

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-938 (GIST)

NDA 21-968(MRCC)

Administrative/Correspondence Reviews

EXCLUSIVITY SUMMARY

NDA # 21-938 and 21-968

SUPPL #

HFD # 150

Trade Name SUTENT Capsules

Generic Name sunitinib malate

Applicant Name Pfizer, Inc.

Approval Date, If Known January 26, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

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

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question-3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Christy Cottrell
Title: Consumer Safety Officer
Date: 1/24/06

Name of Office/Division Director signing form: Robert L. Justice, M.D.
Title: Acting Division Director

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

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

/s/

Christy Cottrell
2/2/2006 01:56:50 PM

Robert Justice
2/2/2006 06:09:10 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: NDA 21-938 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: August 11, 2005 Action Date: February 11, 2006

HFD-150 _____ Trade and generic names/dosage form: SUTENT® (sunitinib malate) Capsules

Applicant: Pfizer, Inc. Therapeutic Class: 1 P

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: For the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate

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

Yes: Please proceed to Section A.

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

NOTE: More than one may apply

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

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

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

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

Reason(s) for deferral:

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

Other: _____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

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

Comments:

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

This page was completed by:

{See appended electronic signature page}

Christy Cottrell
Regulatory Project Manager

cc: NDA 21-938
HFD-960/ Grace Carmouze

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

(revised 12-22-03)

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

/s/

Christy Cottrell
1/24/2006 11:51:17 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-938 and Supplement # Efficacy Supplement Type SE-
21-968

Trade Name: SUTENT
Established Name: sunitinib malate
Strengths: 12.5 mg, 25 mg, and 50 mg

Applicant: Pfizer, Inc.
Agent for Applicant: N/A

Date of Application: August 10, 2005
Date of Receipt: August 11, 2005
Date clock started after UN: N/A
Date of Filing Meeting: September 29, 2005
Filing Date: October 10, 2005
Action Goal Date (optional): January 2006 User Fee Goal Date: February 11, 2006

Indication(s) requested: For the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate and for the treatment of advanced renal cell carcinoma.

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

NOTE:

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

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

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

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

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

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

Version: 12/15/2004

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

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

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
Additional comments:
- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO
- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.
Additional comments:
- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 5 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO

If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 62,382
- End-of-Phase 2 Meeting(s)? Date(s) 11/10/03; 1/23/04; 2/23/05 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 9/23/04; 1/19/05; 4/19/05 NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Risk Management Plan consulted to ODS/IO? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

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

Chemistry

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

**Appears This Way
On Original**

**Appears This Way
On Original**

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 29, 2005

BACKGROUND: This is an NME NDA. The NDA was originally submitted under NDA 21-938 but the Division administratively split it into two NDAs (21-938 and 21-968). NDA 21-938 is seeking full approval for the treatment of Gleevec-refractory or intolerant GIST. NDA 21-968 is seeking accelerated approval under Subpart H for the treatment of metastatic renal cell carcinoma.

ATTENDEES: Dr. Robert Justice, Acting Director
Dr. Ramzi Dagher, Clinical Team Leader
Dr. John Johnson, Clinical Team Leader
Dr. Vicki Goodman, Clinical Reviewer
Dr. Edwin Rock, Clinical Reviewer
Dr. Janet Jiang, Statistical Reviewer
Dr. S. Leigh Verbois, Pharm/Tox Reviewer
Dr. Brian Booth, Clinical Pharmacology Team Leader
Dr. Roshni Ramchandani, Clinical Pharmacology Reviewer
Dr. Sophia Abraham, Clinical Pharmacology Reviewer
Dr. Nallaperumal Chidambaram, Chemistry Team Leader
Christy Cottrell, Consumer Safety Officer

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

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Edwin Rock (21-938) and Vicki Goodman (21-968)
Secondary Medical:	Ramzi Dagher
Statistical:	Janet Jiang (21-938) and Shenghui Tang (21-968)
Pharmacology:	S. Leigh Verbois
Statistical Pharmacology:	N/A
Chemistry:	Chengyi Liang
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Roshni Ramchandani and Sophia Abraham
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	J. Lloyd Johnson
Regulatory Project Management:	Christy Cottrell
Other Consults:	DDMAC, DMETS, DMIHDP

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site inspection needed? YES NO

• Advisory Committee Meeting needed? YES, date if known _____ NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. inspection needed? YES NO

PHARMACOLOGY N/A FILE REFUSE TO FILE

- GLP inspection needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
Any comments: N/A

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

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

ACTION ITEMS:

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

Christy Cottrell
Regulatory Project Manager, HFD-150

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

/s/

Christy Cottrell
1/24/2006 02:40:07 PM
CSO

MEMORANDUM

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

DATE: February 7, 2006

TO: NDA 21-938 and 21-968 archival file

FROM: Christy Cottrell, Consumer Safety Officer
Division of Drug Oncology Products

SUBJECT: **Carton labels**
NDA 21-938 and NDA 21-968
SUTENT (sunitinib malate) Capsules

On January 26, 2006, the Division acknowledged having container labels, but asked the sponsor to provide carton labels for review and attachment to the approval letter for NDAs 21-938 and 21-968 for SUTENT (sunitinib malate) Capsules. In a reply email dated January 26, 2006, the sponsor clarified that they do not have carton labels for SUTENT. The bottles are put in shippers for shipment to the distribution site. The sponsor further explained that the package insert is glued to the bottles with transfer tape allowing it to be removed without tearing.

Dr. John Simmons, Director of the Division of Pre-Marketing Assessment III & Manufacturing Science agreed that this was acceptable.

Appears This Way
On Original

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

/s/

Christy Cottrell
2/7/2006 10:45:43 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

George Demetri, M.D.
Dana Farber Cancer Institute
44 Binney Street, SW530
Boston, MA 02115

2/9/06

Dear Dr. Demetri:

Between October 12, and October 19, 2005, Ms. Ellen P. Madigan representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the clinical investigations (Protocol A6181004 entitled: "A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of SU011248 in the Treatment of Patients with Imatinib Mesylate (Gleevec®, Glivec®)-Resistant or Intolerant Malignant Gastrointestinal Stromal Tumor") of the investigational drug Gleevec®, Glivec (Imatinib Mesylate), performed for Pfizer, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Madigan during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

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

/s/

Leslie Ball
2/9/2006 09:52:33 PM



Manisha H. Shah, M.D.
OSU Medical Center, James Cancer Hospital
320 W 10th Avenue, Starling-Loving Hall
Columbus, OH 43210-1240

2/9/06

Dear Dr. Shah:

Between October 24 and November 8, 2005, Mr. Hugh McClure representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the clinical investigations (Protocol A6181004 entitled: "A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of SU011248 in the Treatment of Patients with Imatinib Mesylate (Gleevec®, Glivec®)-Resistant or Intolerant Malignant Gastrointestinal Stromal Tumor") of the investigational drug Gleevec®, Glivec (Imatinib Mesylate), performed for Pfizer, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Mr. McClure, discussed with you Form FDA 483, Inspectional Observations. We concur with the observations and wish to emphasize the following:

1. You did not prepare and maintain adequate and accurate records [21 CFR 312.62(b)].
 - a. In at least four subjects with abnormal ECGs (Subjects #000050, Screening ECG; #00133, Cycle 1, Day 28 ECG; #00010 Screening ECG and Cycle 1, Day 28 ECG; and #000158 Screening ECG), there was no documentation that ECGs required during screening and subsequent visits were evaluated for clinical significance in a timely manner.

- b. In at least two subjects (Subjects #000190 Cycle 2; and #000300 Cycle 1, Day 28), there were incomplete entries and discrepancies found between study case report forms and subject diary source documents for Pain and Analgesic Medications.

