under consideration for presentation to the ODAC?

FDA Response: The focus of the ODAC meeting will be a discussion of the risk/benefit ratio in the proposed patient population.

Additional Comment:

Please clarify whether your ongoing trials are requiring LFTs at Week 4.

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

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

/s/

VIRGINIA E MAHER
10/07/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 65,747

GlaxoSmithKline
Attention: Susan P. Spooner, Ph.D.
Assistant Director, CMC Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. Spooner:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor).

We also refer to the meeting between representatives of your firm and the FDA on Friday, June 13, 2008. The purpose of the meeting was to discuss pre-NDA Chemistry, Manufacturing and Controls issues and Quality by Design elements.

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

If you have any questions, call me at (301) 796-4023.

Sincerely,

{See appended electronic signature page}

Deborah Mesmer
Regulatory Health Project Manger for Quality
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG OUALITY ASSESSMENT

Sponsor Name:	GlaxoSmithKline
Application Number:	IND 65747
Product Name:	Pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor)
Meeting Type:	Type B
Meeting Category:	Pre-NDA CMC (Quality by Design)
Meeting Date and Time:	Friday, June 13, 2008 1030 – 1200 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package:	May 12, 2008
Meeting Requestor:	Susan Spooner, Ph.D., Assistant Director, CMC Regulatory Affairs
Meeting Chair:	Ravi Harapanhalli, Ph.D, Branch Chief, ONDQA
Meeting Recorder:	Deborah Mesmer, Project Manager - Quality

FDA ATTENDEES:

CENTER FOR DRUG EVALUATION RESEARCH

Office of New Drug Quality Assessment

Michael M Folkendt, Supervisory Project Manager
Debasis Ghosh, Ph.D., Review Chemist
Ravi Harapanhalli, Ph.D., Branch Chief
Ravindra Kasliwal, Ph.D., Review Chemist
Deborah Mesmer, Project Manager – Quality
Christine Moore, Ph.D., Deputy Director (Acting)
Moheb M. Nasr, Ph.D., Office Director

EXTERNAL ATTENDEES:

GLAXOSMITHKLINE

Michael McGuire, Ph.D., Team Manager, Synthetic Chemistry
Tom Roper, Ph.D., Director, Synthetic Chemistry
Alireza Kord, Ph.D., Director, Analytical Sciences
Manish Gupta, Ph.D., Investigator, Pharmaceutical Development
Sherry Watson, Director, CMC Regulatory Affairs
Susan Spooner, Ph.D., Assistant Director, CMC Regulatory Affairs
Helen Fitton, Ph.D., Vice President, CMC Regulatory Affairs
Rosemary Leak, Ph.D., Vice President, Design for Manufacture
Andrew Harris, Site Validation Manager, Ware
Boon Kee Ong, Site Quality Director, Jurong
Andrew Scott, Director, Pharmaceutical Development
Al Kearney, Ph.D., Vice President, Pharmaceutical Development
John Upfield, Director, Dose Form Quality

1.0 BACKGROUND

GlaxoSmithKline (GSK) submitted IND 65747 on September 9, 2002, received on September 10, 2002, for pazopanib (GW786034 – VEGF Tyrosine Kinase Inhibitor) tablets proposed for the treatment of advanced Renal Cell Carcinoma. A Special Protocol Assessment: Stability was submitted on May 21, 2007 and received on May 22, 2007. Corresponding FDA comments were dated June 18, 2007. A Type B (follow-up to End of Phase 2/Pre-Phase 3) CMC Specific Meeting Request dated August 3, 2007, was received on August 6, 2007, with meeting briefing package received on August 24, 2007. Preliminary responses from the Agency were dated September 17, 2007; the meeting was subsequently cancelled. A pre-NDA CMC meeting request was submitted on April 7, 2008, and received on April 8, 2008. The meeting was granted on April 24, 2008, for a face-to-face meeting to be held on June 13, 2008, from 1030 to 1200 ET. The meeting briefing package was received on May 12, 2008. Preliminary responses were archived and shared with GlaxoSmithKline to promote an efficient discussion at the meeting scheduled for June 13, 2008. The minutes of the meeting discussion follow. These meeting minutes reflect the FDA's view at this time based on preliminary data and evaluation; they do not constitute a complete evaluation or commitment.

2.0 DISCUSSION

2.1 Opening Comments from Meeting Discussion

FDA emphasized that Quality by Design (QbD) is intended to enhance the efficiency of product and process and doesn't mean less filing or less testing. It is meant to ensure that higher product knowledge and process understanding with less reliance on end testing is the most effective way to assure quality. FDA suggested that a better approach is to

provide more time for FDA to respond to QbD questions. GSK is eager to increase communications before filing and will pursue such through Regulatory Project Manager for Quality. GSK acknowledged and thanked FDA for the preliminary responses.

2.2 Drug Substance

Question 1: GSK has demonstrated that for Stages 1 and 2 there are no process parameters linked to drug substance CQAs, therefore we propose not to register process parameters ranges or values for these stages in S2.2 in the NDA. For the remaining stages, only ranges for process parameters that are linked to drug substance CQAs will be registered. Does the Agency agree with this approach?

FDA Response to Question 1: The approach appears to be acceptable, provided adequate data from DOE and/or other studies are submitted (NDA) to indicate that variations in the (b) (4) processes will not impact purging of impurities (b) (b) (4) to acceptable TTC levels in the drug substance. Provide an overall description of the process in S2.2 section of the NDA.

Meeting Discussion: GSK acknowledged receipt of FDA's response and sought clarification regarding the acceptability of the process description. Risk management was discussed. FDA explained that the forthcoming CMC post-approval management plan could be useful to describe elements of risk management. The firm explained that they are using DOE to determine critical process parameters. Batch records are kept updated. FDA stated that GSK should evaluate risk and implement appropriate control strategies. Sponsor should understand that if less testing is proposed, more process understanding and supporting data is required. FDA pointed out that the approach proposed by GSK regarding the level of detail for stages 1 and 2 could allow them to use conditions outside of those which they have explored, which could negatively impact the concentration of these impurities. Therefore, the recommendation was to include the details of the DOE's and other supporting studies in support of the established design space.

Question 2(a): GSK proposes to control the genotoxic impurities (b) (4) (Stage 1 proposed registered starting material) specification rather than in the final drug substance. Does the FDA agree with the proposed control strategy?

FDA Response to Question 2(a): The approach appears to be acceptable provided the data in the NDA supports acceptability and would depend on the proposed control levels of each. We note that in the first step of the process you are using (b) (4) . Clarify whether you have seen any other materials derived from (b) (4) in the reaction leading to stage 1 product. If other (b) (4) compounds are formed they should be controlled appropriately.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 2(b): In addition, GSK proposes to discontinue testing for genotoxic impurity [redacted] (b) (4) for the current suppliers. GSK has tested for genotoxic impurity [redacted] (b) (4) in 20 batches of [redacted] (b) (4) (Stage 1 proposed registered starting material). The levels of [redacted] (b) (4) in all 20 batches were found to be below the Threshold of Toxicological Concern (TTC). In the event of a supplier change or change in synthetic route, GSK proposes to test for [redacted] (b) (4) in the first 5 batches of the [redacted] (b) (4) to ensure conformance to specification. Does the Agency agree with the above proposed control strategy?

FDA Response to Question 2(b): Your approach is acceptable, provided the Certificate of Analyses (COA) from the manufacturer for each batch contains the test results for [redacted] (b) (4) and you have adequate monitoring and change control.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 2(c): GSK proposes to control the genotoxic impurity [redacted] (b) (4) (Stage 1 proposed registered starting material) in [redacted] (b) (4) (Stage 1 intermediate) specification rather than in the drug substance. Does the FDA agree with GSK's proposed analytical control strategy?

FDA Response to Question 2(c): The approach appears to be acceptable, provided proposed control level and the supporting data submitted in the NDA are adequate. Provide data concerning impact of change in scale, equipment and operating conditions on this control.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 2(d): GSK proposes to control the genotoxic impurity [redacted] (b) (4) in [redacted] (b) (4) (Stage 3 proposed registered starting material) specification rather than in the drug substance. Does the FDA agree with GSK's proposed analytical control strategy?

FDA Response to Question 2(d): See response to 2 (c).

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 2(e): GSK proposes to control the genotoxic impurity [redacted] (b) (4) (Stage 2 intermediate/Stage 3 starting material) in [redacted] (b) (4) rather than in the drug substance. Does FDA agree with the proposed control?

FDA Response to Question 2(e): See response to 2 (c)

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 3: Does FDA agree with GSK's tests proposed for the proposed registered starting materials (b) (4)

FDA Response to Question 3:

- Add a test for appearance f (b) (4)
- Include specifications for assay for all three starting materials.
- If another catalyst is used in place c (b) (4) it should be appropriately controlled. Accordingly, reflect this as a footnote in the specifications for these starting materials.
- Starting material (b) (4) ir proposed limit o (b) (4) s not acceptable without additional justification. Higher levels of degradation of the starting material may lead to partially (b) (4) impurity as well as corresponding equivalent of (b) (4) therefore, the NDA should describe how these impurities would impact Stage 1 process.
- Starting (b) (4): Reduce the limit (b) (4) to not more than (b) (4) to accommodate (b) (4)
- Acceptability of the proposed limits for the impurities in the three starting materials and in the intermediates is contingent upon adequate data from the impurity fate analysis and purging studies.

