CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-923

Administrative/Correspondence Reviews

1.3.5.2 Patent Certifications

All investigations relied upon by Bayer in this original NDA were conducted by or for Bayer, and accordingly neither 21 U.S.C. 355 (b)(2) nor (j)(2)(A) are applicable.

1.3.5.1 Patent Information

Bayer Pharmaceuticals Corporation is the owner of several US patent applications directed to the drug substance, formulations comprising the drug substance, and methods of using the drug substance. The patent information for this NDA will be amended to include each of these patents upon issuance.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-923

NAME OF APPLICANT / NDA HOLDER
Bayer Pharmaceuticals Corporation

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
NEXAVAR

ACTIVE INGREDIENT(S)	STRENGTH(S)
sorafenib tosylate	200 mg

DOSAGE FORM
tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent

d. Name of Patent Owner	Address *(of Patent Owner)*	
Bayer Pharmaceuticals Corporation	400 Morgan Lane	
	City/State: West Haven, CT	
	ZIP Code: 06516	FAX Number *(if available)*
	Telephone Number: (203) 812-2000	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

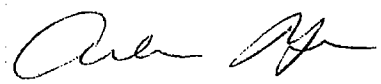
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes	

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	June 22, 2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Aileen Ryan Director, Global Regulatory Affairs Therapeutic Area Oncology	
Address Bayer Pharmaceuticals Corporation 400 Morgan Lane	City/State West Haven/CT
ZIP Code 06516	Telephone Number (203) 812 - 6377
FAX Number *(if available)* (203) 812 - 6113	E-Mail Address *(if available)* Aileen.Ryan.b@bayer.com

EXCLUSIVITY SUMMARY

NDA # 21-923 SUPPL # HFD # 150

Trade Name Nexavar

Generic Name sorafenib

Applicant Name Bayer Pharmaceuticals Corporation

Approval Date, If Known December 20, 2005

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

505(b)(1)

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 (five)

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 ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

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: Patricia Garvey, R.Ph.
Title: Regulatory Project Manager
Date:

Name of Office/Division Director signing form: Robert 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/

Robert Justice
1/17/2006 04:33:32 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA# : 21-923 **Supplement Type (e.g. SE5): _____** **Supplement Number:**

Stamp Date: July 8, 2005 **Action Date: January 8, 2005**

HFD-150 **Trade and generic names/dosage form: Nexavar (sorafenib tosylate) Tablets 200mg**

Applicant: Bayer Pharmaceuticals Corporation **Therapeutic Class: 1**

Indication(s) previously approved:

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

Number of indications for this application(s): 1

Indication #1: Nexavar is indicated for the treatment of patients with advanced renal cell carcinoma.

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

X 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**
- X **Other: Orphan Drug Designation**

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}

_____
Regulatory Project Manager

cc: **NDA 21-923**
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)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

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 copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA ##-###**
HFD-960/ Grace Carmouze

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

(revised 10-14-03)

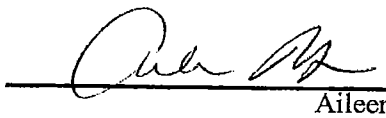
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Garvey
12/1/2005 12:07:19 PM

1.3.3 Debarment Certification

Bayer hereby certifies under FD&C Act, Section 306(k)(1) 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.



Aileen Ryan
Director Global Regulatory Affairs
Theraputic Area Oncology

Fax

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Aileen Ryan, M.Sc. – Bayer Pharmaceutical Corp.	**From:**	Patty Garvey, R.Ph.
Fax:	203-812-6113	**Fax:**	301-796-9867
Phone:	203-812-6377	**Phone:**	301-796-1356
Pages (including cover):	3	**Date:**	December ~~18~~ 19, 2005
Re:	NDA 21-923 Nexavar – Phase 4 commitment		

☐ **Urgent** X **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Comment:

Dear Aileen,

Please refer to your NDA 21-923 Nexavar. We have made minor revisions to the phase 4 commitments.

Please review and let me know if these are acceptable. Please provide me with your responses as soon as possible.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Regulatory Project Manager
Division of Drug Oncology Products

Post-Marketing Commitments:

Clinical

Regarding Study 11213, "A phase 3 randomized study of BAY43-9006 in patients with unresectable and/or metastatic renal cell cancer":

1. Provide the results of the second interim analysis of overall survival (cutoff date of November 30, 2005) by February 2006.

2. Provide the complete study report and datasets with the definitive statistical analysis of overall survival (after approximately 540 events) by March 2007.

Chemistry

3. The FDA acknowledges your commitment to make appropriate changes as recommended by USAN if USAN does not accept your proposed name.

Clinical Pharmacology and Biopharmaceutics

4. Please provide a full report for the dose-ranging Phase 1 study in Japan (Study 11497) and additional data in Asian patients from ongoing studies.

   The evaluation and submission of data from the Phase 1 study in Japan and other ongoing studies will be completed in December 2006.

   Based on a review of these data, the FDA will determine whether further study is warranted. If the FDA concludes that further study is warranted, you will:

   a) conduct modeling and simulation to determine a dosing regimen to achieve similar exposures in Asians and Caucasians, and
   b) FDA will review this modeling and simulation and the proposed dosing regimen. After agreement on the proposed dosing regimen and study design, a pharmacokinetic study will be performed in Asian patients.

   The modeling to determine a dosing regimen will be completed in March 2007.

   If a PK study to evaluate an alternative dosing regimen in Asian patients is warranted, the study will be reported by June 2008.

   Protocol submission: March 2007
   Study start: July 2007
   Final report submission: June 2008

5. Complete the ongoing study of the effect of sorafenib on paclitaxel (a CYP 2C8 substrate) pharmacokinetics: Study 100375.

   Protocol submission: November 29, 2001 (IND 60,453, serial number 038)
   Study start: July 15, 2002
   Final report submission: June 2006

6. Complete the ongoing investigation of the ability of biomarkers to identify patients who respond to sorafenib.

   This request will be fulfilled based on data from two studies; 100391 and 11213.

   Study 100391
   Protocol Submission: April 12, 2002 (IND 60,453, serial number 67)
   Study start: September 25, 2002
   Final report submission: September 2006

   Study 11213
   Protocol Submission: October 16, 2003 (IND 60,453, serial number 317)
   Study start: November 15, 2003
   Final report submission: September 2006

7. Complete the ongoing study examining the ability of rifampin to alter the pharmacokinetics of sorafenib.

   Protocol submission: October 3, 2005 (IND 60,453, serial number 1109)
   Study start: October 27, 2005
   Final report submission: June 2006

8. Complete the ongoing study examining the pharmacokinetics of sorafenib in patients with renal impairment.

   Protocol submission: April 4, 2005 (IND 60,453, serial number 798)
   Study start: June 3, 2005
   Final report submission: September 2006

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

/s/

Patricia Garvey
12/20/2005 07:31:37 AM
CSO
Sent to the sponsor via email on December 19, 2005

Bayer HealthCare
Pharmaceuticals

December 19, 2005

Robert Justice, M.D., Acting Director
Division of Drug Oncology Products
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: **NDA 21,923**
NEXAVAR® (sorafenib) tablets 200 mg
Post-Marketing Commitments

Bayer Pharmaceuticals
Corporation
400 Morgan Lane
West Haven, CT 06516

Tel: 203 812-2000
www.bayer.com

Dear Dr. Justice:

Reference is made to our original New Drug Application for Nexavar® (sorafenib) tablets 200 mg for the treatment of advanced renal cell carcinoma (RCC) submitted on July 8, 2005. Reference is also made to a December 19, 2005 email from Patty Garvey providing the final list of Post-Marketing Commitments.

The purpose of this submission is to indicate that the Post-Marketing Commitments as outlined are acceptable to us.

If there are any questions regarding this submission, please contact me at (203) 812-6377.

Sincerely,

Aileen Ryan, M.Sc.
Director, Global Regulatory Affairs Therapeutic Area Oncology

Attachments

12/1/05

NDA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

NDA # 21-923 Supplement # Efficacy Supplement Type SE-

Trade Name: Nexavar
Established Name: sorafenib
Strengths: 200 mg

Applicant: Bayer Pharmaceuticals Corporation
Agent for Applicant:

Date of Application: July 6, 2005
Date of Receipt: July 8, 2005
Date clock started after UN: Not Applicable
Date of Filing Meeting: August 23, 2005
Filing Date: September 8, 2005
Action Goal Date (optional): User Fee Goal Date: January 8, 2006

Indication(s) requested: NEXAVAR is indicated for the treatment of patients with 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.) Orphan

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 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*

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? All

  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: 60,453

- End-of-Phase 2 Meeting(s)? Date(s) August 6, 2003 (Clinical); January 13, 2004 (CMC) NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) December 14, 2004 (Clinical); March 9, 2005 (CMC); May 24, 2005 (CMC and Clinical Biopharmaceutics) 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 ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 23, 2005

BACKGROUND:

This is a New Drug Application (NDA) 21-923 for NEXAVAR (sorafenib) 200 mg tablets indicated for the treatment of patients with advanced renal cell carcinoma.

This NDA is currently being reviewed under the Continuous Marketing Application Pilot 1 program. Nexavar was accepted into the CMA Pilot 1 program on April 20, 2005. The non-clinical reviewable unit (RU1) was submitted on June 17, 2005 and the complete study report for the Phase III randomized study entitled "A Phase III randomized study of BAY 43-9006 in patients with unresectable and/or metastatic renal cell carcinoma" (RU2) was submitted on June 1, 2005. The study reported was submitted by itself per the request of the clinical team. The chemistry, manufacturing, and controls reviewable unit (RU3) was submitted on June 17, 2005, and clinical pharmacology and biopharmaceutics and clinical (final submission) was submitted on July 6, 2005. The PDUFA goal date is January 8, 2006, which is based on the receipt date of the final reviewable unit submission.

On March 26, 2004, the Division of Oncology Drug Products granted fast track designation for sorafenib (BAY43-9006) for treatment of metastatic renal cell carcinoma. On October 8, 2004, the Office of Orphan Products Development granted sorafenib orphan drug designation for the treatment of renal cell carcinoma.

This NDA was not presented to the Oncologic Drug Advisory Committee.

ATTENDEES: Robert Justice, M.D., Ann Farrell, M.D., Robert Kane, M.D., David Morse, Ph.D., Haleh Mahloogi, Ph.D., Shengui Tang, Ph.D., Atiqur Rahman, Ph.D., Gene Williams, Ph.D., Patricia Garvey, R.Ph.

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

Discipline	**Reviewer**
Medical:	Robert Kane, M.D.
Secondary Medical:	----------
Statistical:	Shenghui Tang, Ph.D.
Pharmacology:	Haleh Mahloogi, Ph.D.
Statistical Pharmacology:	----------
Chemistry:	Josephine Jee, MS, Chengyi Liang, Ph.D.
Environmental Assessment (if needed):	----------
Biopharmaceutical:	Gene Williams, Ph.D.
Microbiology, sterility:	----------
Microbiology, clinical (for antimicrobial products only):	----------
DSI:	Robert Young, M.D.
Regulatory Project Management:	Patricia Garvey, R.Ph.