We appreciate the cooperation shown Investigator McClure during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

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

/s/

Leslie Ball
2/9/2006 10:20:15 PM

Summary Review of NDA

NDA Numbers : 21938 Gastrointestinal Stromal Tumors (GIST)
21968 Renal Cell Cancer (RCC)

Drug : Sutent (sunitinib malate)

Sponsor : Pfizer

Indications : gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate

advanced renal cell carcinoma

Authors : Dr. Ramzi Dagher, Acting Deputy Division Director, DDOP

Dr. Robert Justice, Acting Division Director, DDOP

Date : January 25, 2006

Recommendations

The Division of Drug Oncology Products (DDOP), OODP, CDER, USFDA recommends approval of sunitinib (SUTENT® capsules 12.5 mg, 25 mg and 50 mg, Pfizer Corp.), a small molecule receptor tyrosine kinase (RTK) inhibitor, for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate. This indication is based on demonstration of improved time to progression in a randomized double-blind placebo controlled study. Approval is also recommended for the treatment of advanced renal cell carcinoma under subpart H (accelerated approval) based on partial response rates and duration of response.

Efficacy in GIST and in RCC

Efficacy and safety in GIST patients were evaluated in a randomized, double-blind placebo-controlled trial in patients who had disease progression during prior imatinib treatment or who were intolerant of imatinib. The primary endpoint was time-to-progression (TTP). Two-hundred seven patients were randomized (2:1) to sunitinib and 105 to placebo. Baseline age, gender, race and performance status (PS) were comparable between the two treatment arms. Most patients enrolled (96% in both arms) had progressed on or within 6 months of completing prior imatinib therapy. Approximately 30% of patients were \geq 65 years of age and more than 98% had an ECOG PS of 0/1.

A planned interim efficacy and safety analysis was performed after 149 TTP events had occurred. There was a significant advantage for sunitinib over placebo in TTP. There was also an advantage for sunitinib in progression-free survival. Survival data were not mature enough for evaluation. Objective responses were observed in patients receiving sunitinib. Efficacy findings are summarized in Table 1

Table 1

Efficacy Parameter	Study A			
	SUTENT (N = 207)	Placebo (N = 105)	P-value (log-rank test)	HR (95% CI)
Time to Tumor Progression ^a [median, weeks (95% CI)]	27.3 (16.0, 32.1)	6.4 (4.4, 10.0)	<0.0001*	0.33 (0.23, 0.47)
Progression Free Survival ^b [median, weeks (95% CI)]	24.1 (11.1, 28.3)	6.0 (4.4, 9.9)	<0.0001*	0.33 (0.24, 0.47)
Objective Response Rate (PR) [% (95% CI)]	6.8 (3.7, 11.1)	0	0.006 ^c	

CI=Confidence interval, HR=Hazard Ratio, PR=Partial response

* A comparison is considered statistically significant if the p-value is < 0.0042 (O'Brien Fleming stopping boundary)

^a Time from randomization to progression; deaths prior to documented progression were censored at time of last radiographic evaluation

^b Time from randomization to progression or death due to any cause

^c Pearson chi-square test

A separate single arm phase 1 / 2 study conducted in patients with GIST following progression on or intolerance to imatinib enrolled 55 patients after identification of the recommended phase 2 regimen. Partial responses were observed in 5 patients for a PR rate of 9.1% (95% C.I. 3.0, 20.0)

Efficacy and safety for advanced renal cell carcinoma (RCC) were evaluated in two open-label, single-arm, multicenter trials (study 1 and study 2) enrolling a total of 169 patients with metastatic disease. All patients had experienced disease progression or intolerance to interleukin-2 and/or interferon- α . The median age across the two studies was 57 years (range 24-87). 65% of patients were male, and 86-94% were white. All patients had an ECOG performance score of < 2 at screening.

95% of the treated population had a component of clear cell histology and 97% had undergone prior nephrectomy. Approximately half of the patients had 3 or more sites of disease at study entry; common sites included lung, liver and bone. Patients with known brain metastases or leptomeningeal disease were excluded from both studies.

The primary endpoint for both studies was overall response rate (ORR). All responses on both trials were partial responses. Study 1 had a 25.5% (95% CI 17.5, 34.9) partial response rate as assessed by a core radiology laboratory. Duration of response data for study 1 are immature as only 4/27 responders had progressed at the time of the analysis, with a median duration of response of 27 weeks (95% CI 24.4, upper limit could not be estimated). Study 2 had a 36.5% (95% CI 24.7, 49.6) partial response rate as assessed by the investigators. The median duration of response was 54 weeks (95% CI 34.3, 70.1).

Several regulatory issues were discussed as part of the review process for the RCC indication. First, approval under subpart H requires demonstration of an improvement over available therapy or an effect in a population for which no available therapy exists. Clearly, the patients enrolled to the two single arm trials no longer had interleukin-2 and/or interferon- α available as viable options. Even if these options were still considered possible, they would be associated with limited clinical effects, and certainly no expectation of a survival benefit. Although sorafenib has recently been approved for advanced RCC based on a placebo-controlled trial with demonstration of a progression-free survival effect, sorafenib was associated with an objective partial response rate of 2%, compared with approximately 25-35% with sunitinib. Furthermore, sunitinib has also demonstrated a clinical benefit in a separate population of patients with advanced cancer, namely imatinib refractory or intolerant GIST patients. At a regulatory briefing conducted in November 2005, the office and center leadership agreed that the totality of evidence supports the view that sunitinib has demonstrated an improvement over available therapy.

A second issue was the specific wording of the RCC indication. Although patients evaluated in the RCC studies all had metastatic disease and had progressed or were intolerant to cytokine therapy, discussion with the OODP leadership resulted in agreement to grant approval for advanced RCC. It was determined that requiring patients to receive cytokine therapy, whether in the context of advanced or metastatic disease, before considering sunitinib would be overly burdensome, especially given the limited benefits and substantial toxicity associated with cytokine use.

Finally, approval under subpart H requires confirmation of clinical benefit. An ongoing trial comparing sunitinib to interferon- α as first-line therapy for patients with metastatic RCC with progression-free survival as the primary efficacy endpoint will provide evidence of clinical benefit.

Safety

The safety database for this action consists of 450 patients with solid tumors including 257 patients (57%) with GIST and 169 patients (38%) with cytokine-refractory metastatic RCC who were treated in 7 completed non-randomized, open-label, single arm clinical trials and 1 randomized, double-blind, placebo-controlled clinical trial. All patients received sunitinib once daily as a 50-mg oral capsule on Schedule 4/2.

The most common treatment-emergent adverse events occurring more frequently in the sunitinib arm of the placebo-controlled GIST study included (sunitinib versus placebo) diarrhea (40% vs. 27%), skin discoloration (30% vs 23%), mucositis/stomatitis (29% vs 18%), asthenia (22% vs. 11%), and altered taste (21% vs. 12%) . Hypothyroidism was observed in 4% of patients receiving sunitinib; hypothyroidism was not observed on the placebo arm. Grade 3/4 events that were more common with sunitinib included diarrhea (4% vs. 0%), hypertension (4% vs. 0%), and asthenia (5% vs. 3%). Grade 3/4 treatment-emergent laboratory abnormalities occurring more commonly with sunitinib included neutropenia (10% vs. 0%) and thrombocytopenia (5% vs. 0%). The safety profile in the RCC single-arm trials was similar to that in the GIST randomized study.

The following is a summary of adverse events that the DDOP recommends describing in the PRECAUTIONS section of the labeling.

Left Ventricular Dysfunction

Decreases in LVEF were observed in patients receiving sunitinib. In the randomized GIST Study, 22 patients (11%) on sunitinib and 3 patients (3%) on placebo had treatment-emergent LVEF values below the LLN. Nine of twenty-two GIST patients on sunitinib with LVEF changes recovered without intervention. Five patients had documented LVEF recovery following intervention (dose reduction- 1 patient; addition of antihypertensive or diuretic medications- 4 patients). Six patients went off study without documented recovery. Additionally, three patients (1%) on SUTENT had Grade 3 reductions in left ventricular systolic function to LVEF < 40%; two of these patients died without receiving further study drug. No GIST patients on placebo had Grade 3 decreased LVEF. Congestive heart failure was observed rarely in both arms.

Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF), cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from clinical studies. Patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving sunitinib. Baseline and periodic evaluations of LVEF should also be considered during treatment. In patients without cardiac risk factors, a baseline evaluation of ejection fraction may be considered.

In the presence of clinical manifestations of CHF, discontinuation of sunitinib is recommended. The dose should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

Hemorrhagic Events

Bleeding events have occurred in patients receiving sunitinib. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events in MRCC or GIST patients included rectal, gingival, upper GI, genital, and wound bleeding. Most events in MRCC patients were Grade 1 or 2; there was one Grade 3 event (bleeding foot wound). In GIST Study A, 14/202 patients (7%) receiving sunitinib and 9/102 patients (9%) on placebo had Grade 3 or 4 bleeding events. In addition, one patient in Study A taking placebo had a fatal gastrointestinal bleeding event during cycle 2.

Tumor-related hemorrhage has been observed. Fatal pulmonary hemorrhage occurred in 2 patients receiving sunitinib on a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Both patients had squamous cell histology. Treatment-emergent Grade 3 and 4 tumor hemorrhage occurred in 5 of 202 patients (3%) with GIST receiving sunitinib on Study A. Tumor hemorrhages were observed as early as cycle 1 and as late

as cycle 6. One of these five patients received no further drug following tumor hemorrhage. None of the other four patients discontinued treatment or experienced dose delay due to tumor hemorrhage. No patients with GIST in the Study A placebo arm were observed to undergo intratumoral hemorrhage. Tumor hemorrhage has not been observed in patients with MRCC. Clinical assessment of these events should include serial complete blood counts (CBCs) and physical examinations.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation, have occurred rarely in patients with intra-abdominal malignancies treated with sunitinib.

Hypertension

Hypertension (all grades) was reported in 48/169 MRCC patients (28%), 31/202 GIST patients on sunitinib (15%), and 11/102 GIST patients on placebo (11%). Grade 3 hypertension was reported in 10 MRCC patients (6%), 9 GIST patients on sunitinib (4%), and none of the GIST patients on placebo. No Grade 4 hypertension was reported. Sunitinib dosing was reduced or temporarily delayed for hypertension in 6/169 MRCC patients (4%) and none of the patients in GIST Study A. No patients were discontinued from treatment due to systemic hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 10/169 MRCC patients (6%), 8/202 GIST patients on SUTENT (4%), and 1/102 GIST patients on placebo (1%).

Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In cases of severe hypertension, temporary suspension of sunitinib is recommended until hypertension is controlled.

Adrenal Function

Adrenal toxicity was noted in non-clinical repeat dose studies in rats and monkeys. Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of therapy demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials. Among patients with normal baseline ACTH stimulation testing, one patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12-16.4 mcg/dL (normal >18 mcg/dL) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency.

Physicians are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.

The following represent summary findings and recommendations from Clinical Pharmacology/Biopharmaceutics, Statistical/Biometrics, Pharmacology/Toxicology, Chemistry, Division of Drug Marketing and Advertising, Division of Scientific Investigations, and Division of Medication Errors and Technical Support (DMETS).

Clinical Pharmacology / Biopharmaceutics

The clinical pharmacology/biopharmaceutics review team recommends approval of sunitinib for the indications discussed above.

The following summarizes findings and recommended labeling regarding potential drug interactions.

Co-administration of sunitinib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase sunitinib plasma concentrations. Co-administration with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations. St. John's Wort may decrease sunitinib plasma concentrations unpredictably. Patients receiving sunitinib should not take St. John's Wort concomitantly. Sunitinib dose modification is recommended in patients who must use CYP3A4 inhibitors or inducers concomitantly.

Statistical / Biometrics

The statistical/biometrics review team recommends approval of sunitinib for the indications discussed above. Efficacy findings from clinical studies as summarized above were confirmed by the statistical reviewers. In addition, multiple sensitivity analyses were conducted based on the results of the randomized trial in GIST patients. Results of these analyses were consistent with the primary efficacy findings.

Pharmacology / Toxicology

The pharmacology / toxicology review team recommends approval of sunitinib for the indications discussed above. Review findings regarding mechanism of action, carcinogenicity, mutagenicity, and impairment of fertility including recommendations for designation as pregnancy category D have been incorporated into the labeling.

Chemistry

The chemistry review team recommends approval of sunitinib for the indications discussed above. A number of deficiencies related to drug product and drug substance identified during the review process have been addressed. In addition, the Office of Compliance has given an overall acceptable recommendation.

Division of Drug Marketing and Advertising (DDMAC)

Recommendations from DDMAC have been considered in the labeling process.

Division of Scientific Investigations

Audits of clinical sites enrolling patients to clinical studies of sunitinib in metastatic renal cell cancer and GIST indicated no violations that would likely influence study outcomes.

Division of Medication Errors and Technical Support, Office of Drug Safety (DMETS)

DMETS has no objections to the proprietary name Sutent. Labeling recommendations have been taken into consideration.

*Appears This Way
On Original*

Subpart H Commitments for NDA 21-968 (RCC)

1. Provide the response rate and duration of response data from the first interim efficacy analysis of study titled “A Phase 3, Randomized Study of SU011248 versus Interferon- α as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma”. Also, submit the comparative safety data that are available at the time of data cutoff for the interim analysis. This will include an interim study report as well as raw and derived datasets.
2. Submit efficacy data obtained at the final analysis, including progression-free survival, overall survival, response rate and duration of response; as well as updated safety data for study titled “A Phase 3, Randomized Study of SU011248 versus Interferon- α as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma”. This submission will include the final study report as well as raw and derived data sets.
3. Submit updated case report tabulations that include the core imaging facility assessments used to derive the median duration of response on study titled “A Pivotal Study of SU011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma”.
4. Submit follow-up left ventricular ejection fraction (LVEF) data for patients 16, 46, and 81 on the study titled “A Pivotal Study of SU011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma”. Case narratives should be submitted and should include additional cardiac evaluations that were performed and treatments that were administered for congestive heart failure. Additionally, submit LVEF data and clinical narratives for any patient who, after the data cutoff for the initial NDA submission, had a documented LVEF of $\leq 40\%$ and/or signs and symptoms of cardiac failure.
5. Submit comparative LVEF and cardiac safety data for patients enrolled on the adjuvant renal cell carcinoma trial, E2805 titled “A Randomized, Double-Blind Phase III Trial of Adjuvant Sunitinib versus Sorafenib versus Placebo in Patients with Resected Renal Cell Carcinoma”. The protocol will be revised to include a plan acceptable to the FDA for ejection fraction monitoring at baseline and follow-up.

Post-Marketing Commitments (both NDAs)

6. Provide an analysis of the relationship between exposure and efficacy outcomes from the study titled “A Phase 3, Randomized Study of SU011248 versus Interferon- α as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma”.
7. Submit the completed report and datasets for study titled “A Phase 1 Study to Evaluate the Effect of SU011248 on Cardiac Repolarization Following Repeat Doses of SU011248 in Patients with Advanced Solid Tumors”.
8. Submit the completed report and datasets for study titled “A Phase 1 Study to Evaluate the Pharmacokinetics of SU011248 in Subjects with Impaired Hepatic Function”.
9. Submit completed final study report for study titled “A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of SU011248 in the Treatment of Patients with Imatinib Mesylate (Gleevec®, Glivec®)-Resistant or Intolerant Malignant Gastrointestinal Stromal Tumor”.

*Appears This Way
On Original*

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

/s/

Ramzi Dagher
1/25/2006 05:41:15 PM
MEDICAL OFFICER

Robert Justice
1/25/2006 06:42:10 PM
MEDICAL OFFICER

REQUEST FOR CONSULTATION

TO (Division/Office):
HFD-160/Division of Medical Imaging and Hematology Drug
Products

FROM:
HFD-150/Division of Drug Oncology Products
Christy Cottrell, Consumer Safety Officer

DATE
January 20, 2006

IND NO.