Meeting Discussion: GSK acknowledged receipt of FDA's response. GSK requested clarification on the limit for impurities. FDA responded that non-genotoxic impurities in the starting material that are carried through to the drug substance, either as is or via chemical transformations, should not exceed (b) (4) GSK explained that starting material (b) (4) is the source of the process impurity generated in stage 3. FDA stated that GSK should provide qualification data for pharm-tox review showing the impurity does not affect patient safety. GSK agreed to include that in the NDA.

Post-meeting Note: As indicated above, qualification of impurities derived from impurities in the starting materials is not a desirable approach to the control of impurities in the starting materials. Qualification is largely allowable for impurities that are formed from the starting materials onwards in the synthesis and that cannot be controlled to below the qualification thresholds via synthesis and/or purification. Hence, every effort should be made to minimize the impurities in the starting material (b) (4) such that they or their transformed impurities are within the qualification threshold.

Question 4: Does FDA agree with the proposed tests for control of the intermediates (b) (4)

FDA Response to Question 4:

- The proposed test attributes are acceptable. The adequacy of the acceptance criteria for the attributes would be determined at the time of NDA review and would depend on the supporting data submitted in the NDA.

- Provide data on your process robustness (e.g., demonstration of purging of all impurities if they are present in their highest proposed levels together in a batch).

- Intermediat (b) (4): Tighten the limit o (b) (4). to not more than (b) (4). Provide data to assess whether the impurity (b) (4) has been found to be genotoxic or not (e.g., DEREK analysis, Ames test). If it is a positive genotoxin, then it needs to be controlled at no more than the TTC amount in the drug substance. If (b) (4) is not genotoxic, clarify whether it's purged to a level of no more than the unspecified impurity level in the drug substance. If not, it should be specified and should be limited to no more than (b) (4) in the drug substance.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 5(a): Does FDA agree with the tests proposed in the specification for drug substance?

FDA Response to Question 5(a):

- The acceptability of the acceptance criteria would be determined at the time of NDA review and would depend on the supporting data submitted in the NDA.
- The limits for residual solvents should be consistent with the ICH Q3C, the residual solvents impurities guidance.
- Data should be provided to support that manufacturing process if carried out within the proposed design space, would always provide the anhydrous, Form I of the drug substance. Additionally, justification for the presence of single polymorph should be provided based on kinetic and thermodynamic considerations and stability.
- Reduc (b) (4) o no more than (b) (4).
- Add a specification for heavy metals.
- In the specification table, include a footnote listing all the genotoxic impurities and indicate that genotoxic impurities are controlled upstream in the synthesis.

Meeting Discussion: GSK acknowledged receipt of FDA's response. GSK requested clarification on the specification for heavy metals in the drug substance. FDA stated our concern about potential heavy metals. Potential sources include starting materials, water, or equipment used during manufacturing. FDA recommended using a risk-based approach to evaluate potential for heavy metals due to potential changes in equipment or facilities and indicated that inclusion of a USP test for heavy metals is desirable.

Question 5(b): GSK proposes to carry out appearance, identity by IR, (b) (4) content by KF, and particle size testing on (b) (4) drug substance and all other tests may be conducted on either (b) (4) drug substance. Does FDA agree with this approach?

FDA Response to Question 5(b): This will depend on demonstration that (b) (4) process scale-up will not have significant effect on the degradation of the drug substance. Also, you need to have appropriate monitoring and change controls in place to reassess the effect of change in (b) (4) equipment, scale, etc. on drug substance degradation.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 6: Does the FDA have any further comment on the data packages to be presented in the original application and stability updates during NDA review for the drug substance?

FDA Response to Question 6: The stability update should be accompanied by the statistical analysis of stability indicating quality attributes as indicated in ICH Q1E. The stability updates are expected by the mid cycle for a timely assessment. Late submissions, if considered major, may not be reviewed or may result in the extension of clock.

Polymorphic changes should be evaluated during stability or adequate justification provided. Data should be provided on solubility and inter-conversion of polymorphic forms. Also provide a description of the BCS classification.

Provide data to indicate that there is no potential for microbial growth in the drug substance.

Provide data to assess whether the impurity (b) (4) (b) (4) listed in the Appendix I, have been found to be genotoxic or not (e.g., DEREK analysis, Ames test). If an impurity is a positive genotoxin, then it needs to be controlled at no more than the TTC amount in the drug substance.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 7(a): Based on the understanding gained, GSK seeks the flexibility to change the HPLC method post-approval and to validate according to ICH Q2 with no regulatory action required, provided the conditions of the new method are included in the experimental design (Section 3.1.) and the method meets the method performance criteria listed above. Does the Agency agree with this approach?

FDA Response to Question 7(a): If the method meets the updated performance criteria indicated in response to Question 7 (c) and the changes are within the specified and approved design space, such a change and the updated regulatory method, with appropriate supporting data to show equivalence may be provided in the next annual report and/ or a special report.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 7(b): GSK seeks the flexibility to employ new HPLC columns outside of the experimental design to change the method post approval, if needed. In this case GSK will follow the method development process described in Section 3.1 to 3.4.3.2. The new method will be validated according to ICHQ2. The new method will meet the method performance criteria listed above (Section 3.5). GSK propose to implement this change with no regulatory action required. Does the Agency agree with this approach?

FDA Response to Question 7(b): Changes to the regulatory method outside of the specified and approved design space should be implemented according to the existing guidance and regulations on post-approval changes. However, you may implement an equivalent or a superior alternate method to the regulatory method in accordance with 21 CFR 314 (d) (2) (vii). Implementation of such method, method detail, validation and summary of supporting equivalency data should be submitted in the next annual report. Detail data should be available on site or provided upon request.

Meeting Discussion: GSK acknowledged FDA's response. See discussion for Question 10b.

Question 7(c): For the drug substance HPLC method, GSK proposes to register only the method performance criteria (Section 3.5) in the Analytical Procedures sections (m3.2.S.4.2/m3.2.P.5.2 of NDA) and to provide detailed method in the Method Validation Package (m3.2.R.2 of NDA). The drug substance method contained in the Method Validation Package is to aid in laboratory testing and would not be considered registered detail. Does the Agency agree with this approach?

FDA Response to Question 7(c): The section P3.5 of the NDA should propose a regulatory method for which full details need to be included. Appropriate design space information with ranges as supported by the DOE experiments may be incorporated in the method. Section P3.5 may indicate that changes within the approved design space may be implemented without prior notification. If changes to a regulatory method are made within the design space, such change and an updated regulatory method with appropriate supporting data may be provided in the next annual report and or a special report. Supporting validation data should be provided in the method validation section of the NDA.

With respect to the HPLC performance criteria, ICH Q2 recommendations should be followed. We suggest the following:

- Change the specificity criteria to reflect that "all impurities are resolved from each other and the drug substance peak with a resolution of greater than (b) (4)
- Incorporate a "tailing factor" criterion of no more than 1.5 (b) as part of the method performance criteria.
- Incorporate a criterion for minimum number of theoretical plates.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

2.2 Drug Product

Question 8(a): A (b) (4) model in combination with (b) (4) is predictive of Pazopanib Tablet dissolution, and a process control strategy is in place which ensures acceptable tablet dissolution. GSK requests feedback on the following:

1. Does FDA agree with the number of batches used to demonstrate comparability?
2. Does FDA agree with Acceptance Criteria for demonstration of comparability?
3. Based on the demonstration of comparability, does the FDA agree that, with the combined (b) (4) strategy in place, end product dissolution testing need not be performed at release?

FDA Response to Question 8(a):

- The number of batches should be justified based on statistical analysis of the data using a suitable confidence interval.
- The acceptance criteria for demonstration of comparability will be evaluated during the review of the NDA.
- If appropriately justified and implemented, the approach appears to be feasible. Parameters that effect dissolution, including material attributes should be understood and incorporated into the model and the model should be periodically updated and verified.

Meeting Discussion: GSK acknowledged receipt of FDA's response. GSK explained that they have developed a model, verified it, and looked at all aspects that could impact dissolution. These data will be provided to the NDA. GSK stated that the model is expected to predict at the 99% interval. FDA stated that we will need to see the details of the model including the acceptance criteria and how confidence intervals are determined. FDA would require a statistically valid approach. FDA will evaluate the goodness of model fit and its ability to predict dissolution. GSK should provide data for variation of process inputs, including material attributes. Both the model and process need to be verified. FDA recommended establishing a relationship between dissolution and disintegration and indicated that all measured in-process quality attributes related to dissolution be included in the model to increase its predictability. GSK stated that reviewing the model in the absence of change shows the model is working. FDA stated that validation is a continuous exercise, and encouraged the firm to put in place a system that would allow continual evaluation and updating of the model. GSK stated that it is helpful to have further informal discussions outside of written responses. FDA suggested that such a discussion could occur, at the discretion of the reviewer(s), prior to writing an Information Request letter.

Question 8(b): Control of tablet weight during [redacted] (b) (4) has been demonstrated. Does FDA agree that end product testing of Uniformity of Dosage Units by Weight can be replaced by in-process control during compression?

FDA Response to Question 8(b): The proposed approach is acceptable pending review of the data. Appropriate time point events, sample numbers, and acceptance criteria should be proposed for the routine in-process content uniformity control.