Other Consults:

DDMAC	Joseph Grillo, Pharm.D.
DSRCS	Jeanine Best, MSN, RN, RNP
DMETS	Kristina Arnwine, Pharm.D.
ODAC	Maha Hussain, M.D.
Patient Consultant	Robert Mayer

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: Submitted in CTD format

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:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ 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.

3.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Patricia Garvey, R.Ph.
Regulatory Project Manager, HFD-150

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   ***NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

    - Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

      YES ☐ NO ☐

    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

      YES ☐ NO ☐

    - EITHER

      The number of the applicant's IND under which the studies essential to approval were conducted.

      IND# _____ NO ☐

      OR

      A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

      YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

    YES ☐ NO ☐

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

/s/

Patricia Garvey
12/5/2005 08:16:53 AM
CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA **21-923**	Efficacy Supplement Type SE-	Supplement Number	
Drug: **Nexavar (sorafenib) 200 mg Tablets**		Applicant: Bayer Pharmaceuticals Corporation	
RPM: **Patricia Garvey, R.Ph.**		HFD-**150**	Phone # **301-796-1356**

Application Type: **(X)** 505(b)(1) ( ) 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.) **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.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	( ) Standard **(X)** Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	Orphan
❖ User Fee Goal Dates	January 8, 2006
❖ Special programs (indicate all that apply)	( ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) **(X)** Fast Track **(X)** Rolling Review **(X)** CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	( ) Paid UF ID number _____
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify) _____
• User Fee exception	**(X)** Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify) _____
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *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 (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) 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**," 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)? *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).*	( ) Yes ( ) No
(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? (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.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• 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.)	**January 12, 2006**
• 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.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	**Filing review – December 5, 2005**

General Information	
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	**Not Applicable**
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) 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)** Others - **ASCO Burst**
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	**Included in the package**
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	**July 6, 2005**
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**Included in the package**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	Included with PI
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	**December 19, 2005 and December 12, 2005**
• Documentation of discussions and/or agreements relating to post-marketing commitments	**December 19, 2005 and December 15, 2005**
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**Included in the package**
❖ Memoranda and Telecons	**Included in the package**
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**January 13, 2004 (CMC)** **August 6, 2003 (Clinical)**
• Pre-NDA meeting (indicate date)	**May 24, 2005 (CMC & Clinical Biopharmaceutics)** **March 9, 2005 (CMC)** **December 14, 2004 (Clinical)**
• Pre-Approval Safety Conference (indicate date; approvals only)	**December 12, 2005**
• Other	
❖ Advisory Committee Meeting	Not Applicable
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	**Not Applicable**

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	**DD – December 14, 2005** **MTL – December 20, 2005 and December 14, 2005**
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	**December 1, 2005**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	**Not Applicable**
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**Included in clinical review – page 38**
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	**Not Applicable**
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	**December 1, 2005**
❖ Statistical review(s) *(indicate date for each review)*	**November 23, 2005**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**November 28, 2005**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**Not Applicable**
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**December 14, 2005 and October 27, 2005**
• Bioequivalence studies	**Not Applicable**
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**December 13, 2005 (2 reviews)**
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	**December 13, 2005**
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**Not Applicable**
❖ Facilities inspection (provide EER report)	Date completed: **August 16, 2005** **(X)** Acceptable ( ) Withhold recommendation
❖ Methods validation	**(X)** Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**November 3, 2005**
❖ Nonclinical inspection review summary	**Not Applicable**
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	**Not Applicable**
❖ CAC/ECAC report	**Not Applicable**

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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

/s/

Patricia Garvey
1/12/2006 01:48:04 PM

Bayer HealthCare
Pharmaceuticals

December 15, 2005

Robert Justice, M.D., Acting Director
Division of Drug Oncology Products
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: **NDA 21,923**
NEXAVAR® (sorafenib) tablets 200 mg
Phase 4 Commitments

Bayer Pharmaceuticals
Corporation
400 Morgan Lane
West Haven, CT 06516

Tel 203 812 2000
www.bayer.com

Dear Dr. Justice:

Reference is made to our original New Drug Application for Nexavar® (sorafenib) tablets 200 mg for the treatment of advanced renal cell carcinoma (RCC) submitted on July 8, 2005. Reference is also made to a December 13, 2005 email from Patty Garvey providing the list of Phase 4 commitments being proposed by the Division and requesting dates by which these commitments will be fulfilled.

The purpose of this submission is to respond to this request.

If there are any questions regarding this submission, please contact me at (203) 812-6377.

Sincerely,

Aileen Ryan, M.Sc.
Director, Global Regulatory Affairs Therapeutic Area Oncology

Attachments

NEXAVAR (sorafenib) tablets NDA 21-923

Phase 4 Post Marketing Commitments

Clinical

1) Provide the results of the statistical analyses of overall survival with the number of events reported with a cut off date of November 30, 2005 and after approximately 540 events as described in the "modified analysis plan for overall survival for study 11213" dated August 18, 2005

   DESCRIPTION OF COMMITMENT:
   Survival analysis 11/05 events: February 2006
   Survival analysis 540 events [redacted] (actual date will be dependant on when 540 events are reached.)

2) Provide the complete study report when the definitive statistical analysis of overall survival is completed on the following study: Study 11213: "A phase 3 randomized study of BAY43-9006 in patients with unresectable and/or metastatic renal cell cancer"

   DESCRIPTION OF COMMITMENT:
   The complete and definitive study report will be submitted to the FDA within 6 months of the final overall survival analysis report, by 03/07 the latest.

Chemistry

Please provide a commitment to the effect that in the event USAN does not accept your proposal, you will commit to making appropriate changes as recommended by USAN.

In the event USAN does not accept our proposal we will make the appropriate changes as recommended by USAN.

Clinical Pharmacology and Biopharmaceutics

1. FDA proposal for the first Phase IV commitment

"Explore alternative dosing regimens in Asian patients, with the goal of arriving at a regimen that will produce the concentration time profile seen in non-Asians. First, modeling and simulation should be used to identify an alternative dosage regimen that is predicted to result in Asian patients having a similar exposure as non-Asians. This regimen should then be administered to Asian patients in a multiple-dose pharmacokinetic study to determine if it performs as predicted."

BAYER's counter proposal

"In order to further explore the observed systemic exposure differences between Asians (n=6) and Caucasians (n=25), the sponsor shall provide a full report for the dose-ranging Phase I study in Japan (Study 11497) and additional data in Asian patients from ongoing

studies. Based on a review of these data, FDA will determine whether further study is warranted. If FDA concludes that further study is warranted, the sponsor shall:

1. conduct modeling and simulation to determine a dosing regimen to achieve similar exposures in Asians and Caucasians, and

2. upon FDA review of this modeling and simulation and agreement on the regimen to be investigated and the study design, *administer this regimen to Asian patients in a pharmacokinetic study to determine if the regimen performs as predicted.*

BAYER will evaluate data from ongoing studies to obtain additional data in Asian and Caucasian patients. These additional data will provide a better estimate of systemic exposure in Japanese patients.

The first part of this request will be completed in 12/06.

If cumulative PK data in Asian and Caucasian patients show significant differences, BAYER will conduct modeling and simulation, with all available data, to determine an alternative dosing regimen to achieve similar exposures in Asians and Caucasians.

This modeling will be completed in 03/07.

The proposed PK study to evaluate an alternative dosing regimen in a special patient population (older Asian patients) will be difficult to enroll. Given the complexity of conducting such a study and reporting clean safety and PK data, we anticipate this study to be reported by 2Q2008.

DESCRIPTION OF COMMITMENT:

Protocol submission:	**by 03/07**
Study start:	**by 07/07**
Final report submission:	**by 06/08**

Rationale for Bayer's counter-proposal

Limited pharmacokinetic data on sorafenib 400 mg twice daily in a study in Japanese patients (n=6) showed a 45% lower systemic exposure (mean steady state AUC) as compared to pooled Phase I pharmacokinetic data in Caucasian patients (n=25). Sorafenib exhibits moderate to high interpatient pharmacokinetic variability. Given the high interpatient PK variability, it is not clear if the apparent difference (45%) in systemic exposure noted in this cross-studies comparison between Japanese and Caucasian patients is real.

NEXAVAR (sorafenib) tablets NDA 21-923

Phase 4 Post Marketing Commitments

Additional Phase II clinical studies are ongoing in Japan and China/Taiwan from which PK data will be available in at least 30 Asian patients (4Q2006) at 400 mg bid. In addition, PK data will be available in additional Caucasian patients.

Data from Japanese Study 11497 and the aforementioned ongoing studies will be provided to the agency. Following this, BAYER would like an opportunity to discuss with the agency all available data and define next steps to clarify if there are clinically relevant pharmacokinetic differences between Asians and Caucasians.

2. Complete the ongoing study of the effect of sorafenib on paclitaxel (a CYP 2C8 substrate) pharmacokinetics: Study 100375.

   DESCRIPTION OF COMMITMENT:
   Protocol submission: **November 29, 2001 (SN 038)**
   Study start: **July 15, 2002**
   Final report submission: **by 06/06**

3. Complete the ongoing investigation of the ability of biomarkers to identify patients who respond to sorafenib.

   DESCRIPTION OF COMMITMENT:
   Final report submission: **09/06**

4. Complete the ongoing study examining the ability of rifampin to alter the pharmacokinetics of sorafenib.

   DESCRIPTION OF COMMITMENT:
   Protocol submission: **October 3, 2005 (SN 1109)**
   Study start: **October 27, 2005**
   Final report submission: **06/06**

5. Complete the ongoing study examining the pharmacokinetics of sorafenib in patients with renal impairment.

   DESCRIPTION OF COMMITMENT:
   Protocol submission: **April 4, 2005 (SN 798)**
   Study start: **June 3, 2005**
   Final report submission: **09/06**

Division Director Summary Review of a New Drug Application

NDA: 21-923
Drug: Nexavar (sorafenib) Tablets
Applicant: Bayer Pharmaceuticals Corporation
Date: December 14, 2005

This NDA was submitted on July 8, 2005. The proposed indication is "for the treatment of patients with advanced renal cell carcinoma." The following summary information comes from the negotiated package insert. See Dr. Kane's Clinical Review for a complete summary of the study information.

Sorafenib is a multikinase inhibitor that decreases tumor cell proliferation *in vitro*. Sorafenib inhibited tumor growth of the murine renal cell carcinoma, RENCA, and several other human tumor xenografts in athymic mice. A reduction in tumor angiogenesis was seen in some tumor xenograft models. Sorafenib was shown to interact with multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT- 3, VEGFR- 2, VEGFR- 3, and PDGFR- ß). Several of these kinases are thought to be involved in angiogenesis...