NDA NO.
NDA 21-938 and
NDA 21-968

TYPE OF DOCUMENT
N(000)

DATE OF DOCUMENT
August 10, 2005

NAME OF DRUG
Sutent (sunitinib malate)
Capsules

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
January 25, 2006

NAME OF FIRM: Pfizer

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | Imaging data for NDA |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

As previously discussed, please review all relevant imaging data for these NDAs. PDUFA due date is February 11, 2006.

Medical Officers are Vicki Goodman, MD (NDA 21-968) and Edwin Rock, MD (NDA 21-938)
Project Manager is Christy Cottrell

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)
X MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

/s/

Christy Cottrell
1/24/2006 01:31:56 PM

From: Cottrell, Christy
Sent: Friday, January 06, 2006 3:16 PM
To: 'Strawn, Laurie'
Subject: RE: Urgent Teleconference
Laurie,

As discussed, we have scheduled a telecon for **Monday, 1/9 at 12:00pm EST** to discuss both the CMC deficiencies and your proposal for addressing the clinical pharmacology comments regarding the 25 mg strength capsule. Please send me call-in information when it is available.

We also have another CMC comment to convey:

- We can only grant [] shelf life for DP based on [] primary stability test data. The DP shelf life can be extended after the updated stability test data are submitted.

If you have any questions, let me know.

Christy

Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9849

-----Original Message-----

From: Strawn, Laurie [mailto:laurie.strawn@pfizer.com]
Sent: Friday, January 06, 2006 12:53 PM
To: Cottrell, Christy
Subject: Urgent Teleconference

Hi Christy,

As I mentioned on the voice mail I just left, we would like to have a teleconference ASAP to discuss the chemistry reviewer's comments on the bottle labels. Please call me on my cell phone at your earliest convenience to set something up.

Thanks,
Laurie

Laurie M. Strawn, Ph.D.
SUTENT Global Regulatory Leader
Worldwide Regulatory Strategy
Pfizer Inc.
10777 Science Center Dr.
San Diego, CA 92121
Office: (858)526-4815

LEGAL NOTICE

Unless expressly stated otherwise, this message is confidential and may be privileged. It is intended for the addressee(s) only. Access to this E-mail by anyone else is unauthorized. If you are not an addressee, any disclosure or copying of the contents of this E-mail or any action taken (or not taken) in reliance on it is unauthorized and may be unlawful. If you are not an addressee, please inform the sender immediately.

"MMS <secure.pfizer.com>" made the following annotations on 01/06/2006 12:53:06 PM

LEGAL NOTICE:

Unless expressly stated otherwise, this message is confidential and may be privileged. It is intended for the addressee(s) only. Access to this e-mail by anyone else is unauthorized. If you are not an addressee, any disclosure or copying of the contents of this e-mail or any action taken (or not taken) in reliance on it is unauthorized and may be unlawful. If you are not an addressee, please inform the sender immediately.

Legal Notice

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

/s/

Christy Cottrell
1/6/2006 03:24:14 PM
CSO

From: Cottrell, Christy
Sent: Wednesday, January 04, 2006 8:15 PM
To: 'Strawn, Laurie'
Subject: NDAs 21-938 and 21-968 for Sutent

Importance: High
Laurie,

Please refer to your pending NDAs 21-938 and 21-968 for Sutent. See below for comments and deficiencies from the clinical pharmacology and chemistry reviewers. Please provide a response to the clinical pharmacology comments and a commitment for the chemistry deficiencies as soon as possible.

Thanks,
Christy

Clinical Pharmacology

There appears to be no bioequivalence data for the 25 mg capsule.
In the absence of any clinical data, you could request a biowaiver for the 25 mg capsule.

To provide the biowaiver you would need to provide the following information:

- You will need to submit comparative dissolution profiles (which should include early time points, e.g., 5 and 10 min) for the 25 mg commercial product compared to the 50 mg commercial product.
- This data should be tabulated and include an f2 analysis for three dissolution media: 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer.

Chemistry

Drug Substance

1. We recommend using USAN chemical name No.1 in the drug Package Insert.

Drug Product

1. The statement of DP strength in DP bottle label should be changed to "Each capsule contains sunitinib malate equivalent to 12.5 mg (or 25 mg or 50 mg) sunitinib" to reflect that the printed strength of 12.5 mg or 25 mg or 50 mg is calculated based on DS free base.
2. The DP manufacturer information should be changed to "Manufactured by Pfizer Italia S.p.A. Italy", because Pfizer Cork Limited deals with DS manufacture.

Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9849

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

/s/

Christy Cottrell
1/4/2006 09:13:05 PM
CSO



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

MEMORANDUM

DATE: August 16, 2005

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

SUBJECT: Sutene (sunitinib maleate SU011248) Capsules

TO: File NDA 21-938 and NDA 21-968

We are unbundling this NDA into two NDAs, both of which will reside in HFD-150. Two indications are included in this NDA and must be separated because one is for accelerated approval and the other is for regular approval, and one is more likely to be approved than the other. Additionally, different medical officers will be assigned. It has also not been determined whether either or both will be a priority review.

NDA 21-938 will be for gastrointestinal stromal tumors (GIST)
NDA 21-968 will be for metastatic renal cell carcinoma (RCC)

This is an electronic NDA complete in one submission (not rolling), so we do not anticipate renumbering jackets other than the original "shell" jacket 1.1 for the n-doc.

RQAT and CDR have been notified of this split.

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

/s/

Dotti Pease
8/16/2005 02:07:22 PM
CSO

From: Cottrell, Christy
Sent: Monday, December 12, 2005 12:16 PM
To: 'Strawn, Laurie'
Subject: NDA 21-938 for Sutent (GIST indication)
Laurie,

Please refer to your pending NDA 21-938 for Sutent (GIST indication). See below for an inquiry from the clinical reviewer.

The following questions refer to Study A6181004 for the GIST indication.

1) Of 6513 lines in dataset BAE.XPT, 136 lines have no recorded AE Grade. Of these 136 lines, 14's have a listed adverse event under AETX. Why is this so? How have you treated these AE's in your safety analysis. Of 136 lines without recorded AE Grade, 122 have no listed adverse event under AETX. Why is this so? What led to generation of these lines in the dataset? What is their significance?

2) Of 1022 lines in PSS.XPT, 73 lines have no recorded maximum CTC Grade severity. Of these 73 lines, 2 have a listed sign/symptom (edema; distended veins). Please clarify how the empty lines in this dataset were generated, as well as their significance.

If you have any questions, feel free to call me.

Christy

*Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9849*

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

/s/

Christy Cottrell
12/12/2005 12:24:14 PM
CSO

From: Cottrell, Christy
Sent: Monday, December 05, 2005 11:54 AM
To: 'Strawn, Laurie'
Subject: NDA 21-968 for Sutent (MRCC indication)
Laurie,

Please refer to your pending NDA 21-968 for Sutent (MRCC indication). The attached document is a summary of an exposure-response (E-R) analyses of the efficacy data for sunitinib in GIST patients and in MRCC patients.

E-R analysis in GIST patients

Our analysis in GIST patients indicates that higher AUCs show a longer time to tumor progression. This is as would be expected.

E-R analysis for MRCC patients

Our analysis in MRCC patients on the other hand indicates that patients with higher AUCs show a shorter time to tumor progression and higher AUCs show lower response rates compared to patients with lower AUCs. Contrary to the results in the GIST study this is the inverse of what we would have expected, and we are unsure what the reasons for such a finding would be. We would like to seek your input in interpreting these results and possible mechanisms underlying these findings.

- In the meantime, to confirm or refute this finding you should collect PK data (using optimal sparse sampling) in your ongoing phase 3 MRCC study, if you are not doing so already. Please submit an amendment to the protocol for our review.
- Our current E-R analysis employed response rates as the pharmacodynamic endpoint. We plan to extend this analysis by using continuous tumor size data, to confirm the finding.