Meeting Discussion: GSK acknowledged receipt of FDA's response and sought clarification on appropriate time-points. GSK explained reject limits and stated that the relationship between compression force and weight would be provided in the NDA. GSK stated that compression force is a surrogate for weight. FDA inquired about comparison data for relationship between weight and compression over the length of a run. Consideration should be made for the physical properties of the blend that can vary over the course of a compression run and any factors affecting blend segregation should be adequately controlled. Milled granule size, blend homogeneity, bulk density and segregation were discussed. Continuous assurance is necessary and monitoring of the compression force and weight relationship over time is encouraged.

Question 8(c): Does the FDA agree that at-line [redacted] (b) (4) pazopanib content is suitable to replace the drug product content test currently performed by HPLC at release? Can the FDA provide feedback that the model development and validation approach is complete and suitable to support the use of the method for assurance of tablet content?

FDA Response to Question 8(c):

- If appropriately justified and implemented, the approach appears to be feasible. Parameters that effect content, including appropriate material attributes should be understood and incorporated into the model and the model should be periodically updated and verified.
- Evidence of correlation should be provided that the proposed IPC and its level can provide the required product quality attribute. Validation and sufficient sensitivity toward content variation should be shown.
- Provide clarification concerning what value will be used as the release content value for the batches placed on stability.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 8(d): Given the proposal for model development, does the FDA agree that at-line (b) (4) for the identification of pazopanib during compression is suitable to replace the drug product ID test currently performed by UV at release?

FDA Response to Question 8(d): The approach appears to be suitable, provided adequate data are provided in the NDA that support the correlation and method is adequately validated.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 8(e): Based on the summary of the AQL testing performed in process, does the FDA agree that end product description testing can be replaced at time of launch by in-process AQL testing?

FDA Response to Question 8(e): The approach may be viable provided an acceptable level of AQL is achieved and evidence is provided that product will not be affected between the time IPC is performed and the product is packaged.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 8(f): Since the drug substance is tested for impurities, and that GSK have confirmed that no degradation products are formed during the secondary process, GSK proposes not to test for impurities in the drug product at release. Does FDA agree?

FDA Response to Question 8(f): The approach may be acceptable, provided there is adequate data to show that there is no degradation during (b) (4) and during the drug product manufacture throughout the design space and that you clarify what values would be used as the release values for impurities in the stability batches.

You should show that the drug product excipients do not impact the stability characteristics of the drug substance.

The drug product impurity method should be adequately validated including that all the peaks are well resolved (resolutior (b) (4))

Clarify if the HPLC method for assay and impurities is the same. If so, you should consider evaluating impurities for the batches in a similar fashion as your proposal for content evaluation.

Meeting Discussion: GSK acknowledged receipt of FDA's response. GSK would like to provide a scientific explanation why impurities wouldn't be expected during manufacturing using a chemical mechanistic explanation. FDA is agreeable to that approach. FDA cautioned to keep in mind that local conditions during (b) (4) (e.g., surface temperature) are different than ambient and to provide data that no change occurs to excipients or drug substance to strengthen the argument.

Question 9: Does the Agency agree with the tests proposed in the specification for the drug product?

FDA Response to Question 9: (b) (4) content of the tablets may directly affect tablet hardness, friability, and other attributes and should be included in the specification and monitored during stability. Alternatively, adequate justification should be provided.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

2.3 General

Question 10(a): The briefing document contains an approach for Continuous Verification instead of the traditional three batch process performance qualification approach to assure the suitability of the drug substance and drug product commercial manufacturing processes. Is GSK's approach to using Continuous Verification for release of the first commercial batches and all subsequent batches acceptable to FDA?

FDA Response to Question 10(a): Your approach may be acceptable, provided relationships between material attributes, process parameters and CQA are well understood and documented in the NDA and appropriate controls at input stage and during the process are in place to assure that product of purported quality attributes is manufactured with high level of confidence at the commercial scale and on routine basis. Please refer to the Compliance Policy Guide entitled *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval* (CPG 7132c.08), March, 2004, for details and also seek additional feedback from the local district office of FDA.

Meeting Discussion: GSK acknowledged receipt of FDA's response. Discussion on this question was deferred for a future meeting with the Office of Compliance to discuss continuous verification. A possible venue for this may be the forthcoming CMC management plan, which is not yet finalized. The firm should understand that if less testing is proposed, more understanding and supportive evidence is required. More detail is required to support the different proposed processes in drug substance manufacturing. FDA stated that GSK should consider the potential consequences of using conditions outside of those which they have explored.

Question 10(b): Does the Agency endorse the CV approach outlined above for managing changes to elements of the manufacturing process, and then utilizing a Continuous Verification approach to ensure and demonstrate that material of appropriate quality is still routinely produced? GSK will provide such amendments via annual report instead of by supplement.

FDA Response to Question 10(b): Currently changes outside the approved design space should be implemented according to 21 CFR 314.70.

Meeting Discussion: GSK acknowledged receipt of FDA's response. GSK provided an example of change for discussion dealing with a change in the (b) (4) site, wanting to clarify if they could propose changes without a comparability protocol. FDA responded that until PMP is finalized, a comparability protocol may be appropriate. The comparability protocol would generally describe how the change will be handled post-approval, and it should include both the manufacturing comparison as well as testing based comparison.

Question 11: Does the FDA agree that the proposed stability data tables are in a suitable format for the NDA, and that no additional types of tables are necessary?

FDA Response to Question 11: The format of the table is acceptable. If a reported result is an average of multiple determinations, ranges and standard deviations should be provided. Statistical analysis of the stability data of stability indicating quality attributes to support the proposed expiration dating period should be provided as per ICH Q1E. A master table comparing results of different batches should be included.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 12: GSK propose that stability data from the annual batches will be generated and held internally for review at inspections rather than submitted routinely in the annual report. Any unexpected results would be notified to the Agency. Does the Agency agree with this approach?

FDA Response to Question 12: The tabular summary of the stability data for the annual batches should be submitted in the annual report. The detailed data can be held internally for review at the time of inspection or upon request.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 13: Due to the extensive Quality by Design information that will be provided in the NDA, GSK would like to discuss the possibility of a more interactive NDA review that could be beneficial to both GSK and FDA (i.e. informal teleconferences to respond to Agency concerns in real time, reviewer participation in PAI, etc.). Is FDA receptive to alternative approaches where appropriate?

FDA Response to Question 13: FDA appreciates your willingness to work toward enhanced communication. Your requests for additional meetings should be initiated with the project manager. Your offer for informal teleconferences will be communicated with the reviewer(s). Reviewer participation in PAI is encouraged and would depend on available time and resources.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

Question 14: GSK proposes submitting a single executed batch record for each drug product and strength (Pazopanib Tablets, 200 mg and 400 mg,) in the NDA, with all batch records being available at the sites or upon request. These batch records would be for stability batches representative of the proposed commercial process. Is this approach acceptable to the Agency?

FDA Response to Question 14: The submission of one executed batch record for 200 mg and one batch record for 400 mg, under the conditions specified in the question, is acceptable.

Meeting Discussion: GSK acknowledged FDA's response. No further discussion occurred during the meeting.

3.0 ISSUES REQUIRING FURTHER DISCUSSION FROM THE MEETING

GSK requested guidance on the next regulatory step. The NDA submission is anticipated for December 2008. FDA requested that the firm restate and submit specific questions for a meeting to include the Office of Compliance in the Fall of 2008.

4.0 ACTION ITEMS

There were no other action items from the meeting other than those specified in the discussion section above.

5.0 CONCURRENCE

{See appended electronic signature page}

Deborah Mesmer
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment III and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

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

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts distributed during the meeting for inclusion in the meeting minutes.

Linked Applications	Sponsor Name	Drug Name
IND 65747	GLAXOSMITHKLINE	VEGFR TYROSINE KINASE INHIBITOR

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

/s/

DEBORAH M MESMER
07/15/2008

RAVI S HARAPANHALLI
07/15/2008

Pre-NDA Meeting Questions

Indication (b) (4) (pazopanib) Tablets are indicated for the treatment of advanced renal cell carcinoma (RCC).

Dose: 800 mg (2 x 400 mg) orally once daily.

Studies supporting the proposed indication:

- Pivotal Study: VEG105192 is a pivotal Phase III, randomized, double-blind, placebo-controlled, international, multicenter study to evaluate the efficacy and safety of pazopanib in subjects with locally advanced and/or metastatic RCC.

  This study is being conducted under a Special Protocol Assessment (SPA) with the Agency.

- Supportive Study: VEG102616 is a Phase II, multicenter study to evaluate the efficacy and safety of pazopanib in patients with locally recurrent or metastatic RCC.

- Additional Study: VEG107769 is an open-label extension study to the Phase III VEG105192, including placebo crossovers to pazopanib.

Questions Related to the Non-clinical data

The non-clinical development program is summarized in section 2 of the briefing document. A table of the non-clinical studies to be included in the NDA submission is provided in Attachment 1.

Question 1: Does the Agency agree the nonclinical studies conducted are sufficient to support the planned NDA filing for use of pazopanib in advanced RCC patients?

FDA Response: The studies summarized appear sufficient for submission of an NDA. However, a final determination of their acceptability for filing will be a review issue.