The safety and efficacy of NEXAVAR in the treatment of advanced renal cell carcinoma (RCC) were studied in the following 2 randomized controlled clinical trials.

Study 1 was a Phase 3, international, multicenter, randomized, double blind, placebo-controlled trial in patients with advanced renal cell carcinoma who had received one prior systemic therapy. Primary study endpoints included overall survival and progression-free survival (PFS). Tumor response rate was a secondary endpoint. The PFS analysis included 769 patients stratified by MSKCC (Memorial Sloan Kettering Cancer Center) prognostic risk category (low or intermediate) and country, and randomized to NEXAVAR 400 mg twice daily (N=384) or to placebo (N=385).

Table 1 summarizes the demographic and disease characteristics of the study population analyzed. Baseline demographics and disease characteristics were well balanced for both treatment groups. The median time from initial diagnosis of RCC to randomization was 1.6 and 1.9 years for the NEXAVAR and placebo groups, respectively.

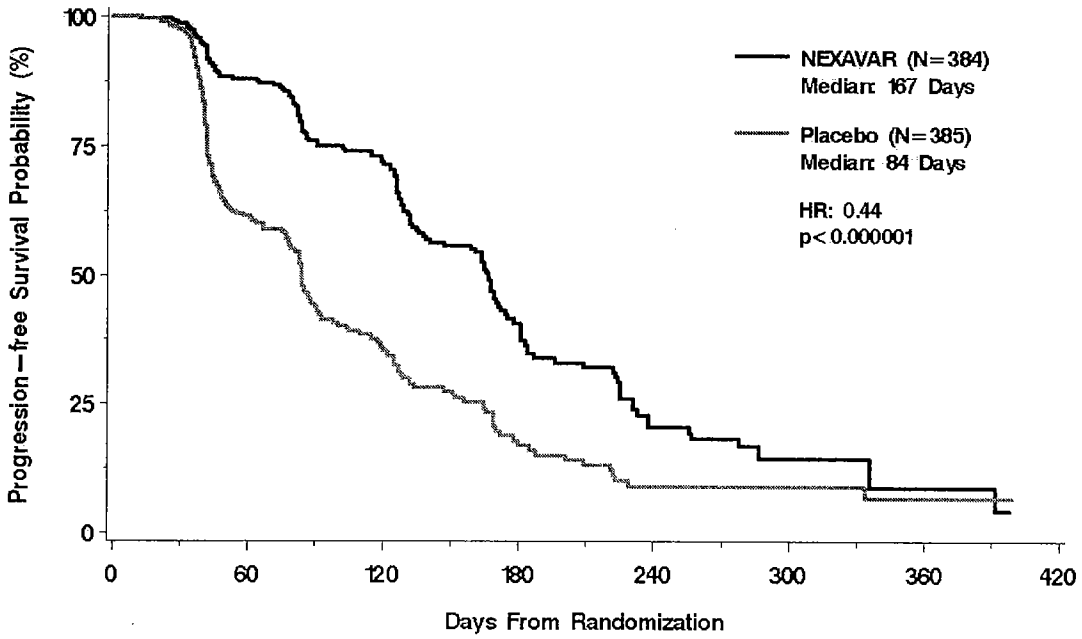
Table 1: Demographic and Disease Characteristics - Study 1

Characteristics	NEXAVAR N=384 N	(%)	Placebo N=385 n	(%)
Gender				
Male	267	(70)	287	(75)
Female	116	(30)	98	(25)
Race				
White	276	(72)	278	(73)
Black/Asian/ Hispanic/Other	11	(3)	10	(2)
Not reported [a]	97	(25)	97	(25)
Age group				
< 65 years	255	(67)	280	(73)
≥ 65 years	127	(33)	103	(27)
ECOG performance status at baseline				
0	184	(48)	180	(47)
1	191	(50)	201	(52)
2	6	(2)	1	(<1)
Not reported	3	(<1)	3	(<1)
MSKCC prognostic risk category[1]				
Low	200	(52)	194	(50)
Intermediate	184	(48)	191	(50)
Prior IL-2 and/or interferon				
Yes	319	(83)	313	(81)
No	65	(17)	72	(19)

a. Race was not collected from the 186 patients enrolled in France due to local regulations. In 8 other patients, race was not available at the time of analysis.

Progression-free survival, defined as the time from randomization to progression or death from any cause, whichever occurred earlier, was evaluated by blinded independent radiological review using RECIST criteria. Figure 1 depicts Kaplan-Meier curves for PFS. The PFS analysis was based on a two-sided Log-Rank test stratified by MSKCC prognostic risk category and country.

Figure 1: Kaplan-Meier Curves for Progression-free Survival – Study 1



NOTE: HR is from Cox regression model with the following covariates: MSKCC prognostic risk category[1] and country. P-value is from two-sided Log-Rank test stratified by MSKCC prognostic risk category[1] and country.

The median PFS for patients randomized to NEXAVAR was 167 days compared to 84 days for patients randomized to placebo. The estimated hazard ratio (risk of progression with NEXAVAR compared to placebo) was 0.44 (95% CI: 0.35, 0.55).

A series of patient subsets were examined in exploratory univariate analyses of PFS. The subsets included age above or below 65 years, ECOG PS 0 or 1, MSKCC prognostic risk category, whether the prior therapy was for progressive metastatic disease or for an earlier disease setting, and time from diagnosis of less than or greater than 1.5 years. The effect of NEXAVAR on PFS was consistent across these subsets, including patients with no prior IL-2 or interferon therapy (n=137; 65 patients receiving NEXAVAR and 72 placebo), for whom the median PFS was 172 days on NEXAVAR compared to 85 days on placebo.

Tumor response was determined by independent radiological review according to RECIST criteria. Overall, of 672 patients who were evaluable for response, 7 (2%) NEXAVAR patients and 0 (0%) placebo patients had a confirmed partial response. Thus the gain in PFS in NEXAVAR-treated patients primarily reflects the stable disease population.

At the time of a planned interim survival analysis, based on 220 deaths, overall survival was longer for NEXAVAR than placebo with a hazard ratio (NEXAVAR over placebo) of 0.72. This analysis did not meet the prespecified criteria for statistical significance. Additional analyses are planned as the survival data mature.

Study 2 was a Phase 2 randomized discontinuation trial in patients with metastatic malignancies, including RCC. The primary endpoint was the percentage of randomized patients remaining progression-free at 24 weeks. All patients received NEXAVAR for the first 12 weeks. Radiologic assessment was repeated at week 12. Patients with <25% change in bi-dimensional tumor measurements from baseline were randomized to NEXAVAR or placebo for a further 12 weeks. Patients who were randomized to placebo were permitted to cross over to open-label NEXAVAR upon progression. Patients with tumor shrinkage ≥25% continued NEXAVAR, whereas patients with tumor growth ≥25% discontinued treatment.

Two hundred and two patients with advanced RCC were enrolled into Study 2, including patients who had received no prior therapy and patients with tumor histology other than clear cell carcinoma. After the initial 12 weeks of NEXAVAR therapy, 79 RCC patients continued on open-label NEXAVAR, and 65 patients were randomized to NEXAVAR or placebo. After an additional 12 weeks, at week 24, for the 65 randomized patients, the progression-free rate was significantly higher in patients randomized to NEXAVAR (16/32, 50%) than in patients randomized to placebo (6/33, 18%) (p=0.0077). Progression-free survival was significantly longer in the NEXAVAR group (163 days) than in the placebo group (41 days) (p=0.0001, HR=0.29)...

Safety evaluation of NEXAVAR is based on 1286 cancer patients who received NEXAVAR as monotherapy and 165 patients who received NEXAVAR concurrently with chemotherapy. A total of 346 patients were exposed to NEXAVAR monotherapy for greater than 6 months. A total of 664 RCC patients received NEXAVAR monotherapy, of whom 215 were treated for at least 6 months.

Table 2 shows the percent of patients experiencing treatment-emergent adverse events that were reported in at least 10% of patients who received NEXAVAR in Study 1. CTCAE Grade 3 treatment-emergent adverse events were reported in 31% of patients receiving NEXAVAR compared to 22% of patients receiving placebo. CTCAE Grade 4 treatment-emergent adverse events were reported in 7% of patients receiving NEXAVAR compared to 6% of patients receiving placebo.

Table 2: Treatment-Emergent Adverse Events Reported in at Least 10% of NEXAVAR-Treated Patients – Study 1

Adverse Event NCI-CTCAE v3 Category/Term	NEXAVAR N=451			Placebo N=451		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any Event	95	31	7	86	22	6
Cardiovascular, General						
Hypertension	17	3	<1	2	<1	0
Constitutional symptoms						
Fatigue	37	5	<1	28	3	<1
Weight loss	10	<1	0	6	0	0
Dermatology/skin						
Rash/desquamation	40	<1	0	16	<1	0
Hand -foot skin reaction	30	6	0	7	0	0
Alopecia	27	<1	0	3	0	0
Pruritus	19	<1	0	6	0	0
Dry skin	11	0	0	4	0	0
Gastrointestinal symptoms						
Diarrhea	43	2	0	13	<1	0
Nausea	23	<1	0	19	<1	0
Anorexia	16	<1	0	13	1	0
Vomiting	16	<1	0	12	1	0
Constipation	15	<1	0	11	<1	0

Adverse Event NCI-CTCAE v3 Category/Term	NEXAVAR N=451			Placebo N=451		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Hemorrhage/bleeding						
Hemorrhage – all sites	15	2	0	8	1	<1
Neurology						
Neuropathy-sensory	13	<1	0	6	<1	0
Pain						
Pain, abdomen	11	2	0	9	2	0
Pain, joint	10	2	0	6	<1	0
Pain, headache	10	<1	0	6	<1	0
Pulmonary						
Dyspnea	14	3	<1	12	2	<1
Cough	13	<1	0	14	<1	0

The rate of adverse events (including events associated with progressive disease) resulting in permanent discontinuation was similar in both the NEXAVAR and placebo groups (10% of NEXAVAR patients and 8% of placebo patients).

Safety was also assessed in a Phase 2 study pool comprised of 638 NEXAVAR-treated patients, including 202 patients with RCC, 137 patients with hepatocellular carcinoma, and 299 patients with other cancers. The most common drug-related adverse events reported in NEXAVAR-treated patients in this pool were rash (38%), diarrhea (37%), hand-foot skin reaction (35%), and fatigue (33%). The respective rates of CTC (v 2.0) Grade 3 and 4 drug-related adverse events in NEXAVAR-treated patients were 37% and 3%, respectively...

The following laboratory abnormalities were observed in Study 1:

Hypophosphatemia was a common laboratory finding, observed in 45% of NEXAVAR-treated patients compared to 11% of placebo patients. CTCAE Grade 3 hypophosphatemia (1-2 mg/dL) occurred in 13% of NEXAVAR-treated patients and 3% of patients in the placebo group. There were no cases of CTCAE Grade 4 hypophosphatemia (<1 mg/dL) reported in either NEXAVAR or placebo patients. The etiology of hypophosphatemia associated with NEXAVAR is not known.