We recommend that you schedule a telecon with the Division of Drug Oncology Products to discuss your findings, as early as is convenient.

Please let me know if you require any additional information from us.

Thanks,
Christy



Results and
ethods- PK issue.

Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9849

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

/s/

Christy Cottrell
12/5/2005 11:59:41 AM
CSO

MEMO

To: Robert Justice, MD
Acting Director, Division of Drug Oncology Products
HFD-150

From: Felicia Duffy, RN
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Alina R. Mahmud, RPh, MS, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Date: December 7, 2005

Re: ODS Consult 04-0152-1
Sutent (Sunitinib Malate) Capsules; 12.5 mg, 25 mg, 50 mg
NDAs 21-938 and 21-968

This memorandum is in response to a November 18, 2005 request from your Division for a re-review of the proprietary name, Sutent (NDAs 21-938 and 21-968). Container labels and package insert labeling were provided for review and comment as well.

The proposed proprietary name, Sutent, was found acceptable by DMETS in a review dated July 6, 2004 (ODS consult 04-0152). Since the July 7, 2004 review, DMETS has identified two additional proprietary names, Intal and Striant, as having look-alike similarities to Sutent. Additionally, DMETS would like to acknowledge that a search found two look-alike and sound-alike medications marketed in other countries, which are as follows: Sutin- from Mexico and Sutril- torsemide in Spain. Although the look-alike and sound-alike characteristics are obvious, DMETS believes the actual possibility for confusion with these product names to be minimal due to the areas of marketing.

Although Intal and Sutent were identified as sharing some orthographic similarities, there are numerous differentiating product characteristics such as indication for use, product strength, usual dosage, frequency of administration, and dosage form. Thus, due to the numerous differentiating product characteristics, Intal will not be further reviewed.

Striant was also identified as a name with similar appearance to Sutent when scripted. Striant (testosterone buccal system) is an anabolic steroid indicated for the treatment of male hypogonadism. Striant is a schedule III controlled substance and is available as a 30 mg buccal system. The usual dose is one buccal system twice daily. Striant and Sutent begin with the letter "S" and share a similar ending ("-ant" vs. "ent"). However, the

middle of the names helps to differentiate them (“-tri” vs. “-ut”). Product differences include strength (30 mg vs. 12.5 mg, 25 mg, and 50 mg), frequency of administration (twice daily vs. once daily), indication for use (male hypogonadism vs. metastatic renal cancer and gastrointestinal stromal tumor), and drug schedule (schedule III controlled substance vs. schedule V non-controlled substance). Because Sutent will be available in multiple strengths as opposed to Striant, which is available in only one strength, prescriptions for Sutent will likely indicate the intended strength. This will further differentiate the products. Despite some orthographic similarities, DMETS believes the likelihood for confusion between Striant and Sutent is minimal due to the aforementioned reasons.

Sutent
Striant

In review of the proposed container labels and package insert labeling for Sutent. We have identified the following areas of improvement, in the interest of minimizing potential user error and improving patient safety.

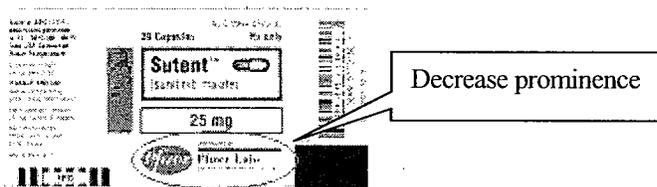
A. CONTAINER LABEL

1. The strength of this product is based on the active moiety Sunitinib and not the salt Sunitinib Malate. The current label presentation does not qualify this fact. Therefore, we recommend revising the labels and labeling to read in one of the following presentations:

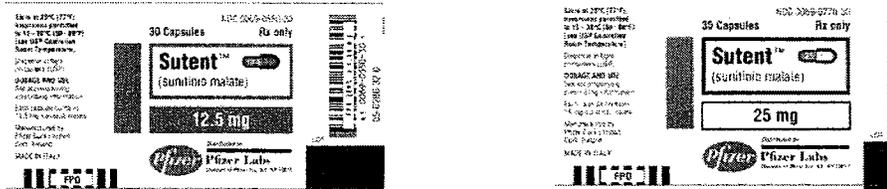
- a. Sutent
(Sunitinib Capsules)
XX mg
- b. Sutent
(Sunitinib Malate Capsules)
XX mg*
*Each tablet contains Sunitinib Malate equivalent to XX mg of Sunitinib
- c. Sutent
(Sunitinib Malate Capsules)
equivalent to XX mg of Sunitinib

Note: DMETS prefers the first option because this nomenclature is consistent with USP recommendations on ‘amount of ingredient per dosage unit’.

2. We note the dosage form is not included with the established name. Revise the established name to include the dosage form as noted in comment A1.
3. Decrease the prominence of the sponsor’s logo and distribution information as it appears more prominent than the proprietary name.



4. De-bold the net quantity (30 Capsules) in order to decrease its prominence, thus minimizing the likelihood “30” being confused as the product strength.
5. The image of the capsule on the primary display panel is described in the “How Supplied” section of the package insert as: 12.5 mg (orange cap and orange body), 25 mg (caramel cap and orange body), and 50 mg (caramel cap and caramel body). However, the color of the 12.5 mg capsule appears more \square rather than orange. Additionally, the body of the 25 mg capsule also appears \square rather than orange. Please clarify the coloring, or ensure the color described in the package insert accurately reflects the color on the container label.



6. Since the bottles are unit-of-use, please ensure they have child-resistant caps (CRC) in compliance with the Poison Prevention Act.

B. PACKAGE INSERT

1. When the product strengths are written in succession at the beginning of the package insert and in the “Description” section, the quantifying unit is omitted (e.g., 12.5, 25, and 50 mg). To avoid confusion with the product strengths, include the “mg” abbreviation after each number (e.g., 12.5 mg, 25 mg, and 50 mg).
2. Since Sudent has two indications, clarify in the “Dosage and Administration” that 50 mg by mouth once daily is for both indications.

In summary, DMETS has no objections to the proprietary name Sudent. We also recommend implementation of the labeling recommendations outlined in this memo that may lead to safer use of the product. Additionally, DDMAC has no objections to the name from a promotional perspective. We consider this a final review. However, if the approval of the NDAs is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before the NDAs approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

If you have any questions or need clarification, please contact DMETS Project Manager, Diane Smith, at 301-796-0538.

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

/s/

Felicia Duffy
12/13/2005 09:41:00 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/13/2005 09:57:20 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/13/2005 10:04:41 AM
DRUG SAFETY OFFICE REVIEWER

9 Page(s) Withheld



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

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

From: Cottrell, Christy
Sent: Monday, November 28, 2005 1:31 PM
To: 'Strawn, Laurie'; 'Meader, Melinda'; 'jaimie.walsh@pfizer.com'
Subject: NDA 21-938 for Sutent (GIST indication)
Laurie,

Please refer to your pending NDA 21-938 for Sutent (GIST indication). See below for inquiries from the clinical reviewer.

The following questions all concern Phase 3 GIST Study A6181004.

1. Please clarify why file BRADTMPT.XPT contains multiple dates of progression for some patients (including PTNO 1, 2, 16, 19, 26, 34, 39, 60, 69, 100, 103, 110, 123, 124, 131, 140, 147, 156, 160, 164, 170, 180, 183, 198, and 216).
2. To verify your efficacy analyses, we intend to use progression dates provided in file BDERRADT.XPT. However, we are not able to verify all of these progression dates. The table on the next page lists patients whose progression dates we believe are different from those in BDERRADT.XPT, as well as our rationale for choosing an alternate date. Please indicate for each of these patients whether you are in agreement with our modification. If you are not in agreement, please explain why.
3. For numerous but not all patients in file BDERRADT.XPT (examples: PTNO 28, 36, 38, 51, 52, 54, 68, 89, 91, 96, 104, 125, 165, 193, 194, 208, 221, 224, 286, 290, etc.), the progression date is one day following the exam date in file BRADLESI.XPT. Please explain why this is so.