Discussion Point: No further discussion was necessary.

Questions Related to Module 5 Clinical Studies

Study Reports

A table of all studies to be included in the NDA is provided in Attachment 2. The table includes a description of how the studies will be reported (full report, abbreviated report,

2-page summary). Section 4.2 provides an overview of our approach for these study reports.

A cut off date of 6 months prior to the anticipated NDA filing will be used for reporting of safety data from ongoing clinical studies.

Question 2: Does the Agency agree with the proposal for submission of clinical study results for completed and ongoing clinical studies?

FDA Response: Yes.

GSK Responded: *We would like to provide clarification of the format for the following study reports:*

VEG20002 (EORTC, Phase 2 sarcoma): EORTC statistical report instead of GSK report The EORTC statistical report reads as a statistical report with comprehensive set of tabular and graphical summaries but very limited methods section or text that accompanies results tables. Summarization of results is limited in text paragraphs. The tables and figures are used as stand-alone elements of the EORTC statistical report. GSK will provide a brief stand-alone text summary for this report.

VEG105281 (Ph 2 cervical - pazopanib vs lapatinib vs pazopanib+lapatinib): change from interim report to abbreviated interim report (focus on safety of pazopanib)

VEG10006 (Ph 1 pazopanib + lapatinib) change to abbreviated report (focus on safety)

Discussion Point: The Agency stated that this approach is acceptable.

VEG105192 Clinical Study Report and RAP

Question 3: Does the Agency agree with proposed approach for the clinical study report for the pivotal study VEG105192 described in section 4.2.1?

FDA Response: Your proposed approach appears acceptable.

Discussion Point: No further discussion was necessary.

Question 4: Does the Agency agree with the proposed sensitivity analyses for PFS? Does the FDA have any suggestions for additional sensitivity analyses?

FDA Response: Your proposed sensitivity analyses for PFS appear acceptable. We do not have suggestions for additional sensitivity analyses.

Discussion Point: No further discussion was necessary.

Question 5: Does the Agency agree with the proposed set of subgroup analyses?

FDA Response: Yes. The proposed exploratory subgroup analyses are acceptable.

Discussion Point: No further discussion was necessary.

Question 6: What are the Agency's requirements in terms of imaging formats for this submission?

FDA Response: The Agency only accepts images in .pdf format. Please clarify what images you plan to submit. If you plan to submit radiologic images, please be aware that we do not accept them.

GSK Responded: *Requirements for imaging formats - - (b) (4). is the vendor for the imaging scans. We can have the independent reviewer select example images and provide the .pdf files (single shot, 2-dimensional compact "still"). Are there any specific elements of subject's images that you prefer to receive (e.g., presentations of response, progression)? Alternatively, (b) (4) can provide a workstation to display images electronically. These are .img files (processed at . (b) (4) and provide full imaging with a query tool. This can be provided with the NDA submission or upon request during the review.*

Discussion Point: The sponsor should submit the NDA and for those cases that seem problematic, the Agency may request .pdf files.

<u>Scope and Format on Datasets</u>

The proposal for submission of datasets is provided in Section 4.2.2.

Question 7: Does the Agency agree with the proposal regarding the scope and format of the datasets?

FDA Response: Yes.

All clinical pharmacology study reports should be submitted in pdf file format and the raw PK data sets for these studies should be submitted in SAS transport files. The following datasets should be submitted in support of the population PK analysis:

- **All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been <u>excluded from the analysis</u> should be flagged and maintained in the datasets.**
- **Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).**

- **A model development decision tree and/or table which gives an overview of modeling steps.**

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Case Report Forms and Narratives

The proposals for submission of case report forms (CRFs) and case narratives are provided in Section 4.2.4 and 4.2.3, respectively.

Discussion Point: No further discussion was necessary.

Question 8: Does the Agency agree with this approach?

FDA Response: Yes.

Discussion Point: No further discussion was necessary.

Integrated Summaries Data integration proposal

Efficacy

Question 9: Does the Agency agree that a link to direct the reviewer to the Summary of Clinical Efficacy in m2.7.3 is acceptable in lieu of a separate ISE?

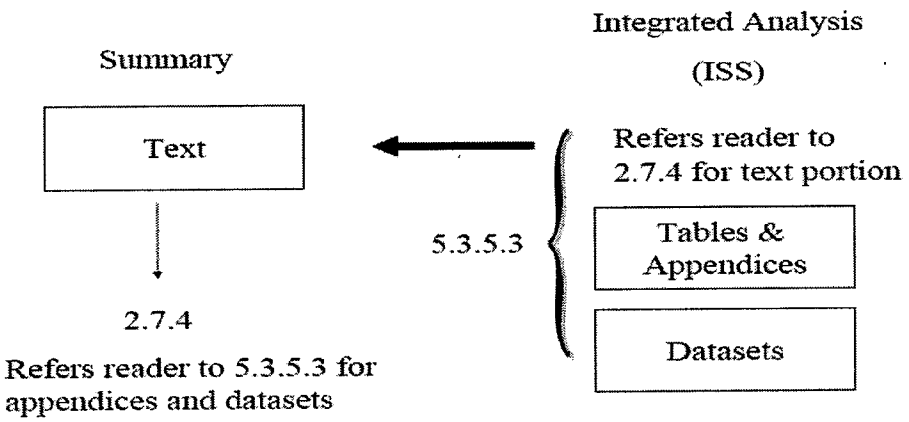
FDA Response: Yes.

Discussion Point: No further discussion was necessary.

Safety

As described in Section 4.2.5.1, we propose that a separate text portion of Integrated Summary of Safety and Integrated Summary of Efficacy is not helpful or needed. In accordance with the draft *Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* GSK proposes that a single text Clinical Summary of Safety will be sufficient, as illustrated by the figure below, taken from the draft guidance:

Figure 4



Question 10: Does the Agency agree with our proposals regarding integration and presentation of safety data?

FDA Response: No, we do not agree. You must submit an ISS in Module 5.

GSK Responded: *Further discussion / clarification regarding the need for an ISS. As with our recent NDA submissions for Tykerb and casopitant, we have found that inclusion of the integrated data in the SCS provides a more complete means to thoroughly assess the overall safety profile. As the integrated data are limited, primarily based on one pivotal study, VEG105192, and two additional studies conducted in patients with RCC (VEG102616 and VEG107769), we do not anticipate this would lead to a cumbersome SCS nor exceed the page limit for the Summary section.*
The proposed SCS (m2.7.4) would include analysis of (1) integrated safety data from the three pazopanib monotherapy studies in RCC and (2) integrated safety data from all completed pazopanib monotherapy studies. Thus, this module would contain analysis of all the integrated safety data that is possible with our studies.
Our proposal: Include the entire text of m2.7.4 in m5.3.5.3 in place of a traditional ISS.

Discussion Point: The Agency finds the sponsor's proposal acceptable.

Questions Related to Module 2 Clinical Summaries

Data Presentation - - Efficacy

Section 4.3.1 provides an overview of the efficacy data to be available in the NDA and describe our plans for the presentation of efficacy data in the Summary of Clinical Efficacy (m2.7.3) of the NDA.

Question 11: Does the Agency agree with the proposed presentation of efficacy data?

FDA Response: Yes.

Discussion Point: No further discussion was necessary.

Data Presentation - - - Safety

Section 4.2.5.1 provides an overview of the safety data to be available in the NDA and describe our plans for the presentation of safety data in the Summary of Clinical Safety (m2.7.4) of the NDA, including the pooling of safety data. Appendix 4 provides the tables and figures to be included in the Summary of Clinical Safety.

Question 12: Does the agency agree with the proposed presentation of safety data?

FDA Response: Your presentation appears acceptable. Please see our response to Question #10.

Discussion Point: No further discussion was necessary.

Questions Related to 4-month Safety Update

Question 13: Does the Agency agree with the proposed approach for the 4-month safety update described in Section 4.4?

FDA Response: Yes.

Discussion Point: No further discussion was necessary.

Questions Related to the Format of the NDA

Proposal for eCTD

The NDA will be submitted in eCTD format according to the April 2006 "Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications".

We commit to submit any amendments (or responses to FDA's requests during the review cycle) with an eCTD backbone file, with the supporting data located at the appropriate level of granularity, appropriate meta-data.

Proposed eCTD Specifications and File Formats

Specifications

GSK will submit the eCTD conforming to the following specifications and file formats:

- ICH M2 eCTD: Electronic Common Technical Document Specification version 3.2 (2004-02-04)
- US FDA eCTD Backbone Files Specification for Module 1 Version 1.3 (2006-12-13)
- US FDA's Implementation of STF DTD v2.2 (v2.6 / 2005-07-25)
- Portable Document Format Specifications (v1 / 2005-04-18)

Study Data

Blank Case Report Forms (CRFs) and Data Definition Files will be provided with the datasets. The data definition file will be provided as a PDF.

Datasets

We will be submitting all required datasets in the format specified in the January 1999 guidance entitled "*Providing Regulatory Submissions in Electronic Format – General Considerations*" rather than the Study Data Tabulation Model (SDTM) structure. These will include datasets for all of the pazopanib clinical studies. Annotated Blank Case Report Forms (aCRFs) and Data Definition Files will be provided with the datasets. The data definition file will be provided as a PDF.