Elevated lipase was observed in 41% of patients treated with NEXAVAR compared to 30% of patients in the placebo group. CTCAE Grade 3 or 4 lipase elevations occurred in 12% of patients in the NEXAVAR group compared to 7% of patients in the placebo group. Elevated amylase was observed in 30% of patients treated with NEXAVAR compared to 23% of patients in the placebo

group. CTCAE Grade 3 or 4 amylase elevations were reported in 1% of patients in the NEXAVAR group compared to 3% of patients in the placebo group. Many of the lipase and amylase elevations were transient, and in the majority of cases NEXAVAR treatment was not interrupted. Clinical pancreatitis was reported in 3 of 451 NEXAVAR-treated patients (one CTCAE Grade 2 and two Grade 4) and 1 of 451 patients (CTCAE Grade 2) in the placebo group.

Lymphopenia was observed in 23% of NEXAVAR-treated patients and 13% of placebo patients. CTCAE Grade 3 or 4 lymphopenia was reported in 13% of NEXAVAR-treated patients and 7% of placebo patients. Neutropenia was observed in 18% of NEXAVAR-treated patients and 10% of placebo patients. CTCAE Grade 3 or 4 neutropenia was reported in 5% of NEXAVAR-treated patients and 2% of placebo patients.

Anemia was observed in 44% of NEXAVAR-treated patients and 49% of placebo patients. CTCAE Grade 3 or 4 anemia was reported in 2% of NEXAVAR-treated patients and 4% of placebo patients.

Thrombocytopenia was observed in 12% of NEXAVAR-treated patients and 5% of placebo patients. CTCAE Grade 3 or 4 thrombocytopenia was reported in 1% of NEXAVAR-treated patients and 0% of placebo patients.

Medical Officer Review

The initial Clinical Review by Robert Kane, M.D. was completed on December 1, 2005. Dr. Kane made the following recommendation for regulatory action.

I recommend approval of sorafenib under subpart H of 21 CFR 314, accelerated approval, for the applicant's proposed indication, the treatment of patients with advanced renal cell carcinoma (RCC), on the basis of substantial evidence of effectiveness and safety derived from a single, large, adequate and well-controlled, double-blind study comparing sorafenib with placebo for this patient population. Confirmatory evidence is provided by a supportive phase 2 study also submitted for the NDA.

Advanced renal cell carcinoma (including unresectable and metastatic disease) is a serious and life- threatening disease for which there is no standard therapy of general benefit to patients. Effectiveness is demonstrated by statistically compelling and clinically convincing evidence of prolongation in progression-free survival (PFS) for sorafenib treated patients after receiving one prior therapy

as well as for a patient group who had not received previous treatment specifically directed toward metastatic disease (the prior therapy occurred pre- or post-operatively). While PFS has been shown to convey clinical benefit in other disease states, this relationship has not been established for advanced RCC. A hazard ratio of 0.44, indicating a relative improvement for PFS of 56%, is substantial and likely to convey clinical benefit. Notably, the response rate is low – 2.1% – when measured using traditional RECIST criteria.

Safety is demonstrated in the context of this therapy by the low frequency and/ or low severity of adverse effects, dose reductions, and withdrawals for drug- related toxicity. The applicant examined one fixed dose schedule, 400 mg twice daily by mouth, and found it to be well tolerated by a large majority of the patients. Hand-foot skin reaction, blood pressure elevation, and sensory neuropathy may require interruption of therapy. Temporary dose interruptions occurred in 14% of sorafenib patients, and dose reductions were employed in 10% of sorafenib patients for AEs. The label adequately conveys the clinical information and directions for use.

Bayer should continue to follow all patients for the survival outcome results. However, given the early study termination and cross- over of patients to sorafenib, regular approval should be granted based on the completion of the survival analysis as pre- specified and provided there is no finding of an adverse survival effect of sorafenib.

Dr. Kane made the following recommendations on postmarketing actions.

1.2.1 Risk Management Activity

Blood pressure should be monitored weekly during the first 6 weeks of treatment with sorafenib to allow detection and management of the 10% of patients who may experience hypertension on sorafenib therapy. This monitoring is described in the label. No unique risk management actions are evident at present.

1.2.2 Required Phase 4 Commitments

Bayer should continue to follow all patients for the survival outcome and provide those results to the FDA. However, given the early study termination and cross-over of patients to sorafenib, regular approval should be granted upon a finding of statistically significant improvement in overall survival or upon the completion of the survival analysis provided there is no finding of an adverse survival effect of sorafenib. The study also should continue to follow all patients to provide further experience regarding duration of exposure for sorafenib safety and tolerance.

Sorafenib is a new molecular entity, small molecule, and it would be the first in the class of raf-kinase inhibitors to receive FDA approval. It is also a VEGF- R inhibitor. Bevacizumab, a monoclonal antibody VEGF inhibitor, has been associated with thrombosis, hemorrhage, and surgical wound healing delays. In the controlled studies of sorafenib to date, only a modest number of patients have been at risk for such complications. The applicant should propose and implement (with FDA concurrence on the details) a plan: (1) to monitor arterial thrombosis and hemorrhage in a larger population of patients and (2) to monitor wound healing in patients requiring surgical procedures while receiving sorafenib.

1.2.3 Other Phase 4 Requests

Hemorrhage has been reported in association with sorafenib, in particular involving the skin, nails, and GI tract. The applicant should perform a study of platelet function [ ] assay) in patients before and during sorafenib therapy to ascertain if platelet function is impaired by sorafenib.

Hypophosphatemia occurs commonly and is an unusual AE of anti- neoplastic therapy. The applicant should study further the mechanism of hypophosphatemia. If renal tubular re-absorptive function is altered by sorafenib, other substances in plasma may have altered renal handling as well.

Thyroid changes and hypothyroidism were observed in some nonclinical studies of sorafenib and are associated with tyrosine kinase inhibitory activity. The sponsor should conduct a prospective study to assess changes in thyroid function in a cohort of sorafenib-treated patients over time. Although only 2 sorafenib-treated patients were diagnosed with clinical hypothyroidism in the phase 3 study, this was not prospectively assessed in the study.

The applicant should inform physicians specifically of the unusual AE findings associated with sorafenib therapy, in particular the expected elevations in lipase, reductions in phosphate, and the elevations in blood pressure which may occur.

Addendum to the Clinical Review

An Addendum to the Clinical Review was completed by Dr. Kane on December 14, 2005. Dr. Kane revised the required phase 4 commitments and other phase 4 requests:

1.2.2 Required Phase 4 Commitments

Bayer should continue to follow all patients in study 11213 "A phase 3 randomized study of BAY43- 9006 in patients with unresectable and/or metastatic renal cell cancer" for the survival outcome and provide those results to the FDA. However, given the early study termination and cross-over of patients to sorafenib, regular approval should be granted upon a finding of statistically significant improvement in overall survival or upon the completion of the survival analysis

provided there is no finding of an adverse survival effect of sorafenib. The study also should continue to follow all patients to provide further experience regarding duration of exposure for sorafenib safety and tolerance.

Clinical-Required post-marketing commitments:

1) Provide the results of the statistical analyses of overall survival after approximately 270 events and after approximately 540 events as described in the "modified analysis plan for overall survival for study 11213" dated August 18, 2005

2) Provide the complete study report within 6 months of the time that the definitive statistical analysis of overall survival is performed on the following study: Study 11213: " A phase 3 randomized study of BAY43- 9006 in patients with unresectable and/or metastatic renal cell cancer"

1.2.3 Other Phase 4 Requests

A: Hemorrhage has been reported in association with sorafenib, in particular involving the skin, nails, and GI tract. The applicant should perform a study of platelet function ([ ] assay) in patients before and during sorafenib therapy to ascertain if platelet function is impaired by sorafenib.

B: Hypophosphatemia occurs commonly and is an unusual adverse event of anti-neoplastic therapy. The applicant should study further the mechanism of hypophosphatemia. If renal tubular re- absorptive function is altered by sorafenib, other substances in plasma may have altered renal handling as well.

C: Thyroid changes and hypothyroidism were observed in some nonclinical studies of sorafenib and are associated with inhibition of tyrosine kinase activity. Although only 2 sorafenib-treated patients were diagnosed with clinical hypothyroidism in the phase 3 study, this was not prospectively assessed in the study. The sponsor should conduct a prospective study to assess changes in thyroid function in a cohort of sorafenib- treated patients over time.

D. Sorafenib is the first in the class of raf- kinase inhibitors to receive FDA approval. It is also a VEGF- R inhibitor. Bevacizumab, a monoclonal antibody VEGF inhibitor, has been associated with thrombosis, hemorrhage, and surgical wound healing delays. In the controlled studies of sorafenib to date, only a modest number of patients have been at risk for such complications. The applicant should propose and implement a plan: (1) to monitor arterial thrombosis and hemorrhage in a larger population of patients and (2) to monitor wound healing in patients requiring surgical procedures while receiving sorafenib.

Medical Team Leader Review

The Medical Team Leader Review by Ann Farrell, M.D. was completed on December 14, 2005. Dr. Farrell's conclusions and recommendations are quoted below.

> On July 6, 2005, Bayer Pharmaceuticals submitted this New Drug Application (NDA) for sorafenib, an oral multi-kinase inhibitor, a new molecular entity, for the treatment of patients (pts) with advanced renal cell cancer (RCC). The submission consisted of two studies for the proposed indication in this population.
>
> In the phase 3 study, sorafenib treatment resulted in an improvement PFS for RCC patients compared with control. The median PFS was improved from 84 days in the control group to 167 days for sorafenib; hazard ratio = 0.44; $p < 0.000001$. In the phase 2 randomized discontinuation trial for the subset of patients with RCC. The study demonstrated that the progression-free rate at the end of the 12-week randomization period was statistically significantly different (i.e., higher) for the sorafenib group than that for the placebo group. Overall, 50.0% (16/32) of subjects randomized to sorafenib and 18.2% (6/33) of subjects randomized to placebo were progression-free at 12 weeks after randomization (P value = 0.0077). The median progression-free survival (PFS) was also statistically significantly different (i.e., longer) for subjects randomized to sorafenib (163 days) than for subjects randomized to placebo (41 days, P value = 0.0001).
>
> The major toxicities observed with sorafenib treatment included: dermatologic (rashes, hand- foot syndrome), gastrointestinal (diarrhea), constitutional (fatigue, fever, weight loss, sweating, other), cardiovascular (hypertension), blood/ bone marrow (decreased hemoglobin) and neurologic (neuropathy).
>
> The sponsor presented a review of the literature and listed 6 randomized trials which had positive overall survival results and the corresponding PFS result. Five out of six of these trials had a statistically significant improvement in PFS. This reviewer reviewed the 6 articles the sponsor presented and concurred with the sponsor's assessment. An effect on PFS resulting in prolongation over control appears to translate into a similar result for survival; thus, this application is recommended for regular approval.
>
> Based on the results contained in this NDA submission, this reviewer recommends regular approval.
>
> Bayer should continue to follow patients enrolled in study 11213 and provide the division with a final safety and survival analysis based on mature data for all patients enrolled in the major study.
>
> Dr. Kane's review has a number of suggestions for additional study. These suggestions should be forwarded to the company.