If you have any questions, feel free to call me.

Thanks,
Christy

Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9849

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

/s/

Christy Cottrell
11/28/2005 01:38:42 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: (Division/Office) HFD-420/DMETS ATTN: Diane Smith			FROM: HFD-150/Division of Drug Oncology Products Christy Cottrell, CSO	
DATE November 18, 2005	IND NO.	NDA NO. NDA 21-938 and NDA 21-968	TYPE OF DOCUMENT N (000) New NDAs	DATE OF DOCUMENT August 11, 2005
NAME OF DRUG Sutent (sunitinib malate)		PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE December 15, 2005
NAME OF FIRM Pfizer, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY				
<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT				
<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER (fax) <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW)- UPDATED TRADENAME REVIEW				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> LABELING REVISIONS/CLINICAL PHARMACOLOGY & PRECAUTIONS <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: Please re-review the following tradename: SUTENT . This tradename was originally reviewed under IND 62,382, by Jinhee Jahng, Pharm.D. on 11/19/04. Desired completion date for this request is December 15, 2005. Division goal date for action on the NDAs is December 23, 2005. The NDAs are identical (just provide for different indications- same labeling for both) and are available in the EDR. Labeling is attached to this consult request.				
Medical Officers are Edwin Rock, MD (NDA 21-938) and Vicki Goodman, MD (NDA 21-968) Project Manager is Christy Cottrell (x 6-1347)				
SIGNATURE OF REQUESTER Christy Cottrell			METHOD OF DELIVERY (Check One) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

21 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(4) Draft Labeling

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

/s/

Christy Cottrell

11/18/2005 02:51:43 PM

DR1: Please process this outgoing consult to HFD-420 (DMETS).

From: Cottrell, Christy
Sent: Friday, November 18, 2005 10:42 AM
To: 'Strawn, Laurie'
Cc: 'Meader, Melinda'; 'Walsh, Jaimie'
Subject: NDA 21-968 for Sutent (MRCC indication)
Laurie,

Please refer to your pending NDA 21-968 for Sutent (MRCC indication). See below for a request from the clinical reviewer.

- During your presentation to us, you reported duration of response data for study 1006 that was different than the submitted data and was marked "updated" on the slides. We do not believe that we have the primary data. Can you please submit the duration of response data with the updated information for study 1006?

If you have any questions, feel free to call me at (301) 796-1347.

Thanks,
Christy

Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9849

-----Original Message-----

From: Strawn, Laurie [mailto:laurie.strawn@pfizer.com]
Sent: Thursday, November 17, 2005 1:28 PM
To: Cottrell, Christy
Cc: Meader, Melinda; Walsh, Jaimie
Subject: Out of the Office

Hi Christy,

I will be out of the office on vacation the week of November 21 and on business travel November 28 – 30. In case you can't reach me by e-mail or cell phone, please include Mindy Meader and Jaimie Walsh on all e-mails, or call them for urgent matters. Their contact information is:

Mindy
e-mail: mindy.meader@pfizer.com
phone: (858)622-7559

Jaimie
e-mail: jaimie.walsh@pfizer.com
phone: (858)622-8812

Thanks,
Laurie

Laurie M. Strawn, Ph.D.
SUTENT Global Regulatory Leader
Worldwide Regulatory Strategy
Pfizer Inc.
10777 Science Center Dr.
San Diego, CA 92121
Office: (858)526-4815

LEGAL NOTICE

Unless expressly stated otherwise, this message is confidential and may be privileged. It is intended for the addressee(s) only. Access to this E-mail by anyone else is unauthorized. If you are not an addressee, any disclosure or copying of the contents of this E-mail or any action taken (or not taken) in reliance on it is unauthorized and may be unlawful. If you are not an addressee, please inform the sender immediately.

"MMS <secure.pfizer.com>" made the following annotations on 11/17/2005 01:28:08 PM

LEGAL NOTICE:

Unless expressly stated otherwise, this message is confidential and may be privileged. It is intended for the addressee(s) only. Access to this e-mail by anyone else is unauthorized. If you are not an addressee, any disclosure or copying of the contents of this e-mail or any action taken (or not taken) in reliance on it is unauthorized and may be unlawful. If you are not an addressee, please inform the sender immediately.

Legal Notice

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

/s/

Christy Cottrell
11/18/2005 12:17:06 PM
CSO

From: Cottrell, Christy
Sent: Friday, November 18, 2005 11:05 AM
To: 'Strawn, Laurie'
Cc: 'Meader, Melinda'; 'Walsh, Jaimie'
Subject: NDA 21-938 for Sutent (GIST indication)

Laurie,

Please refer to your pending NDA 21-938 for Sutent (GIST indication). See below for a request for clarification from the statistical reviewer.

1) Were the 41 patients (which do not have entries in dataset BDERRADT), excluded from the analysis results (such as median PFS and Hazard ratio) that are displayed in table 13.4.4.1. of the study report?

2) Please provide the PFS censoring scheme for the 41 patients mentioned above.

3) Please provide a dataset which contains the following information (variables) based on the central radiologist assessment for ITT population (312 patients) in the study. Please submit one record per patient.

patid (patient id), ptno (patient number), tmt (treatment group), PD_DT (date of progression), RANDDTS (Randomized date), DEATHDTS (patient death date), patient death cause, PFS_DT (PFS end date), PFS_V (Duration of PFS wks), PFS_C (PFS censored flag) and other variables if necessary.

If you have any questions, feel free to call me at (301) 796-1347.

Thanks,
Christy

*Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9849*

-----Original Message-----

From: Strawn, Laurie [mailto:laurie.strawn@pfizer.com]
Sent: Thursday, November 17, 2005 1:28 PM
To: Cottrell, Christy
Cc: Meader, Melinda; Walsh, Jaimie
Subject: Out of the Office

Hi Christy,

I will be out of the office on vacation the week of November 21 and on business travel November 28 – 30. In case you can't reach me by e-mail or cell phone, please include Mindy Meader and Jaimie Walsh on all e-mails, or call them for urgent matters. Their contact information is:

Mindy
e-mail: mindy.meader@pfizer.com
phone: (858)622-7559

Jaimie
e-mail: jaimie.walsh@pfizer.com
phone: (858)622-8812

Thanks,
Laurie

Laurie M. Strawn, Ph.D.
SUTENT Global Regulatory Leader
Worldwide Regulatory Strategy
Pfizer Inc.
10777 Science Center Dr.
San Diego, CA 92121
Office: (858)526-4815

LEGAL NOTICE

Unless expressly stated otherwise, this message is confidential and may be privileged. It is intended for the addressee(s) only. Access to this E-mail by anyone else is unauthorized. If you are not an addressee, any disclosure or copying of the contents of this E-mail or any action taken (or not taken) in reliance on it is unauthorized and may be unlawful. If you are not an addressee, please inform the sender immediately.

"MMS <secure.pfizer.com>" made the following annotations on 11/17/2005 01:28:08 PM

LEGAL NOTICE:

Unless expressly stated otherwise, this message is confidential and may be privileged. It is intended for the addressee(s) only. Access to this e-mail by anyone else is unauthorized. If you are not an addressee, any disclosure or copying of the contents of this e-mail or any action taken (or not taken) in reliance on it is unauthorized and may be unlawful. If you are not an addressee, please inform the sender immediately.

=====
Legal Notice
=====

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

/s/

Christy Cottrell
11/18/2005 12:15:42 PM
CSO

From: Cottrell, Christy
Sent: Monday, November 14, 2005 3:04 PM
To: 'Strawn, Laurie'
Subject: NDA 21-938 for Sutent (GIST)
Laurie,

Please refer to your pending NDA 21-938 for Sutent (GIST indication). See below for a request from the statistical reviewer.