Case Report Forms

As this is an eCTD no CRF Tables of Content will be provided.

Question 14: Does the Agency agree that the proposed specifications and file formats meet the requirements for an eCTD?

FDA Response: Yes.

Discussion Point: No further discussion was necessary.

Questions related to Module 1 - Administrative and Regulatory Information

Labeling

Because Study VEG105192 provides data that are placeb0-controlled, we propose that the primary efficacy and safety analyses from this trial should be detailed in labeling. This is further discussed in the introduction to Question 7. Additional text will describe additional analyses based on pooled safety data from other studies as appropriate.

Question 15: Does the Agency agree with the proposed approach for the labeling?

FDA Response: This will be a review issue.

Discussion Point: No further discussion was necessary.

Risk Management Plan

GSK's approach for the risk management plan is described in Section 4.5.2.

Question 16: Does the Agency agree with the use of the EURMP format for the presentation of the Risk Management Plan in m1.16?

FDA Response: This will be a review issue.

GSK Responded: *Confirm that EURMP format is acceptable for m1.16 Risk Management Plan.*

Discussion Point: The sponsor will submit a trial TOC for review and upon submission the Agency will determine if the sponsor's EURMP proposal is acceptable for final submission.

Question 17: Are there other concerns that the Agency considers appropriate for inclusion in the Risk Management Plan?

FDA Response: Please see our response to Question #16.

Discussion Point: No further discussion was necessary.

Financial Disclosure

GSK has determined that studies VEG105192, VEG102616 and VEG107769 are covered studies under 21 CFR Part 54. Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and, if applicable, Form 3455 (Disclosure Financial Interests and Arrangements of Clinical Investigators) will be included in the NDA submission for these studies

Question 18: Is this proposal acceptable as a means of complying with 21 CFR Par 54 and 314.500(k) for financial disclosure?

FDA Response: Yes, your proposal appears acceptable.

Discussion Point: No further discussion was necessary.

Pediatric Waiver

In the Division's June 26, 2007 draft responses to GSK's questions in our June 1, 2007 briefing document pertaining to the development program of pazopanib in patients with RCC, the Division agreed that a request for a full waiver under 505(a) of the Act for the requirement under the Pediatric Research and Equity Act (PREA) would be appropriate for the RCC indication.

Question 19: Does the Agency continue to believe that the proposed indication qualifies for a waiver of the pediatric rule?

FDA Response: You must request a waiver at the time of the NDA submission.

Discussion Point: No further discussion was necessary.

General

Question 20: Tradename preclearance Please advise regarding the current status of the proprietary name request submitted on October 18, 2007 (sn 0512).

FDA Response: We are still working on the tradename preclearance. Once we have a final review from DMEDP (formerly DMETS), we will notify GSK.

Discussion Point: No further discussion was necessary.

Question 21: Does the FDA agree that the proposed content and format of the NDA as described in the briefing document provides the data in a reviewable format to meet FDA filing requirements?

FDA Response: The proposed content and format of the NDA appears acceptable.

Discussion Point: No further discussion was necessary.

ADDITIONAL COMMENT:

We note that your interim OS analysis will not have 70% of events at the time of filing. Please submit an update of your OS analysis at the time of the safety update submission. The final OS analysis should be submitted as per protocol.

GSK Responded: *re: survival analysis: We agree to provide an update of the OS analysis at the time of the 4 mo safety update. We do not plan to utilize any alpha spend for this analysis.*

Discussion Point: The Agency accepts this proposal with the understanding that no inferential statistics will be conducted at this time.

Meeting Adjourned:

12:22PM

Meeting Chair:

Ann Farrell, M.D.

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG OUALITY ASSESSMENT

Sponsor Name:	GlaxoSmithKline
Application Number:	IND 65,747
Product Name:	Pazopanib Tablets
Meeting Type:	Type C
Meeting Category:	Quality by Design: Chemistry, Manufacturing and Controls with the Office of Compliance
Meeting Date and Time:	Tuesday, November 4, 2008, 15:00 – 16:30 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	September 3, 2008

The following consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled as a **FACE-TO-FACE MEETING** on **TUESDAY, NOVEMBER 4, 2008,** between **15:00-16:30 ET** between **GLAXOSMITHKLINE**. and the Center for Drug Evaluation and Research/Office of New Drug Quality Assessment. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Deborah Mesmer, Regulatory Health Project Manager for Quality, (301) 796-4023). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. **Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.** If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager for Quality to discuss the possibility of including these for discussion at the meeting.

1.0 BACKGROUND

GlaxoSmithKline (GSK) submitted IND 65747 on September 9, 2002, received on September 10, 2002, for pazopanib (GW786034 – VEGF Tyrosine Kinase Inhibitor) tablets proposed for the treatment of advanced renal cell carcinoma. A CMC, Pre-NDA, Quality by Design meeting was held on June 13, 2008. As there was not sufficient time at the meeting to discuss questions related to continuous verification, FDA recommended that GSK request a follow-up meeting to be held in conjunction with the Office of Compliance. A Type B meeting request was submitted by GSK on September 2, 2008, and received on September 3, 2008, to discuss questions related to continuous verification. The meeting request was granted on September 17, 2008, as a Type C, face-to-face meeting to be held on November 4, 2008. The meeting briefing package was received on September 3, 2008. The purpose of this document is to provide preliminary responses to the questions contained in the meeting briefing package. These responses are being archived and shared with GSK to promote an efficient discussion at the meeting scheduled for November 4, 2008.

2.0 SPONSOR QUESTIONS AND FDA PRELIMINARY RESPONSES

Question 1: **Does the FDA agree that the summary provided in this document describes the essential components of continuous verification? Are there any additional components that the agency feel should be considered to underpin our proposals?**

FDA Response to Question 1: While the information provided in this package appears to contain the relevant components of an approach to process validation and on-going demonstration of a state of control with respect to the process, its acceptability would depend on full details. The full details are expected to be available to the inspectors at the time of inspection, and at that time they will be evaluated. GSK and ancillary facilities are expected to conform to all applicable CGMP requirements.

We note that GSK proposes to file the process performance criteria with the NDA. Clarify and be prepared to discuss what the process performance criteria are and how you intend to use them.

Question 2: **Is GSK's approach to using Continuous Verification to support the start of commercial manufacture acceptable to FDA?**

FDA Response to Question 2: The information provided in this package appears to contain the relevant components for this type of approach; however, adequacy of the approach cannot be determined until complete details are provided in a protocol. The acceptability of this approach would be determined during inspection.

GSK should establish a capacity to rapidly detect and respond to market experience should a defect be detected affecting a distributed batch during the PQ2 phase.

GSK should describe in the protocol their statistical treatment of data.

Question 3: **Is GSK's approach to using Continuous Verification for release of all subsequent batches acceptable to FDA?**

FDA Response to Question 3: Insufficient details are provided to make a preliminary assessment. We would like to understand better your approach to review and verification of models using univariate and multivariate tools. Also please explain your release testing program and your overall lot release strategy. What testing do you plan to do on a periodic basis versus every batch? **GMP regulations require some testing of each drug quality attribute before distribution.**

Question 4: **Does the FDA agree that the proposed changes to our quality systems to support the Continuous Verification approach to Performance Qualification are adequate?**

FDA Response to Question 4: It appears that the elements of your quality system discussed here could support these approaches. The success of the quality system approach will be determined at the time of inspection.

Question 5: **To better ensure that GSK meets Agency expectations we would appreciate feedback on the following aspects:**

a) Potential differences in process with respect to the PAI inspection and how GSK, the review division and the inspector could best work together throughout the review and inspection

FDA Response to Question 5a: It is expected that a team approach on the review of this NDA would be taken between reviewer, compliance officer and investigator. You can assist by having appropriate scientific, operational and regulatory personnel available during a PAI.

b) Expectations in terms of availability for dialogue through review and inspection and how communication between GSK, the reviewer and inspector may occur

FDA Response to Question 5b: See 5a. GSK may suggest approaches to enhance dialogue that differ from current procedures.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion at this time.

4.0 CONCURRENCE:

Deborah Mesmer
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment III and Manufacturing Science
Office of New Drug Quality Assessment

Rick L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name
IND 65747	GLAXOSMITHKLINE	VEGFR TYROSINE KINASE INHIBITOR

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

/s/

DEBORAH M MESMER
11/03/2008
Hand-signed. Entered for archival purposes.

Attachment 2
QUESTIONS TO FDA

CLINICAL PHARMACOLOGY

BACKGROUND:

The purpose of the current EOP2 meeting on 01-May-2008 is to discuss the clinical pharmacology program that will support an NDA for pazopanib. The clinical pharmacology program was also previously discussed with the sponsor during an EOP2 meeting on 14-Aug-2007 for the use of pazopanib monotherapy in the treatment of patients with advanced renal cell carcinoma (RCC) (b) (4)

The following questions pertain to the clinical pharmacology studies that are intended to support the initial registration of pazopanib for the treatment of patients with advanced renal cell carcinoma (RCC).

Pazopanib studies that will form the basis of the clinical pharmacology package are listed in Tables 16 and 17 and described in the briefing document.