Clinical Inspection Summaries

Two preliminary clinical inspection summaries were completed. The summary dated October 26, 2005 reported on the inspections of two domestic clinical sites, [ ] (central site for reading images), and the applicant. The summary concluded the following.

> To date nothing has been found that would impair the use of the clinical data in support of approval of the submitted NDA. The principal problem is that clinical inspections were completed at only two of the four clinical investigator sites assigned for inspection and at the sponsor and central image reading facility. This summary will be updated when the results of summary will be shared with the reviewing division.

The summary dated December 14, 2005 reported on the inspections of two foreign sites. The summary concluded the following.

> To date nothing has been found that would impair the use of the clinical data in support of approval of the submitted NDA. EIRs for two sites have not yet been received. This summary will be updated if the EIRs not yet received for two clinical investigator inspections significantly changes the recommendation as to data validity.

Statistical Review and Evaluation

The Statistical Review and Evaluation by Shenghui Tang, Ph.D. was completed on November 11, 2005. Dr. Tang's conclusions are recommendations follow:

> In this reviewer's opinion the study results from the submitted single, Phase III, double-blind, international, randomized, parallel-group, multicenter study, support the claim of efficacy of sorafenib in patients with RCC who received 1 prior regimen of chemotherapy or immunotherapy with respect to progression free survival (PFS). The sorafenib demonstrated a PFS advantage over the placebo in this clinical study. Whether the endpoint and the size of the effect on this endpoint are adequate for approval is a clinical decision.

Pharmacology/Toxicology Review and Evaluation

The Pharmacology/Toxicology Review and Evaluation by Haleh Saber-Mahloogi, Ph.D. was completed on October 28, 2005. Dr. Saber-Mahloogi had the following recommendations.

> A. Recommendation on approvability: There are no Pharmacology/ Toxicology issues which preclude approval of the requested product indication.
>
> B. Recommendation for nonclinical studies: None.

C. Recommendations on labeling: will be provided as a separate addendum review.

Chemistry, Manufacturing and Controls Reviews

Two CMC reviews were completed. The review by Josephine Jee was completed on December 9, 2005. The review recommended the following.

A. Recommendation and Conclusion on Approvability
From a Chemistry, Manufacturing and Controls (CMC) perspective, approval of the application is recommended.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
Bayer will be submitting USAN name.

The CMC review by Chengyi Liang, Ph.D. was completed on December 13, 2005. Dr. Liang's recommendations are as follows:

A. Recommendation and Conclusion on Approvability
This NDA is recommended for approval from the standpoint of CMC. A number of deficiencies related to the drug product have been satisfactorily addressed by the applicant. The Office of Compliance has provided an overall acceptable recommendation.

B. Recommendation on Phase 4 (Post- Marketing) Commitments, Agreements, and/ or Risk Management Steps, if Approvable
Bayer has provided a phase 4 commitment to the effect that in the event USAN does not accept its proposal, Bayer will commit to making appropriate changes as recommended by USAN.

Clinical Pharmacology and Biopharmaceutics NDA Review

The Clinical Pharmacology and Biopharmaceutics Review by Gene Williams, Ph.D., Angela Men, Ph.D., and Carol Noory, Ph.D. was completed on November 23, 2005. The review recommended approval if the dissolution specification is changed. The review also recommended five phase 4 commitments:

1. Explore alternative dosing regimens in Asian patients, with the goal of arriving at a regimen that will produce the concentration time profile seen in non- Asians. First, modeling and simulation should be to identify an alternative dosage regimen that is predicted to result in Asian patients having a similar exposure as non-Asians. This regimen should then be administered to Asian patients in a multiple-dose pharmacokinetic study to determine if it performs as predicted.

2. Complete the ongoing study of the effect of sorafenib on paclitaxel (a CYP 2C8 substrate) pharmacokinetics: Study 100375.

3. Complete the ongoing investigation of the ability of biomarkers to identify patients who respond to sorafenib.

4. Complete the ongoing study examining the ability of rifampin to alter the pharmacokinetics of sorafenib.

5. Complete the ongoing study examining the pharmacokinetics of sorafenib in patients with renal impairment.

DMETS Consultation

The DMETS Consultation was completed on September 30, 2005. DMETS had the following recommendations.

A. DMETS has no objection to the use of the proprietary name, Nexavar. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the signature date of this document, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/ or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product

C. DDMAC finds the proprietary name Nexavar acceptable from a promotional perspective.

The DMETS recommendations for revisions were considered during the reviews of the label and labeling.

DSRCS Review of Patient Labeling (PPI)

The DSRCS review of the PPI was completed on October 28, 2005. The recommendations were incorporated into the revised labeling.

DDMAC Consultation on Draft Labeling

The DDMAC consultation offered comments on the Clinical Pharmacology, Clinical Studies, and the PPI sections of the draft labeling. These were considered during the labeling review and DDMAC provided input at the last team labeling meeting.

Required Phase 4 Commitments

The applicant agreed to the required clinical, clinical pharmacology and biopharmaceutics, and CMC Phase 4 commitments.

Conclusions

I concur with the recommendations for approval of Nexavar for the proposed indication. However, I disagree with Dr. Kane's recommendation for accelerated approval and agree with Dr. Farrell's recommendation for full approval. Dr. Farrell's review points out that in 5 of 6 reported randomized trials in this disease, an improvement in PFS was accompanied by an improvement in survival. In addition, it can also be argued that an improvement in PFS of the magnitude observed in this trial (median of 84 days in the control group to 167 days in the sorafenib group; hazard ratio = 0.44; $p < 0.000001$) is a clinical benefit. Although the data were not collected in the trials, a significant proportion of patients with disease progression are likely to develop new or worsening symptoms or to be treated with other therapies of unproven benefit. A delay in the onset of these events of this magnitude with acceptable toxicity represents clinical benefit. The survival data is also trending in favor of sorafenib. Although the interim analysis p value did not meet the pre-specified value for statistical significance, the hazard ratio was 0.72.

Interleukin-2 is approved for the treatment of advanced or metastatic renal cell cancer. However, as was pointed out in Dr. Kane's review, the approved regimen is extremely toxic and the response rate is only 15%. Interferons are used off-label but are not approved for the treatment of advanced renal cell carcinoma. In the phase 3 sorafenib study, more than 80% of patients had received prior therapy with IL-2 or interferon and 17-19% had not. The effect of sorafenib on PFS in the subset without prior treatment with IL-2 or interferon (n=137; 65 patients receiving sorafenib and 72 placebo) was consistent with the overall result, with a median PFS of 172 days on sorafenib compared to 85 days on placebo (hazard ratio 0.35). For these reasons I concur that the approval should not be limited to patients with prior therapy.

I concur with the required phase 4 commitments and with Dr. Farrell's recommendation for communicating Dr. Kane's requests for additional studies as suggestions for consideration.

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

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/s/

Robert Justice
12/14/2005 08:10:16 PM
MEDICAL OFFICER

✓ Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

12-14-05

Fax

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Aileen Ryan, M.Sc. – Bayer Pharmaceutical Corp.	**From:**	Patty Garvey, R.Ph.
Fax:	203-812-6113	**Fax:**	301-796-9867
Phone:	203-812-6377	**Phone:**	301-796-1356
Pages (including cover):	1	**Date:**	December 12, 2005
Re:	NDA 21-923 Nexavar – Phase 4 commitment		

☐ **Urgent** X **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Comment:

Dear Aileen,

Please refer to your NDA 21-923 Nexavar. The chemistry reviewer has the following phase 4 commitment. Please review and let me know if you agree or object to the commitment. If you have any objection, please provide your propose changes.

> Please provide a commitment to the effect that in the event USAN does not accept your proposal, you will commit to making appropriate changes as recommended by USAN.

Please provide me with your responses as soon as possible. Please contact me if you have any questions.

Sincerely,

Patty Garvey
Regulatory Project Manager
Division of Drug Oncology Products

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/s/

Patricia Garvey
12/12/2005 06:51:06 PM
CSO

INTERNAL MEETING MINUTES

MEETING DATE: December 12, 2005 **TIME:** 1:30 pm

NDA: 21-923

DRUG: Nexavar (sorafenib)

SPONSOR/APPLICANT: Bayer Pharmaceuticals Corporation.

TYPE OF MEETING:

1. Pre-Approval Safety Conference

2. **Proposed Indication:**
   Nexavar (sorafenib) tablets 200mg for the treatment of patients with advanced renal cell carcinoma.

FDA PARTICIPANTS:

Robert Justice, M.D.	--	Acting Division Director, DDOP
Ramzi Dagher, M.D.	--	Acting Deputy Director, DDOP
Robert Kane, M.D.	--	Medical Reviewer, DDOP
Gene Williams, Ph.D.	--	Clinical Pharmacology and Biopharmaceutics Reviewer
Susan Lu, Pharm.D.	--	Team Leader, Division of Drug Risk Evaluation (DDRE), Office of Drug Safety (ODS)
Robert Pratt, Pharm.D.	--	Safety Evaluator, DDRE, ODS
Patty Garvey, R.Ph.	--	Regulatory Project Manager, DDOP

MEETING OBJECTIVE:

To identify potential expected adverse events that the Office of Drug Safety should be aware of for post-marketing surveillance.

DISCUSSION:

Dr. Robert Kane reviewed the label AEs and indicated the possibility of more hemorrhage with Nexavar. There were two serious hemorrhage cases in lung cancer patients. Dr. Kane indicated that there novel laboratory alterations including a 40% incidence of hypophosphatemia and 20% incidence of elevated serum lipase.

Dr. Robert Pratt asked if there were any additional information regarding hypertension. Dr. Kane indicated that hypertension was observed especially during the first 6 weeks on study in about 15% of patients. It will be managed by anti-hypertensive medication.

Dr. Pratt wanted clarification on whether pancreatitis was confirmed by imaging. The diagnosis of pancreatitis in patients taking Nexavar is confounded by the frequent asymptomatic elevations of lipase and amylase. The mechanism is unknown. A diagnosis

of pancreatitis should not be made based on lab values alone. There were only 2 well described patients with pancreatitis on the Nexavar study arm. Imaging results were not reported.

Dr. Pratt asked about the incidences of proteinuria. Dr. Kane indicated that there was not a difference in incidence of proteinuria between the placebo versus the treated group.

Dr. Kane reviewed the sponsor proposed plan for continued data collection and safety reporting under the treatment protocol amendment submitted on November 23, 2005. Dr. Kane indicated that the sponsor proposal was acceptable.