There are discrepancies between the reviewer's table 'Summary Table of Patients Disposition at Cut-off Date for Analysis (ITT)' and the sponsor's Table 7 in the study report regarding patient numbers appearing on the rows 'Adverse events', 'Ongoing in Blinded treatment' and 'Lack of efficacy'. Attached is the reviewer's table.

Please respond to the following requests as soon as possible.

1) In the documentation Define.pdf, there is variable 'ENDREAS' in dataset 'POPGEN'. Code (96) represents 'Lack of efficacy (disease progression)', but there is no value (96) for variable 'ENDREAS' in dataset 'POPGEN'. Please clarify the definition of 'lack of efficacy (disease progression)' in Table 7 in the study report.

2) According to the documentation Define.pdf, the reviewer used the variable 'ENDREAS' in dataset 'POPGEN' to obtain the results in reviewer attached summary table. Please direct the reviewer how to get the numbers of patients in the rows 'Adverse events', 'Ongoing in Blinded treatment' and 'Lack of efficacy (disease progression)' in Table 7 in the study report by specifying the dataset(s) and variable names.

Table 3: Reviewer's Summary of Patient Disposition at Cut-off Date for Analysis (ITT Population)

Reason for Discontinuation	SU011248 (N = 207)	Placebo (N = 105)
Adverse events	18 (9)	12 (11.43)
Consent withdrawn	6 (3)	3 (3)
Lost to follow-up	1 (1)	0 (0)
Lack of efficacy	38 (18)	14 (13)
Crossed over to open-label treatment	19 (9)	59 (56)
Ongoing in blinded treatment	124 (60)	17 (16)

If you have any questions, feel free to call me.

Thanks,
Christy

Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9849

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

/s/

Christy Cottrell
11/14/2005 03:08:16 PM
CSO

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

/s/

Christy Cottrell

11/3/2005 02:44:21 PM

DDR: Please process this outgoing consult.

From: Cottrell, Christy
Sent: Tuesday, November 01, 2005 2:06 PM
To: 'Strawn, Laurie'
Subject: NDA 21-938 for Sutent (GIST)
Laurie,

Please refer to your pending NDA 21-938 for Sutent (GIST indication). See below for a request for clarification from the clinical reviewer.

This regards Study A618X1004. Please answer the following question. In addition, please address this question first, prior to addressing the other questions concerning this study that we submitted to you last week.

What derived dataset contains a single progression date provided by the independent core radiology laboratory for each randomized patient?

If you have any questions, feel free to call me.

Thanks,
Christy

*Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9849*

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

/s/

Christy Cottrell
11/1/2005 02:11:09 PM
CSO

From: Cottrell, Christy
Sent: Friday, October 28, 2005 1:41 PM
To: 'Strawn, Laurie'
Subject: NDA 21-938 for Sutent (GIST)
Laurie,

Please refer to your pending NDA 21-938 for Sutent (GIST indication). See below for several requests for clarification from the clinical and statistical reviewers.

If you have any questions, feel free to call me at (301) 796-1347.

Thanks,
Christy

1. What dataset(s) and programs did you use to define time to event variables and to generate time to event results?
2. Why was no data available to the central radiology laboratory for 41 patients, particularly those whose data should have been available prior to the data cut-off date?
3. Why do some patients have data listed from the central radiology laboratory yet not from the investigators?
4. For patient 169 in Study A6181004, what was the documented source of progressive disease? Was progression documented for patients 12, 211, or 294?
5. Why do sequential patient numbers in Study A6181004 extend to 320 when the ITT population was only 312? What was the disposition of randomized patients 83, 84, 296, 312, and 315-318? Why were they not included in the ITT analysis?
6. We believe the following 51 patients in GIST Phase 3 Study A6181004 should have progression censored at Day 1. Do you agree? If not, please specify patients for whom you do not agree, and explain in detail your reasoning.

A618X1004-086022-00012
A618X1004-127449-00033
A618X1004-130706-00072
A618X1004-086022-00081
A618X1004-103556-00092
A618X1004-113649-00093
A618X1004-039285-00113
A618X1004-088097-00132
A618X1004-129538-00158
A618X1004-016025-00159
A618X1004-133015-00167
A618X1004-094103-00169
A618X1004-132401-00211
A618X1004-127449-00228
A618X1004-067665-00238
A618X1004-129079-00243
A618X1004-113649-00259
A618X1004-038733-00264

A618X1004-125359-00266
A618X1004-127962-00268
A618X1004-129411-00269
A618X1004-100147-00270
A618X1004-091532-00279
A618X1004-103556-00280
A618X1004-177600-00281
A618X1004-127964-00287
A618X1004-103556-00289
A618X1004-133253-00291
A618X1004-138236-00292
A618X1004-100147-00293
A618X1004-088097-00294
A618X1004-177600-00295
A618X1004-129152-00297
A618X1004-038733-00298
A618X1004-133139-00299
A618X1004-129538-00300
A618X1004-014405-00301
A618X1004-133253-00302
A618X1004-177600-00303
A618X1004-129395-00304
A618X1004-127982-00305
A618X1004-038733-00306
A618X1004-129395-00307
A618X1004-131182-00308
A618X1004-110129-00309
A618X1004-038733-00310
A618X1004-129395-00311
A618X1004-131182-00313
A618X1004-113593-00314
A618X1004-129395-00319
A618X1004-129411-00320

*Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9849*

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

/s/

Christy Cottrell
10/28/2005 01:47:20 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-938
NDA 21-968

FILING COMMUNICATION

10/24/05

Pfizer, Inc.
10777 Science Center Drive
San Diego, CA 92121

Attention: Laurie M. Strawn, Ph.D.
Associate Director, Worldwide Regulatory Strategy

Dear Dr. Strawn:

Please refer to your August 10, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SUTENT (sunitinib malate) Capsules.

We also refer to your submissions dated August 31, September 15, 23, and 30, and October 6, 11, and 14 (2), 2005.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on October 10, 2005, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing 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.

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 796-1347.

Sincerely,

[See appended electronic signature page]

Christy Cottrell
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/

Christy Cottrell
10/24/2005 03:23:02 PM

From: Cottrell, Christy
Sent: Thursday, October 20, 2005 1:56 PM
To: 'Strawn, Laurie'
Subject: NDA 21-968 for Sutent (MRCC)
Laurie,

Please refer to your pending NDA 21-968 for Sutent (MRCC indication). See below for inquiries from Dr. Goodman.

1. Please confirm that all lesions identified as target lesions for patient 014-62445-0054 were less than 20 mm and that all assessments of this patient utilized conventional CT (not spiral CT) as the imaging modality.

2. Please provide clarification of the tumor assessment data for patient 014-62445-0029. This patient was initially assessed by the investigator as a PR, then reassigned as NE, but evaluated as a PR by [redacted]. The CRF also describes multiple changes to the list of lesions that were considered in the assessments (e.g. lesions appear to have been deleted and added back).

If you have any questions, feel free to call me at (301) 796-1347.

Christy

Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9849

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

/s/

Christy Cottrell
10/20/2005 02:06:15 PM
CSO

From: Cottrell, Christy
Sent: Friday, October 14, 2005 3:14 PM
To: 'Strawn, Laurie'
Subject: NDA 21-968 for Sutent
Laurie,

Please refer to your pending NDA 21-968 for Sutent (MRCC indication). See below for a request for additional information from the clinical reviewer.

In assessing the duration of treatment and duration of response for patients on study 014, did you include data from the continuation studies RTKC-0511- 017 and A6181030? I have been unable to locate data from these studies documenting date of treatment discontinuation/study termination and date of documented progression. If this data was included in your submission, please provide the location. If this data was used in these analyses and was not submitted, please provide this data for review.

Please let me know if you have any questions.

Christy

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

/s/

Christy Cottrell
10/14/2005 03:19:30 PM
CSO

From: Cottrell, Christy
Sent: Wednesday, October 05, 2005 9:47 AM
To: 'Strawn, Laurie'
Subject: NDAs 21-938 and 21-968
Laurie,

Please refer to your pending NDAs 21-938 and 21-968 for Sutent. Included in this fax are requests for additional information from the PK and clinical reviewers.