1. As described in section 2.4, pazopanib is metabolized primarily by CYP3A4 with minor contributions from CYP1A2 and CYP2C8. Pazopanib inhibits several CYP450 isozymes, OATP1B1, and UGT1A1 in vitro. Pazopanib also is a substrate for BCRP and PGP transporters, and does not inhibit either transporter. Results from study VEG10007 will provide the effect of multiple dose administration of 800 mg pazopanib on the pharmacokinetics of probe substrates for the CYP1A2, CYP2D6, CYP2C9, CYP2C19, and CYP3A4 isozymes. Furthermore, results from study VEG10006 will provide the effects of concomitant administration of an inhibitor of CYP3A4, BCRP, and Pgp on the pharmacokinetics of pazopanib. Study VEG108925 is an ongoing study to investigate the activity, safety and pharmacokinetics of irinotecan and its active metabolite SN-38 (a substrate of OATP1B1 and UGT1A1) and cetuximab when administered with pazopanib.

   Does the FDA agree that the studies being conducted to obtain drug-drug interaction information for pazopanib are sufficient to support the initial registration of pazopanib monotherapy for treatment of patients with advanced or metastatic RCC?

   FDA Response: No.

   - **Lapatinib is not a strong inhibitor of CYP3A4. A study using an FDA recommended strong inhibitor (e.g., ketoconazole) should be conducted per the FDA guidance**

(http://www.fda.gov/cder/drug/drugInteractions/default.htm)

Discussion Point: The sponsor intends to submit the following to their NDA:

There are no clinical data with oral pazopanib administered concurrently with potent inhibitors of CYP3A4.

- ***Describe the data from the MD7110861 utilizing the eye drop formulation.***
- ***Data from VEG10006 demonstrate that administration of 1500 mg lapatinib (an inhibitor of Pgp and BCRP transporters and a weak inhibitor of CYP3A4) once daily with 800 mg pazopanib once daily resulted in an approximately 50% to 60% increase in mean pazopanib AUC(0-24), Cmax, and C24 compared to administration of 800 mg pazopanib alone. The relative contribution of the inhibition of Pgp, BCRP, and/or CYP3A4 by lapatinib on the bioavailability of pazopanib is not known. However, the results from VEG10006 suggest that 1500 mg lapatinib once daily increased absorption and/or decreased clearance of pazopanib.***
- ***An in vitro study using human liver microsomes (Study 04DMM010) demonstrate that the oxidative metabolism of pazopanib is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8.***

The FDA agreed to this plan. The appropriateness of the above studies will be a review issue.

- **Study VEG10007 may provide preliminary information to help guide the need for further in-vivo studies. You will need to provide information to validate the CYP substrate cocktail to ensure that sensitive probe substrates were included and that any interactions which may be present between the probe substrates have been investigated.**

Discussion Point: The Agency considers the cocktail study to be exploratory and results from the study will be a review issue.

- **Pazopanib is a potent CYP3A4 inducer. A multiple dose pazopanib study with a sensitive CYP3A4 substrate is recommended.**

Discussion Point: The sponsor stated that plasma midazolam data from VEG10007 showed no evidence of CYP3A4 induction after 17 days of 800 mg pazopanib once daily. The results of this study will also be a review issue.

2. Pazopanib is metabolized primarily by CYP3A4. Study NCI 8063 (b) (4) (b) (4) is evaluating the pharmacokinetics of pazopanib in patients with varying degrees of liver impairment (section 2.5.1). This study may be ongoing at the time of registration. GSK proposes to submit the final results of this study as a Phase 4 commitment as soon as available.

   Is this approach acceptable to the FDA?

FDA Response: We encourage you to submit the final study report and results of hepatic impairment study at the time of NDA submission. If a final study report is not feasible, a draft report summarizing the PK information at the time of NDA submission (or shortly after NDA submission) would be appropriate.

Discussion Point: The sponsor stated that it is anticipated that a draft report including PK data from the ongoing NCI study evaluating the effect of varying degrees of hepatic impairment on pazopanib will be available near the time of the NDA submission. The sponsor expects that it will include PK data on patients with mild and moderate hepatic impairment. Data on patients with severe hepatic impairment would follow when available. The Agency agreed.

3. A population pharmacokinetics analysis, as described in section 2.6, will be conducted with data from approximately 400 patients and healthy volunteers from 6 studies (4 Phase I studies, 1 Phase II study, and 1 Phase III study). Potential covariates that will be investigated include age, sex, body surface area, body weight, ECOG performance status, ethnicity, creatinine clearance, concomitant lapatinib administration, concomitant administration of potent CYP3A4 inhibitors or inducers, and concomitant administration of medications that affect gastric pH.

   Does the FDA agree with the proposed population pharmacokinetics analysis and covariates to be evaluated as part of the population pharmacokinetics analysis?

   FDA Response: Yes

   - **Please clarify the addition of concomitant administration of medications that alter gastric pH in your covariate analysis. If absorption is dependent upon pH, then a study with pazopanib and pH altering agents may be necessary.**
   - **Please submit the following datasets to support the population analysis:**
     - **All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been <u>excluded from the analysis</u> should be flagged and maintained in the datasets.**
     - **Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).**
     - **A model development decision tree and/or table which gives an overview of modeling steps.**
   - **For the population analysis reports we request that you submit, in**

addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Discussion Point: No further discussion was necessary.

4. The plan for assessing formulation bioavailability is described in section 2.7.

   Does the FDA agree with proposed approach?

   FDA Response: Yes

   Discussion Point: No further discussion was necessary.

5. The briefing document includes a table of clinical studies that will be included in the initial NDA to support an indication for pazopanib for the treatment of patients with advanced RCC.

   Does the FDA agree that the proposed package of clinical pharmacology studies will support the initial registration of pazopanib monotherapy for treatment of patients with advanced or metastatic RCC?

   FDA Response: Please see responses to questions 1, 2 & 3 above. In addition, you should submit all clinical pharmacology study reports in .pdf file and raw PK data sets for these studies in SAS transport files.

   Discussion Point: No further discussion was necessary.

ADDITIONAL DISCUSSION TOPIC:

The following comment was included in the Agency's Apr. 1, 2008 responses to GSK questions in our Mar 7, 2008 briefing document (regarding the pazopanib development in patients with advanced [redacted] (b) (4): You should conduct a study to address the effect of renal impairment on the PK of pazopanib. A reduced design study could be sufficient.
GSK clarification: Patients with mild and moderate renal impairment are included in pazopanib studies VEG102616 (Phase II RCC) and VEG105192 (Phase III RCC). We will evaluate the impact of renal impairment in the population PK analysis. Preliminary results from VEG10004 suggest that approximately 2% of a radiolabeled oral dose is recovered in the urine. Therefore, it is unlikely that renal impairment will alter pazopanib clearance. There are no plans for further

evaluation at this time. We believe that available data will be sufficient to guide labeling. The Agency agrees with the sponsor's plan.

Meeting Adjourned:

2:10PM

Meeting Chair:

Julie Bullock, PharmD.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-65747	GI-1	GLAXOSMITHKLINE	VEGFR TYROSINE KINASE INHIBITOR

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

/s/

JULIE M BULLOCK
10/02/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-465

GlaxoSmithKline
Attention: Susan P. Spooner, Ph.D.
Assistant Director, CMC Regulatory Affairs
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709

Dear Dr. Spooner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VOTRIENT™ (pazopanib hydrochloride) Tablet, 200 mg; 400 mg.

We also refer to the meeting between representatives of your firm and the FDA on July 1, 2009. The purpose of the meeting was to discuss GSK's responses to issues communicated by FDA in the May 7, 2009, CMC Information Request Letter.

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

If you have any questions, call me at (301) 796-4023.

Sincerely,

{See appended electronic signature page}

Deborah Mesmer
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment III and
Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG OUALITY ASSESSMENT

Meeting Date and Time:	July 1, 2009
Meeting Type:	Type C
Meeting Category:	CMC Guidance for NDA
Meeting Location:	10903 New Hampshire Ave Silver Spring, MD 20993
Application Number:	NDA 22-465
Product Name:	VOTRIENT™ (pazopanib hydrochloride) Tablet
Received Briefing Package	June 1, 2009 (part 1) June 5, 2009 (part 2)
Sponsor Name:	GlaxoSmithKline (GSK)
Meeting Requestor:	Susan P. Spooner, Ph.D.
Meeting Chair:	Sarah C. Pope, Ph.D.
Meeting Recorder:	Deborah Mesmer

FDA ATTENDEES:

CENTER FOR DRUG EVALUATION RESEARCH

ONDQA

Sarah C. Pope, Ph.D., Branch Chief
Terrance Ocheltree, Ph.D., R.Ph. Pharmaceutical Assessment Lead (Acting)
Deborah Mesmer, M.S., Regulatory Health Project Manager-Quality
Sharmista Chatterjee, Ph.D., Review Chemist
Brian Rogers, Ph.D., Review Chemist
Christine Moore, PhD, Deputy Director (Acting)
Richard T. Lostritto, Ph.D., Division Director
John Duan, Ph.D., Biopharmaceutics
Bogdan Kurtyka, Ph.D. Review Chemist
Patrick J. Marroum, Ph.D., Expert BioPharmaceutics

OFFICE OF COMPLIANCE

Richard L. Friedman, M.S., Director, DMPQ
Tara Gooen, Senior Regulatory Operations Officer, DMPQ
Giuseppe Randazzo, Project Management Officer
Vibhakar J Shah, Ph.D. Consumer Safety Officer, DMPQ