Dr. Susan Lu requested additional information regarding the hand-foot reaction.

Dr. Lu asked if there is any particular drug interaction that should be monitored. Dr. Gene Williams indicated that Nexavar appears to affect the pharmacokinetics of irinotecan.

ACTION ITEMS: None

{See appended electronic signature page}

/S/

Patty Garvey, R.Ph.
Regulatory Project Manager/Facilitator

Concurrence Chair:

{See appended electronic signature page}

/S/

Robert Kane, M.D.
Medical Reviewer, DDOP

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/s/

Robert Kane
1/12/2006 02:05:25 PM

Fax

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Aileen Ryan, M.Sc. – Bayer Pharmaceutical Corp.	**From:**	Patty Garvey, R.Ph.
Fax:	203-812-6113	**Fax:**	301-796-9867
Phone:	203-812-6377	**Phone:**	301-796-1356
Pages (including cover):	1	**Date:**	December 12, 2005
Re:	NDA 21-923 Nexavar – Phase 4 commitment		

☐ **Urgent** X **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Comment:

Dear Aileen,

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> Please provide a commitment to the effect that in the event USAN does not accept your proposal, you will commit to making appropriate changes as recommended by USAN.

Please provide me with your responses as soon as possible. Please contact me if you have any questions.

Sincerely,

Patty Garvey
Regulatory Project Manager
Division of Drug Oncology Products

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/s/

Patricia Garvey
12/12/2005 06:51:06 PM
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Fax

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Aileen Ryan, M.Sc. – Bayer Pharmaceutical Corp.	**From:**	Patty Garvey, R.Ph.
Fax:	203-812-6113	**Fax:**	301-796-9867
Phone:	203-812-6377	**Phone:**	301-796-1356
Pages (including cover):	2	**Date:**	December 9, 2005
Re:	NDA 21-923 Nexavar – Phase 4 commitments		

☐ **Urgent** X **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Comment:

Dear Aileen,

Please refer to your NDA 21-923 Nexavar. The clinical pharmacology and biopharmaceutics reviewer has the following phase 4 commitments. Please review and let me know if you agree or object to the commitments. If you have any objections, please provide your propose changes.

Please provide me with your responses as soon as possible. Please contact me if you have any questions.

Sincerely,

Patty Garvey
Regulatory Project Manager
Division of Drug Oncology Products

PHASE 4 COMMITMENTS:

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

1. Explore alternative dosing regimens in Asian patients, with the goal of arriving at a regimen that will produce the concentration time profile seen in non-Asians. First, modeling and simulation should be used to identify an alternative dosage regimen that is predicted to result in Asian patients having a similar exposure as non-Asians. This regimen should then be administered to Asian patients in a multiple-dose pharmacokinetic study to determine if it performs as predicted.

2. Complete the ongoing study of the effect of sorafenib on paclitaxel (a CYP 2C8 substrate) pharmacokinetics: Study 100375.

3. Complete the ongoing investigation of the ability of biomarkers to identify patients who respond to sorafenib.

4. Complete the ongoing study examining the ability of rifampin to alter the pharmacokinetics of sorafenib.

5. Complete the ongoing study examining the pharmacokinetics of sorafenib in patients with renal impairment.

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/s/

Patricia Garvey
12/9/2005 05:47:43 PM
CSO

Fax

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Aileen Ryan, M.Sc. – Bayer Pharmaceutical Corp.	**From:**	Patty Garvey, R.Ph.
Fax:	203-812-6113	**Fax:**	301-796-9867
Phone:	203-812-6377	**Phone:**	301-796-1356
Pages (including cover):	3	**Date:**	December 1, 2005
Re:	NDA 21-923 Nexavar		

☐ **Urgent** X **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Aileen,

Please refer to NDA 21-923 Nexavar. The clinical review team has requested the following information.

1. Please provide the methodology used to perform literature search for the articles in advanced/metastatic renal cell cancer (e.g., databases used and search strategy including methods of cross-checking to ensure a comprehensive review of the literature).

2. Figure 11-5 in the clinical study report for the randomized controlled trial is unique. Could you provide additional examples where this type of figure has been used (preferably literature)?

3. Could you either provide the dataset and SAS program used to generate figure 11-5 in the clinical study report for the randomized controlled trial or provide the location of these in the NDA submission?

Please response to our request as soon as possible. Please contact me if you have any questions.

Sincerely,

Patty Garvey
Regulatory Project Manager,
Division of Drug Oncology Products

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/s/

Patricia Garvey
12/1/2005 09:57:04 AM
CSO

Fax

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Aileen Ryan, M.Sc. – Bayer Pharmaceutical Corp.	**From:**	Patty Garvey, R.Ph.
Fax:	203-812-6113	**Fax:**	301-796-9867
Phone:	203-812-6377	**Phone:**	301-796-1356
Pages (including cover):	3	**Date:**	December 1, 2005
Re:	NDA 21-923 Nexavar		

☐ **Urgent** X **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Comment:

Dear Aileen,

Please refer to your NDA 21-923 Nexavar. Attached are the chemistry deficiencies. Please address the deficiencies as soon as possible.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Regulatory Project Manager
Division of Drug Oncology Products

CHEMISTRY, MANUFACTURING AND CONTROLS

A. Drug Substance

We recommend that you provide equivalence to USP for the test methods that use compendial methods other than USP [ ]

B. Drug Product

1. Please include the code number for the test methods in DP specifications.

2. Please test [ ] and propose an acceptance criteria. We recommend that the proposed acceptance criteria be consistent with the drug product release data.

3. Please clarify the observed discrepancy in the specification for total degradation products between drug product release specification [ ] and in the data table listed in drug product batch data [ ] Please provide updated release specifications.

4. Please note that you have not proposed an acceptance criteria for specified impurities in drug product release specifications but you have proposed [ ] limit for [ ] in the specifications (data table) under drug product batch data. Please clarify and provide updated release specifications.

5. Please include initial time point in the stability protocol and we recommend converting test time points from weeks to months to be consistent with ICH guidance. Provide updated stability protocol incorporating those changes.

6. Please provide documentation to show that you have obtained an established name (USAN) for your drug product.

7. We recommend that the trade name and established name be listed as follows:

   Nexavar
   (sorafenib) Tablets

   (or)

   Nexavar
   (sorafenib)
   Tablets

   Each tablet contains sorafenib tosylate equivalent to 200 mg of sorafenib.

8. We note that the drug product is manufactured by Bayer Healthcare, Germany. If Bayer HealthCare, New Haven, CT is involved in marketing of the drug product, please clearly state that in the drug product label. We recommend the following:

[ ]

[ ]

and

Onyx Pharmaceuticals, Inc.
(city), CA (zip code).

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/s/

Patricia Garvey
12/1/2005 07:28:37 AM
CSO

4 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

11/15/05

Fax

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Aileen Ryan, M.Sc. – Bayer Pharmaceutical Corp.	**From:**	Patty Garvey, R.Ph.
Fax:	203-812-6113	**Fax:**	301-796-9867
Phone:	203-812-6377	**Phone:**	301-796-1356
Pages (including cover):	2	**Date:**	November 4, 2005
Re:	NDA 21-923 Nexavar		

☐ **Urgent** X **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Comment:

Dear Aileen,

Please refer to your NDA 21-923 Nexavar. The clinical pharmacology and biopharmaceutics reviewer has the following request for information. We request that you provide us with the requested data as soon as possible.

Please notify me as to when you will be able to submit the data. Please contact me if you have any questions.

Sincerely,

Patty Garvey
Regulatory Project Manager
Division of Drug Oncology Products

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

We are currently unable to conclude that the to-be-marketed formulation is sufficiently similar to the clinical trials formulation. This issue has the potential to affect the timing of our ability to make approval decisions.

In order to determine the comparability of the commercial formulation to the clinical formulation, please generate the following data, for both formulations, using USP Apparatus 2 (paddle) at a rotation speed of — rpm, and submit it as soon as possible:

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

/s/

Patricia Garvey
11/4/2005 11:50:21 AM
CSO

Fax

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Aileen Ryan, M.Sc. – Bayer Pharmaceutical Corp.	**From:**	Patty Garvey, R.Ph.
Fax:	203-812-6113	**Fax:**	301-796-9867
Phone:	203-812-6377	**Phone:**	301-796-1356
Pages (including cover):	1	**Date:**	October 28, 2005
Re:	NDA 21-923 Nexavar		

☐ **Urgent** X **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Comment:

Dear Aileen,

Please refer to your NDA 21-923 Nexavar. The clinical pharmacology and biopharmaceutics reviewer has the following request for information.

Please perform an analysis, across all of the studies where pharmacokinetics data was collected, of whether pharmacokinetics changes as a function of race. Patients should be divided into the following race groups: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. We ask that the data set used to conduct the analysis be submitted electronically. If data in some groups is too small to allow for formal analysis, we ask that the individuals still be included in the electronic dataset.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Regulatory Project Manager
Division of Drug Oncology Products

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/s/

Patricia Garvey
11/4/2005 11:37:42 AM
CSO
Sent to the sponsor on October 28, 2005

MEMORANDUM

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

DATE: October 28, 2005

TO: Robert Justice, M.D., Director
Division of Oncology Drug Products

VIA: Patty Garvey, Regulatory Health Project Manager
Division of Oncology Drug Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review of Patient Labeling for Nexavar (sorafenib tosylate), NDA 21-923

Background and Summary

The following are our recommended revisions for the Patient Labeling (PPI) for Nexavar (sorafenib tosylate), NDA 21-923. We have simplified the wording, made it consistent with the PI, and removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications). We have put this PPI in the patient-friendly format that we are recommending for all patient information, although, this format is not required for voluntary PPIs. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on draft labeling submitted by the sponsor on April 29, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Comments and Recommendations

We also have the following comment:

1. The product information (PI) is missing information under the PRECAUTIONS section, Information for Patients subsection. Refer to 201.57(f)(2): "This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug..." The PI instead refers prescribers to the voluntary Patient Information (PPI). The Information

for Patients subsection should contain specific counseling information for prescribers to provide to patients regarding the safe and effective use of the product. Reference to a voluntary PPI is not a substitute for information under this section. There is no current regulatory requirement to append, print, or distribute voluntary information. The Information for Patients subsection should contain specific counseling information for prescribers to provide to patients regarding the safe and effective use of the product

Comments to the review Division in the attached patient label are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please let us know if you have any questions.