Clinical

Please provide case report forms and additional narrative information concerning listed protocol violations for the following patients.

A6181004-101149-00019
A6181004-130036-00082
A6181004-088097-00132

Please provide case report forms without additional narration for the following patients.

A6181004-129926-00058
A6181004-113649-00070
A6181004-130706-00072
A6181004-067665-00086

Clinical Pharmacology

We would like to request the following information:

- Data sets for the dissolution studies included in the NDA.

PK analyses

- Control streams for all of the models used in the model building of the population PK model. The control stream files should be provided as ASCII (*.txt) files. For e.g., model.ctl should be submitted as "model_ctl.txt".
- A detailed tabulated summary (including parameter estimates, variability estimates, objective function values) of all the models that were sequentially run, i.e., from base model to final model, would be very helpful.

PKPD analyses

- The dataset of the exposure measures (including AUCss, Ctrough, cumulative AUC and 28-day AUCs) for the patients in the 6 studies included in the PK-PD analyses. This data may be combined with the PD dataset (dosepd.xpt), or submitted as a separate dataset (in *.xpt format).
- Control streams for all of the models used in the development for each of the PD

measures. The control stream files should be provided as ASCII (*.txt) files. For e.g., model.ctl should be submitted as "model_ctl.txt".

A detailed tabulated summary (including parameter estimates, variability estimates, objective function values) of all the models that were sequentially run, i.e., from base model to final model, for each of the PD measures, would be very helpful.

If you have any questions, let me know.

Thanks,
Christy

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

/s/

Christy Cottrell
10/5/2005 10:04:48 AM
CSO

From: Cottrell, Christy
Sent: Wednesday, September 28, 2005 1:50 PM
To: 'Strawn, Laurie'
Subject: NDA 21-968 for Sutent (MRCC)
Laurie,

Please refer to your pending NDA 21-968 for Sutent (MRCC indication). Below are requests for additional information from Dr. Goodman.

1. The protocol for study 1006 defines the primary efficacy population as the MITT population (p.54 section 12.2). However, the study report describes the ITT population as the primary efficacy population (p. 66 section 6.3). The data for the ITT population was also presented as the primary efficacy analysis in your presentation to DDOP on September 22. Please explain this discrepancy or provide clarification.
2. According to the title page of the clinical protocol for study 1006, two amendments to the study were enacted after November 20, 2003. The changes made with the first amendment were included in the submission, and a copy of the protocol dated July 28, 2004 (the date of the second amendment) was included. However, I am unable to find a list of changes enacted with that second amendment. Please provide this information or its location in the NDA submission.

Thanks,
Christy

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

/s/

Christy Cottrell
9/28/2005 01:53:13 PM
CSO

From: Cottrell, Christy
Sent: Monday, September 19, 2005 2:55 PM
To: 'laurie.strawn@pfizer.com'
Subject: NDA 21-968: Request for clarification
Laurie,

Please refer to your pending NDA 21-968 for Sutent (MRCC indication). Below is a request for clarification from the clinical reviewer.

- In the clinical study report for study 014, Table 7, you report 3 patients with protocol deviations based on exclusion criteria #1 (patient #s 6, 33 and 38). Please provide a brief explanation of the violations for each patient (e.g., received multiple regimens or received radiation and/or surgery within 4 weeks of study therapy start date).
- Also, please explain why patients 18 and 51, who have received multiple systemic therapy regimens, were not counted among these violations.

Let me know if you have any questions.

Thanks,
Christy

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

/s/

Christy Cottrell
9/19/2005 02:58:14 PM
CSO

From: Cottrell, Christy
Sent: Wednesday, August 24, 2005 9:30 AM
To: 'laurie.strawn@pfizer.com'
Subject: NDA 21-938 for GIST
Laurie,

Please see the following inquiry from the Clinical reviewer regarding the GIST NDA.

Regarding Study A6181004, please address the following two issues:

- 1) GIST Datasets indicate that patients were enrolled at sites 34186, 38733, and 39285. However, there are no centers or investigators identified with these numbers. Please clarify.
- 2) The following six GIST investigators/sites appear not to have enrolled any patients. Please confirm or clarify.

Demetri, 113591
Budd, 114799
Verweij, 26823
Butrynski, 174106
Verrill, 129414
Rosen, 098072

Thanks,
Christy

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

/s/

Christy Cottrell
8/24/2005 09:46:24 AM
CSO

8/16/05

MEMORANDUM

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

TO: Dottie Pease, CPMS
Division of Oncology Drug Products, HFD-150

FROM: Brian Strongin, CPMS
Division of GI and Coagulation Drug Products, HFD-180

SUBJECT: Transfer of NDA 21-938
SUTENT (sunitinib malate) Capsules

- 1) treatment of gastrointestinal stromal tumor (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance
- 2) treatment of metastatic renal cell carcinoma L

In the line with the OND policy of placing administrative responsibility of NDAs within the Division that reviews the principal clinical research activity of the drug, we are forwarding the attached NDA for your acceptance. If you do not concur, please include the reason as a signature comment. If you have any questions, call me at 301-827-7459.

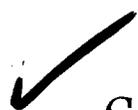
Appears This Way
On Original

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

/s/

Brian Strongin
8/16/2005 12:59:43 PM

18 Page(s) Withheld



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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(4) Draft Labeling

4 Page(s) Withheld



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

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

6 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

3 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-938 and NDA 21-968	Efficacy Supplement Type SE-	Supplement Number
Drug: SUTENT® (sunitinib malate) Capsules		Applicant: Pfizer, Inc.
RPM: Christy Cottrell	HFD-150	Phone # (301) 796-1347
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority 1 P
❖ User Fee Goal Dates		
❖ Special programs (indicate all that apply)		<input type="checkbox"/> None Subpart H (for NDA 21-968) <input checked="" type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input checked="" type="checkbox"/> Fast Track (for both NDAs) <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee • User Fee waiver 		<input checked="" type="checkbox"/> Paid UF ID number 3006158 <input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
<ul style="list-style-type: none"> • User Fee exception 		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

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

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	Included
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	Filing review: 1/24/06

General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	() Materials requested in AP letter (X) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None (X) Press Release () Talk Paper () Dear Health Care Professional Letter (X) ASCO burst email
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Attached to letter
• Most recent applicant-proposed labeling	Attached to letter
• Original applicant-proposed labeling	Included
• Labeling reviews (including DDMAC, DMETS, DSRCs) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC: 11/8/05 DMETS: 11/19/04 and 12/13/05
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Attached to letter
• Applicant proposed	Attached letter
• Reviews	See CMC review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Included
• Documentation of discussions and/or agreements relating to post-marketing commitments	Included
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Included
❖ Memoranda and Telecons	Included
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	11/10/03; 1/23/04; 2/23/05
• Pre-NDA meeting (indicate date)	9/23/04; 1/19/05; 4/19/05
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A: ODS rep attended labeling mtgs
• Other	Included
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	DD Memo: 1/25/06
Clinical Information	
❖ Clinical review(s) <i>(indicate date for each review)</i>	VG (21-968): 1/17/06 ER (21-938): 1/25/06 DMIHDP (21-968): 11/29/05 and 1/24/06
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	N/A
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	See Clinical reviews
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Included
❖ Demographic Worksheet <i>(NME approvals only)</i>	N/A
❖ Statistical review(s) <i>(indicate date for each review)</i>	JJ (21-938): 1/5/06 ST (21-968): 12/21/05
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	1/17/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	11/30/05
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	1/25/06
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	See CMC review
• Review & FONSI <i>(indicate date of review)</i>	N/A
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	N/A
❖ Facilities inspection (provide EER report)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	1/23/06
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
❖ CAC/ECAC report	N/A

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

/s/

Christy Cottrell
2/2/2006 01:52:32 PM