ORA

Rebeca Rodriguez, Consumer Safety Officer, ORA (phone)

BIOMETRICS

Meiyu Shen, Ph.D., Mathematical Statistician
Yi Tsong, Ph.D., Supervisory Mathematical Statistician

EXTERNAL ATTENDEES:

GSK

Manish Gupta, PhD, Manager, Pharmaceutical Development
Tom Wrzosek, Manager, Statistics & Programming
Paul Frake, PhD, Team Leader, Process Engineering
Choon Oh, PhD, Director, Product Development Group
Michael Wilkins, PhD, Director, Global Manufacturing & Supply
Andrew Scott, Director, Pharmaceutical Development
Susan Spooner, PhD, Assistant Director, CMC Regulatory Affairs
Sherry Watson, Director, CMC Regulatory Affairs
Chi Li, Project Owner, Global Manufacturing & Supply
Helen Birkett, Quality Manager, Global Manufacturing & Supply
Rosemary Leak, Vice President, Design For Manufacture, Pharmaceutical Development
Deena McManus, Quality Manager, Global Manufacturing & Supply
Helen Fitton, Vice President, CMC Regulatory Affairs
John Upfield, Head, Product Quality

1.0 BACKGROUND

GlaxoSmithKline submitted a New Drug Application for VOTRIENT™ (pazopanib) Tablets (formerly GW786034) on December 19, 2008, for the treatment of patients with advanced renal cell carcinoma (RCC). (b) (4)

GSK submitted a meeting request dated June 1, 2009, for a CMC teleconference meeting to reach agreement with FDA on their responses to this issue and others communicated in the May 7, 2009, information request letter. The meeting request contained the meeting

background materials for review, and GSK committed to send a second volume of the package by June 5, 2009 which was received on that date.

ONDQA granted the type C meeting request dated June 1, 2009, on June 9, 2009, and that teleconference meeting was scheduled for July 1, 2009.

FDA requested a teleconference with GSK which occurred on June 11, 2009. FDA issued a preliminary response letter on June 11, 2009, prior to the meeting requesting additional information regarding (b) (4) At the meeting, GSK requested to change the teleconference meeting scheduled for July 1, 2009, to a face-to-face meeting.

GSK agreed by phone on June 19, 2009, to submit the complete comparability protocols for dissolution and content by June 24, 2009, which were received on that date.

GSK submitted by email on June 30, 2009, slides for presentation at the July 1, 2009 meeting. FDA provided to GSK on July 1, 2009, slides for the meeting. Both slide sets will be addended to the minutes of the meeting discussion which follow. GSK also submitted minutes of the meeting by email on July 12, 2009.

2.0 GSK AND FDA SLIDES AND MEETING DISCUSSION

2.1 DISCUSSION AND COMMENTS BASED ON FDA SLIDES:

FDA Slide 2: FDA Response to GSK Proposal for Additional Drug Product Packaging Configuration

FDA Slide 2 Meeting Discussion: GSK had no questions. FDA emphasized that this agreement is an exception and is not considered to be an appropriate practice for future products because an original NDA submission is expected to be complete. This exception is contingent on there being no new DMFs that need to be reviewed or sites to be inspected and that the submission includes stand-alone stability data to support the new packaging configuration. GSK stated that they will have no new DMFs or new sites associated with this change and will submit the data as requested. FDA emphasized that a review is required.

FDA Slide 3: FDA Response to GSK Proposal to Add (b) (4) Drug Substance Container Closure

FDA Slide 3 Meeting Discussion: FDA noted that any cross-referenced DMF(s) will be reviewed as necessary, and any noted deficiencies may impact the overall NDA action. GSK stated that the response is acceptable.

FDA Slide 4: FDA Response to GSK Response 17 from June 5, 2009 Amendment (particle size acceptance criteria):

FDA Slide 4 Meeting Discussion: FDA countered GSK's response to Question 17, which proposed updated drug substance particle size acceptance criteria. FDA recommended that GSK adopt the following acceptance criteria for particle size to provide assurance of optimum dissolution rate and secondary processing ability as well as reflecting the range of particle sizes measured in pivotal clinical batches: (b) (4) GSK stated that the response is acceptable and that the proposed acceptance criteria for particle sized appeared reasonable, but that GSK also wishes to review the data before officially agreeing to the proposal.

FDA Slide 5: FDA Response to GSK Response 12 from June 5, 2009 Amendment

FDA Slide 5 Meeting Discussion: FDA stated that the proposal in the footnote in Table 1 of Section 3.2.P.3.4 is not consistent with the current regulatory mechanism. FDA stated that reporting changes via annual report is inconsistent with the current regulatory approaches for some potential changes (e.g., changes to PARs). FDA also stated that existing guidelines and cGMPs are applicable to QbD applications, and that these should continue to be used. FDA recommended that if downgrading of change reporting is sought that GSK submit a proposal for reduced reporting categories as a protocol in accordance with 21 CFR 314.70(e). The Comparability Protocol (CP) draft guidance is based on this regulation. GSK requested that, if a quality attribute is found to be outside of the PAR, GSK would write it up as a single event. FDA referred GSK to the existing guidance for change control.

FDA stated that GSK's definition of design space only including critical process parameters was not typical. GSK confirmed an understanding of FDA's request to include the QAs and QPPs, which are part of the control strategy, and also acknowledged that they are part of the design space.

2.2 DISCUSSION AND COMMENTS BASED ON GSK SLIDES

Dissolution Discussion

FDA requested clarification on Work (load x sec), and specifically requested confirmation regarding GSK's plan to put limits on two individual units, load and time. GSK clarified that Work is essentially an area under the curve using load and time and that they only plan to have limits on Work.

FDA asked if GSK has studied the impact of (b) (4) particle size distribution on (b) (4) particle size distribution (PSD). GSK stated that this information has been included in the NDA and that, in the range investigated, GSK did not observe an impact of (b) (4) PSD on (b) (4) PSD. The three QPPs of material feed rate, grinding gas pressure and Venturi gas pressure provide controls on the (b) (4) process and thus, controls on (b) (4) drug substance PSD. FDA stated that most submissions incorporate controls for (b) (4) particle size distribution and

controls on (b) (4) PSD. FDA recommended that GSK consider implementing controls for PSD on (b) (4) drug substance (considering that future (b) (4) drug substance batches may be outside of the range investigated).

FDA asked if GSK had studied different (b) (4) drug substance PSD (e.g., fines), since differences could result in differences in packing and may impact porosity of the tablets. GSK confirmed that investigations regarding the impact of (b) (4) drug substance PSD on drug product dissolution at pilot scale have been conducted and show the absence of any impact on dissolution at an optimized Work-based (b) (4) endpoint. GSK also noted that this information was included in the NDA. GSK confirmed that the effect of (b) (4) drug substance PSD on drug product dissolution was not performed at commercial scale, nor had they determined the effect of varying particle sizes on the results of their dissolution DOE investigation.

FDA asked if GSK had investigated inputs outside the range of what GSK studied in the DOE, e.g. for excipients. GSK stated that the impact of excipient functional characteristics, such as microcrystalline cellulose particle size and sodium starch glycolate viscosity (outside compendial specifications) has been evaluated. GSK has engaged the vendors by specifically requesting lots at the extremes of these characteristics. As described in the NDA, the use of (b) (4) endpoint, Work, accommodated this variability in microcrystalline cellulose particle size and sodium starch glycolate viscosity at commercial scale without any adverse impact on dissolution of the drug product.

FDA inquired about what would happen if items previously kept constant were varied (reference to GSK response to Question 3, Table 1, in briefing document submitted June 5, 2009), e.g. spray set-up. GSK stated that there is dedicated equipment and specific controls over that equipment. As an example to the specific query regarding spray set-up, the lance and nozzle are engineered for fail-safe orientation to provide an identical spray system for each batch. Any changes to equipment would be made via change control to ensure consistent performance throughout future batch manufacture.

FDA asked if the design space would remain the same if the axis was changed to "work". GSK confirmed that the design space remains the same (e.g., Figure 2 in Sec. P.3.3) in this scenario. FDA asked GSK to provide supporting data to demonstrate this.

FDA asked if the final design space should be the intersection of the three individual design spaces where each is determined as a function of two variables with the third variable varied at set intervals. The review team would like to see the cross sections of the three design spaces.

FDA inquired if GSK had any data to show the impact of tablet thickness variability on dissolution. GSK replied that they had the data and could provide it at the PAI. FDA commented that the current model addresses only uncertainty in response (i.e., dissolution) measurement, but asked GSK how uncertainty in process measurements was handled. GSK's response was that, since the DOE was done at various input parameters, it accounts for uncertainty in process parameters.

FDA questioned whether tablet thickness control might be impacted by any other factors besides (b) (4) GSK explained that (b) (4)

FDA questioned if GSK noted tablet-to-tablet excipient variability. GSK responded that this is highly unlikely and that the use of (b) (4) would identify excipient inhomogeneity (e.g., variability in the disintegrant). FDA stated that variation in excipients between tablets could lead to variation in tablet performance such as dissolution and disintegration. FDA asked if disintegration would continue to be performed in future. GSK noted that disintegration is a part of dissolution control strategy, has proven acceptable ranges associated with it, and confirmed that it will be performed in the future.