Appears This Way
On Original

Patient Information
NEXAVAR *[DSRCS Comment: Add the phonetic spelling.]*
(sorafenib tosylate)
200 mg Tablets

3 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Jeanine Best
10/28/2005 10:08:12 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
10/28/2005 02:48:14 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

7 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

10-26-05

Fax

DIVISION OF DRUG ONCOLOGY PRODUCTS

Center for Drug Evaluation and Research
White Oak Building
10903 New Hampshire Avenue, Bldg. #22, Silver Spring, MD 20993

To:	Aileen Ryan, M.Sc. – Bayer Pharmaceutical Corp.	**From:**	Patty Garvey, R.Ph.
Fax:	203-812-6113	**Fax:**	301-796-9867
Phone:	203-812-6377	**Phone:**	301-796-1356
Pages (including cover):	1	**Date:**	October 25, 2005
Re:	NDA 21-923 Nexavar		

☐ **Urgent** X **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Comment:

Dear Aileen,

Please refer to your NDA 21-923 Nexavar. The clinical pharmacology and biopharmaceutics reviewer has the following request for information.

> Page 3 of "**Quality Overall Summary 2.3.P Drug Product**" classifies sorafenib as highly permeable, but does not show the permeability results obtained. Please submit the results of the permeability experiment(s), including positive and negative controls, from which the conclusion on page 3 was reached.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Regulatory Project Manager
Division of Drug Oncology Products

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/s/

Patricia Garvey
10/25/2005 09:08:02 AM
CSO

Fax

DIVISION OF DRUG ONCOLOGY PRODUCTS

Center for Drug Evaluation and Research
White Oak Building
10903 New Hampshire Avenue, Bldg. #22, Silver Spring, MD 20993

To:	Aileen Ryan, M.Sc. – Bayer Pharmaceutical Corp.	**From:**	Patty Garvey, R.Ph.
Fax:	203-812-6113	**Fax:**	301-796-9845
Phone:	203-812-6377	**Phone:**	301-796-1356
Pages (including cover):	2	**Date:**	October 19, 2005
Re:	NDA 21-923 Nexavar		

☐ **Urgent** X **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Comment:

Dear Aileen,

Please refer to your NDA 21-923 Nexavar. We refer you to the FDA facsimile dated October 14, 2005. Comment #2 of the facsimile is incorrect, please see the following corrected request.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Regulatory Project Manager
Division of Drug Oncology Products

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

- October 14, 2005 facsimile – Please disregarding the comment #2 from this fax.

2. Please provide the raw AUC and Cmax data for each subject that contributes to each of the figures listed below. All of the data for all 7 figures should be submitted in a single file with 5 columns. The 5 columns are: Figure #, Study, Subject ID, AUC and Cmax.

Figure 3-7 AUC vs age
Figure 3-8 AUC vs gender
Figure 3-9 AUC vs dose as a function of ethnicity
Figure 3-10 Cmax vs dose as a function of ethnicity
Figure 3-11 AUC vs body weight
Figure 3-12 AUC vs creatinine clearance
Figure 3-13 AUC vs bilirubin

- **The corrected comment should be as followed.**

Please provide the raw AUC and Cmax data for each subject that contributes to each of the figures listed below. All of the data for all 7 figures should be submitted in a single file with 6 columns. The 6 columns are: Figure #, Study, Subject ID, value for parameter of interest (X-axis: age, gender, etc.), AUC and Cmax.

Figure 3-7 AUC vs age
Figure 3-8 AUC vs gender
Figure 3-9 AUC vs dose as a function of ethnicity
Figure 3-10 Cmax vs dose as a function of ethnicity
Figure 3-11 AUC vs body weight
Figure 3-12 AUC vs creatinine clearance
Figure 3-13 AUC vs bilirubin

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/s/

Patricia Garvey
10/19/2005 03:21:02 PM
CSO

Fax

DIVISION OF DRUG ONCOLOGY PRODUCTS

Center for Drug Evaluation and Research
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Aileen Ryan, M.Sc. – Bayer Pharmaceutical Corp.	**From:**	Patty Garvey, R.Ph.
Fax:	203-812-6113	**Fax:**	301-796-9845
Phone:	203-812-6377	**Phone:**	301-796-1356
Pages (including cover):	2	**Date:**	October 14, 2005
Re:	NDA 21-923 Nexavar		

☐ **Urgent** X **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Comment:

Dear Aileen,

Please refer to your NDA 21-923 Nexavar. The clinical pharmacology/toxicology reviewer has the following information request.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Regulatory Project Manager
Division of Drug Oncology Products

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

1. The below (font change) is reproduced from page 123 of NDA Section **2.7.2 Summary of Clinical Pharmacology Studies**

   3.4.3.1 Cmax/AUC and anti-tumor activity
   The relationship between plasma Cmax,ss/AUC(0-12),ss values and anti-tumor activity was examined. Only two patients demonstrated a partial response to sorafenib. There was no apparent relationship between plasma sorafenib exposure and anti-tumor activity.

   Please submit the data that supports these statements? Specifically, the PK (AUC and Cmax or modeled parameters) and response (no response, minor response, or partial response) for each patient that was assessed for response and PK.

   Given the limited number of responses in the PK studies, statistical analysis of the data is not needed.

2. Please provide the raw AUC and Cmax data for each subject that contributes to each of the figures listed below. All of the data for all 7 figures should be submitted in a single file with 5 columns. The 5 columns are: Figure #, Study, Subject ID, AUC and Cmax.

   Figure 3-7 AUC vs age
   Figure 3-8 AUC vs gender
   Figure 3-9 AUC vs dose as a function of ethnicity
   Figure 3-10 Cmax vs dose as a function of ethnicity
   Figure 3-11 AUC vs body weight
   Figure 3-12 AUC vs creatinine clearance
   Figure 3-13 AUC vs bilirubin

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/s/

Patricia Garvey
10/14/2005 03:15:34 PM
CSO

Fax

DIVISION OF DRUG ONCOLOGY PRODUCTS

Center for Drug Evaluation and Research
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Aileen Ryan, M.Sc. – Bayer Pharmaceutical Corp.	**From:**	Patty Garvey, R.Ph.
Fax:	203-812-6113	**Fax:**	301-594-0498
Phone:	203-812-6377	**Phone:**	301-594-5766
Pages (including cover):	1	**Date:**	October 5, 2005
Re:	NDA 21-923 Nexavar		

☐ **Urgent** X **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your NDA 21-923 Nexavar. The clinical pharmacology/toxicology reviewer has the following information request.

> The below (font change) is reproduced from Page 21 of NDA Section **2.7.2 Summary of Clinical Pharmacology Studies.**
>
> The relationship between steady state sorafenib Cmax,ss and AUC(0-12),ss values and study drug related toxicities was examined at all dose levels. At any given dose, there was no clear relationship between systemic exposure and safety.
>
> Please submit the compiled raw data and analyses that are the basis for these statements.

We anticipate that, for each toxicity, each patient's worst Grade, dose at the time of the worst grade, and PK (AUC and Cmax or modeled parameters), are the basis for the analyses. If this is not the case, please submit these data and analyses, as well as the data used to support the statements.

Please contact me if you have any questions.

Sincerely,

Patty Garvey

Regulatory Project Manager, Division of Drug Oncology Products

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/s/

Patricia Garvey
10/5/2005 03:48:21 PM
CSO

Fax

DIVISION OF DRUG ONCOLOGY PRODUCTS

Center for Drug Evaluation and Research
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Aileen Ryan, M.Sc. – Bayer Pharmaceutical Corp.	**From:**	Patty Garvey, R.Ph.
Fax:	203-812-6113	**Fax:**	301-594-0498
Phone:	203-812-6377	**Phone:**	301-594-5766
Pages (including cover):	1	**Date:**	September 21, 2005
Re:	NDA 21-923 Nexavar		

☐ **Urgent** • **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dear Aileen,

Please refer to your NDA 21-923 Nexavar. The statistical reviewer has the following request.

1. The datasets (Baseline.XPT and PriorTherapy.XPT) submitted by Bayer on 8/8/05 can not be opened. Please submit this again.

2. Please provide a SAS program for Table 11-5 in the study report (Timing of Post-baseline Radiological Scans (Population: Subjects valid for Intent-to-Treat Analyses)).

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Regulatory Project Manager
Division of Drug Oncology Products

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/s/

Patricia Garvey
9/23/2005 04:25:15 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-923

Bayer Pharmaceuticals Corporation
Attention: Aileen Ryan, M.Sc.
Director, Global Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Ms. Ryan:

Please refer to your July 6, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexavar (sorafenib tosylate) Tablets 200 mg.

We also refer to your submissions dated April 28 and June 17, 2005.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on September 6, 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, please contact me at (301) 594-5766.

Sincerely,

{See appended electronic signature page}

/S/

Patricia N. Garvey, R.Ph.
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Patricia Garvey
9/1/2005 05:24:14 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

9/1/05

NDA 21-923

Bayer Pharmaceuticals Corporation
Attention: Aileen Ryan, M.Sc.
Director, Global Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Ms. Ryan:

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

Name of Drug Product:	Nexavar (sorafenib tosylate) Tablets 200 mg
Review Priority Classification:	Priority (P)
Date of Application:	July 6, 2005
Date of Receipt:	July 8, 2005
Our Reference Number:	NDA 21-923

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 6, 2005 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be January 8, 2006.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all submission to the Central Document Room at the following address:

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

If you have any questions, call Patty Garvey, Regulatory Project Manager, at (301) 594-5766.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Patricia Garvey
9/1/2005 04:58:11 PM
Signed for Dotti Pease

Memorandum of a Telephone Call

NDA: 21-923
Drug: Nexavar (sorafenib)
Applicant: Bayer
Date of Call: August 22, 2005

I returned a call from Cheryl Anderson of Bayer concerning this application. She wanted to let me know that they had submitted an overall survival analysis plan by E-mail on August 19, 2005 and wanted statistical comments before they conduct the analysis. I told her that I would check with our statisticians and let them know that Bayer was waiting for their comments.

She also said there were 187 patients so far entered on their treatment protocol who had not received prior treatment for their metastatic disease. She said that similar patients were entered on their submitted pivotal study. They will be submitting a rationale on why this patient population should be included in the indication. I asked her to send me a desk copy of this submission.

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

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/s/

Robert Justice
8/24/2005 12:02:24 PM
MEDICAL OFFICER

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Aileen Ryan, MSc	**From:**	Amy Baird, CSO
Fax:	203-812-6113	**Fax:**	301-827-4590
Phone:	203-812-6377	**Phone:**	301-594-5779
Pages (including cover):	1	**Date:**	August 19, 2005
Re:	NDA 21-923 Nexavar. Proposed labeling.		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ✔ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Please refer to the proposed labeling for Nexavar. Specifically, Table 2 titled [ ] Adverse Events Reported in at Least — of Patients...". This table is insufficient in that it is comprised of drug-related AEs only. Please submit a new label, in Word format, with a revised table 2 that includes all AEs and not just those drug-related. The[ ] frequency is acceptable. Please call should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
8/19/2005 10:34:43 AM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Aileen Ryan, M.Sc. – Bayer Pharmaceuticals Corp.	**From:**	Patty Garvey, R.Ph.
Fax:	203-812-5029	**Fax:**	(301) 594-0498
Phone:	203-812-6377	**Phone:**	(301) 594-5766
Pages (including cover):	2	**Date:**	August 4, 2005
Re:	NDA 21-923 Nexavar (sorafenib)		

☐ **Urgent** ■ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

- **Comments:**

Dear Aileen,

Please refer to NDA 21-923 Nexavar (sorafenib). The chemistry and clinical biopharmaceutics reviewers have the following information request.