GSK further explained the proposed dissolution model. FDA asked if there were changes in the x, y and z axes, would the same design space result due to two-way and three-way interactions. FDA requested the visualization of different cross sections and orientations of the plots in the design space. GSK explained that although the apparent shape of the design space will change, the combinations contained in the design space would be the same regardless of the changes in assigning the factors to the x, y, and z coordinates. GSK also agreed to provide different slices and visualizations using different orientations.

FDA asked for the rationale for setting 45 min as the time point for the dissolution method acceptance criteria, since at 45 min the tablet is almost completely dissolved. FDA indicated that Q (b) (4) at 45 min is not a sufficiently discriminating dissolution acceptance criterion. FDA also stated that a meaningful dissolution acceptance criterion should target approximately (b) (4) of the active released at the endpoint. FDA requested that GSK check the model at different time points to see which time point is most sensitive. FDA asked why the dissolution model acceptance criterion was set based on the mean instead of individual dissolution values. GSK explained that since there was so little variability in the individual values, it is more difficult to meet the specification pertaining to the mean than the individuals. GSK stated that using the individuals versus the mean would actually expand the design space. If GSK were in a situation where the batch data had demonstrated a large spread of individual tablets, then GSK would have based the model and the design space on the individuals rather than the mean. GSK also stated that the individual variability was taken into account by meeting the acceptance criteria of USP which includes S1, S2 and S3 testing. GSK agreed to provide raw data for 30 parallel batches, including dissolution data obtained on individual and mean values.

FDA stated that GSK needs to set a suitable method, including acceptance criteria, as part of their dissolution. The dissolution is a reference for the model; therefore, the reference needs the appropriate criteria based on the extent dissolved and the tested time points. GSK inquired if FDA had a proposal. FDA stated that they did not have enough information to provide a proposal and that GSK should analyze raw data to see how much is dissolved at different time points and set the dissolution specification, accordingly. GSK stated that they have a model at an intermediate dissolution time point, i.e., (b) (4).

FDA asked if GSK had generated data outside of the design space where tablets pass the dissolution specification of (b) (4) GSK confirmed that such data had not been generated. GSK also stated that there were dissolution failures in the DOE, outside of the design space. FDA stated that these data may help support the sensitivity of the proposed specification.

FDA asked about the coded factors in the dissolution model. GSK explained that the factor values were normalized and recoded to a range of -1 to +1. GSK confirmed that the coded factors were fitted in the model as continuous variables.

FDA asked whether GSK has the data to demonstrate the relationship between tablet thickness and porosity for the 200 mg strength; GSK said they do and will provide the data as required during the PAI.

FDA asked GSK if they had similar porosity data for the 200 mg tablets as shown in the GSK presentation for the 400 mg tablets. GSK stated that this information was included in the NDA and agreed to share the 200 mg porosity data with FDA at the PAI.

FDA inquired about how variation in tablet thickness affects dissolution. For example, standard dissolution testing has staged criteria that accounts for variability. GSK said that the bullet that discusses setting of a conservative acceptance criteria based on 95% confidence and prediction intervals, addresses FDA concerns regarding the impact of tablet variability. FDA asked if the model is built around the mean instead of standard deviation. GSK responded that the model is based on the mean; however, the associated tablet thickness standard deviations are in control. The model predicts the standard deviations that are seen.

FDA asked if GSK observed segregation of formulation ingredients. GSK stated that when variability of components was introduced and that no segregation of components was observed. Additionally, GSK stated that they control content uniformity using NIR (b) and that the high drug load reduced the risk of component segregation. FDA asked why 30 batches were chosen for the 30 parallel testing exercises. GSK explained that this number was to provide adequate statistical power for control charting and for setting meaningful control chart limits to demonstrate proper control over key factors.

FDA questioned whether GSK had noted dissolution variability using (b) (4) (b) (4) endpoint but the acceptable Work range proposed was 2 fold. GSK explained that the (b) (4) and has a heavier weighting at

longer time periods. Thus, a two fold increase in Work would not translate to a two fold change in (b) (4) time.

FDA questioned the high variability noted in the dissolution data in Attachment 1, Table 9 in the proposed dissolution comparability protocol submitted on June 24, 2009. GSK pointed out that high variability was due to tablet thickness and Work being outside the PARs. Low variability was observed in the 50-batch DOE when (b) (4) amount, Work, and tablet thickness were within the proposed PARs.

FDA asked why both prediction and confidence intervals were used for the 30 batch parallel acceptance criteria. GSK responded that both were necessary because they were making inferences about the overall 30 batch mean using the confidence interval, and GSK was using the prediction intervals to establish criteria for individual batches.

GSK said they have a multivariate model to track and trend all applicable (b) (4) parameters. GSK stated they would provide additional data about the multivariate model at the PAI.

PAI Discussion:

The topic of PAI readiness was then discussed. GSK described that all (b) (4) would be available for review at the upcoming PAI in July 2009. FDA asked (b) (4) GSK confirmed (b) (4) FDA asked about potential (b) (4) GSK confirmed the use of a (b) (4) and confirmed that these data are included in the NDA. GSK stated that these data showed low RSD for variability in content when the stratified sampling data were compared to blend homogeneity data. FDA asked if disintegration will be part of testing and GSK confirmed that disintegration is indeed performed as part of the overall control strategy.

FDA stated that, as agreed with EMEA, they will lead the joint FDA/EU PAI inspection and begin with the review of (b) (4). FDA requested to see the manufacturing process run during the PAI. FDA confirmed that, if no campaigns were planned, a placebo run would also be acceptable. GSK stated that there were no scheduled manufacturing runs during the time of the planned PAI, but that GSK would look at their schedule and see if they can accommodate the Agency's request. Based on the availability of the (b) (4) controls at the PAI, a subsequent pre-operational review associated with (b) (4) might not be considered necessary.

(b) (4) **Discussion:**

LOD Method
FDA commented that a value of (b) (4) for residual solvents appears large when compared with the RMSEC/RMSEP values quoted for the model. FDA asked that GSK provide a written response explaining the impact of residual solvent level on the errors associated with the reference method and the developed method (model). FDA asked how the 12 sources of variability identified in the reply to Question 14 were included in the model development, e.g., was it via a designed study. GSK replied that they were not accommodated through a designed study. Further information will be provided in the written response. FDA asked about detection and impact of fouling on (b) (4). GSK replied that no fouling of the (b) (4) probes had been observed.

Content Method
FDA recognized that the model submitted in the NDA and the response to Question 16 had changed from a 3-factor model to a 4-factor model. They commented that it would appear that the data added to the model post file has added this factor, and that the explanation provided for LV3 vs. LV4 are conflicting (based upon the samples that have been highlighted). FDA requested that GSK provide clarity on the increase from 3 factors in original NDA submission to 4 factors in the updated (b) (4) Identity and Content method. FDA requested raw data for HPLC and (b) (4) results on individual tablets, means and a summary.

Blending Method
FDA asked about detection and impact of fouling on (b) (4), which could lead to a false positive determination of homogeneity. GSK responded that they had not observed any fouling. FDA asked if GSK considered the dynamics of the blending process, i.e. drum rotation versus presentation of the powder, what was happening with the powder during this time and could they detect changes in materials during this acquisition period. (b) (4)

2.3 MEETING SUMMARY

FDA closed the meeting by stating that they considered this dialogue to be very positive and appreciated the input, commitment and engagement from GSK. FDA had identified many questions prior to the meeting and stated that the exchange of knowledge facilitated their understanding of GSK's proposals. GSK requested a follow-up teleconference to discuss the outstanding dissolution issues. FDA instructed GSK to follow-up with the Project Manager for Quality regarding a possible teleconference. FDA committed to accelerate the distribution of meeting minutes to the degree possible and welcomed GSK's meeting notes.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

GSK requested a teleconference for feedback on dissolution for time point and specification. GSK would also like feedback on question 11. FDA directed GSK to contact the Project Manager for Quality regarding the TCON request.

4.0 ACTION ITEMS

There were no other action items from the meeting other than those specified in the discussion section above.

5.0 POST-MEETING COMMENTS FROM FDA

GSK's request at the meeting for an additional teleconference meeting to discuss dissolution was not granted because FDA did not have sufficient data for a fruitful discussion. An information request letter was sent to GSK on July 13, 2009, requesting additional information regarding dissolution.

6.0 CONCURRENCE:

{See appended electronic signature page}

Deborah Mesmer
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment III and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Sarah C. Pope, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

7.0 ATTACHMENTS AND HANDOUTS

Attachment 1: FDA slides provided to GSK - Slides 1-7

Attachment 2: GSK slides- Meeting between GSK and FDA to Discuss VOTRIENT (Pazopanib) NDA 22-465, Slides 1-24

Attachment 1: *FDA slides provided to GSK - Slides 1-7* follow this page.

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

Attachment 2: *GSK slides- Meeting between GSK and FDA to Discuss VOTRIENT (Pazopanib) NDA 22-465, Slides 1-24* follow this page.

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

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

/s/

Deborah M Mesmer
7/23/2009 01:24:44 PM

Sarah Pope
7/23/2009 01:44:53 PM

_7_ Page(s) Removed.

See the Advisory Committee Meeting Information located on the FDA Website Below.

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/default.htm