Please provide the requested information as soon as possible in order for us to continue with the review of your NDA.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Regulatory Project Manager
Division of Oncology Drug Products

CHEMISTRY, MANUFACTURING AND CONTROLS

Please clearly provide HPLC information for drug product Assay and Degradation products, including:

1. [
2.
3.
4.
5.
6.
7.]

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Please submit the following data and analysis as soon as possible.

9.7.1.5 Pharmacokinetic analyses
Collection of data for PK analyses is ongoing; analyses of PK parameters will be performed and presented separately. Descriptive statistics will be provided for trough plasma sorafenib concentrations. Population PK parameters will be estimated for those subjects from whom approximately 3 PK samples were collected, using available plasma concentration–time data. Appropriate descriptive statistics will be provided for estimated population PK parameters. Additionally, relationships between efficacy and toxicity parameters and population PK parameters and trough plasma concentrations will be evaluated. The relationship between PK, biomarkers, and antitumor activity will be evaluated.

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/s/

Patricia Garvey
8/4/05 04:01:42 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-923/RU-003

7/19/05

Bayer Pharmaceuticals Corporation
Attention: Aileen Ryan
Director Global Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Ms. Ryan:

We have received a reviewable unit (RU) of your new drug application (NDA) submitted under the Continuous Marketing Application (CMA)-Pilot 1 program for the following:

Name of Drug Product:	NEXAVAR (sorafenib tosylate) Tablets 200 mg
Date of Submission:	June 17, 2005
Date of Receipt:	June 20, 2005
Our Reference Number:	NDA 21-923
Reviewable Unit:	RU-003

Unless we notify you otherwise within 60 days of the above receipt date, we will accept this presubmission as an RU. The user fee goal date for us to complete our review of this RU will be December 20, 2005.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed (both electronic and paper) submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Send all other submissions that are paper only to one of the following addresses:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products, HFD-150
Attention: Division Document Room, HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products, HFD-150
Attention: Document Room 3106
1451 Rockville Pike
Rockville, Maryland 20854

If you have any questions, call Amy Baird, Consumer Safety Officer, at (301) 594-5779.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Amy Baird
7/19/05 01:44:31 PM
for Dotti Pease

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: February 28, 2005	**DESIRED COMPLETION DATE:** June 24, 2005 **PDUFA DATE:** January 8, 2006	**ODS CONSULT #:** 05-0038

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

THROUGH: Amy Baird
Project Manager, Division of Drug Oncology Products
HFD-150

PRODUCT NAME: **Nexavar** (Sorafenib Tablets) 200 mg **NDA# 21-923 (IND#** 60,453)	**IND SPONSOR:** Bayer Pharmaceuticals

SAFETY EVALUATOR: Kristina C. Arnwine, PharmD

RECOMMENDATIONS:

1. DMETS has no objection to the use of the proprietary name, Nexavar. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the signature date of this document, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product

3. DDMAC finds the proprietary name, Nexavar, acceptable from a promotional perspective

/S/ /S/

Denise P. Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 27, 2005

NDA#: 21-923 (IND# 60,453)

NAME OF DRUG: Nexavar (Sorafenib Tablets) 200 mg

NDA HOLDER: Bayer Pharmaceuticals

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Drug Oncology Products (HFD-150), for assessment of the proprietary name, Nexavar regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were not provided for review and comment.

PRODUCT INFORMATION

Nexavar is a multikinase inhibitor that decreases tumor cell proliferation *in vitro*. Nexavar is indicated for the treatment of patients with advanced renal cell carcinoma. The usual dose of Nexavar is 400 mg (two 200 mg tablets) [ ] Nexavar is supplied as 200 mg tablets in bottles containing 120 tablets.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Nexavar to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was

[1] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Nexavar. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC has no objections to the proprietary name, Nexavar, from a promotional perspective.

2. The Expert Panel identified nine proprietary names that were thought to have the potential for confusion with Nexavar. These products are listed in table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Nexavar	Sorafenib Tablet, 200 mg	400 mg by mouth twice daily	
Maxair	Pirbuterol Inhalation Aerosol 0.2 mg/actuation	1- 2 puffs every 4 to 6 hours	LA
Mevacor	Lovastatin Tablets, 10 mg, 20 mg, and 40 mg	10 mg to 80 mg once or twice daily	LA
[redacted]			
Niravam	Alprazolam Orally Disintegrating Tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg	0.25 mg three times daily to 5 mg daily in divided doses	LA
Nexium	Esomeprazole Extended-release capsules 20 mg and 40 mg	20 mg to 40 mg once daily	LA
Lexiva	Fosamprenavir Tablets, 700 mg	700 mg to 1400 mg twice daily plus Ritonavir	SA
Narcan	Naloxone Injection, 0.4 mg/mL	0.1 to 2 mg IV; may repeat IV at 2 to 3 minute intervals	LA
Norvasc	Amlodipine Tablets, 2.5 mg, 5 mg, and 10 mg	2.5 mg to 10 mg by mouth once daily	LA
Navane	Thiothixene Capsules 1 mg, 2 mg, 5 mg, 10 mg, 20 mg	6 mg to 60 mg by mouth in divided doses	LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
***Name pending approval. Not FOI releasable.

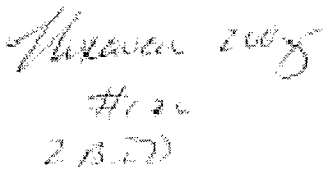
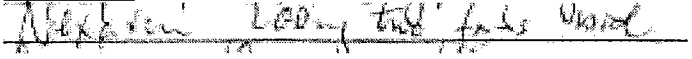
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Nexavar were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Nexavar with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 119 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Nexavar (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	"...Nexavar 200 mg. Take two tablets twice daily."
Inpatient RX: 	

2. Results:

One respondent from the outpatient written study interpreted the proposed name as Nexair. Nexair sounds and looks similar to Maxair, which is a currently marketed U.S. product. See Attachment A for a complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Nexavar, the primary concerns related to look-alike and sound-alike confusion with Maxair, Mevacor, [redacted] Niravam, Nexium, Lexiva, Narcan, Norvasc, and Navane. Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Nexavar.

1. Nexavar and Mevacor can look similar when scripted. Mevacor is an antihyperlipidemic agent indicated as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia, to slow the progression of coronary atherosclerosis in patients with CHD, to reduce risk of MI, unstable angina, and coronary revascularization procedures, and as an adjunct to diet to reduce total and LDL cholesterol and Apo-B levels in adolescent boys and girls with heterozygous familial hypercholesterolemia. The beginnings of each name (Nexa- vs. Meva-) can look similar when scripted (see below).

In addition, the endings of each name (-var vs. -cor) can look similar, depending on how they are scripted. Nexavar and Mevacor overlap with respect with to dosage form (tablet), route of administration (oral), and dosing frequency (twice daily). Although these products share a dosing frequency of twice daily, Mevacor is generally prescribed with a dosing regimen of 'once daily' and not commonly prescribed twice daily. This characteristic should help to distinguish the two products. Additionally, the differing usual doses (400 mg vs. 10 mg to 80 mg) and product strengths (200 mg vs. 10 mg, 20 mg, and 40 mg) help to distinguish the two products from each other as well. Despite some orthographic similarities between the names, the differing dosing frequencies, usual doses, and product strengths decrease the potential for medication errors due to name confusion.

2. Nexavar and Lexiva can sound similar when pronounced. Lexiva is a protease inhibitor antiretroviral agent indicated for the treatment of HIV in adults. Both names contain three syllables and the first syllable ('Necks' vs. 'Lecks') of each name rhyme, however; pronunciation of the beginning letters ('L' vs. 'N') can help to differentiate the names. Additionally, the second syllable of each name ('ahr' vs. 'ee' as in street) are phonetically different, which helps to distinguish the two names. Nexavar and Lexiva overlap with respect to dosage form (tablet), route of administration (oral), and dosing frequency (twice daily). The strengths are different (200 mg vs. 700 mg); however, the number of tablets prescribed for each dose may overlap (two tablets). Since both Nexavar and Lexiva are only available in one strength (200 mg vs. 700 mg) it is possible for either product to be ordered without a product strength specified and with a dose of two tablets twice daily. Therefore, it is possible for Nexavar and Lexiva to be prescribed with overlapping routes of administration, dosage forms, dosing frequencies and usual doses (Nexavar, 2 tablets twice daily vs. Lexiva, 2 tablets twice daily). However, Lexiva is generally prescribed in conjunction with Ritonavir which may help to differentiate the two products. Additionally, Nexavar and Lexiva both have very specific patient populations (cancer patients vs. HIV patients) and prescribers (oncologists vs. infectious disease specialists). Furthermore,

chemotherapy products (i.e. Nexavar) are generally not ordered verbally and are most likely prescribed with a specific dose and strength. Thus the potential for sound-alike name confusion is decreased. Overall, the different phonetic characteristics, different prescriber population and patient population, coupled with conditions of use decrease the potential for name confusion between Nexavar and Lexiva. Thus, DMETS believes these two names can safely co-exist in the marketplace.

3. Nexavar can look similar to Maxair when scripted. Maxair is a sympathomimetic bronchodilator indicated for the prevention and reversal of bronchospasm in patients with reversible bronchospasm including asthma. The first four letters of each name ('Nexa' vs. 'Maxa') can look similar depending on how they are scripted (see below). However, the extra letter in Nexavar causes the name to appear longer when scripted, thereby helping to distinguish the two names. Nexavar and Maxair overlap with respect to route of administration (oral) and have the numeral '2' in their usual doses (2 tablets vs. 2 puffs), and '200' in their product strengths [200 mg vs. 200 mcg (0.2 mg)]. Despite these similarities, Nexavar and Maxair do not overlap with respect to dosage form (tablets vs. inhalation aerosol) and dosing frequency (twice daily vs. every 4 to 6 hours). Although it is possible for Maxair to be prescribed with the directions, 'use as directed,' this would not be the case for Nexavar since Nexavar is part of a chemotherapy regimen, and it is unlikely to be prescribed with a general instruction of 'use as directed.' Chemotherapeutic agents are most likely prescribed with a specific dose and specific dosing frequency. Therefore, the different product characteristics such as the dosage forms and dosing regimen along with the differences in the endings of each name decrease the potential for name confusion between Nexavar and Maxair.

4. [

]

*** **NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

[ ] [ ] [ ]

5. Nexavar and Niravam can look similar when scripted. Niravam is an orally disintegrating benzodiazepine indicated for the management of anxiety disorder. The beginnings of each name (Nex- vs. Nir-) can look similar, especially if the cross of the letter 'x' is not prominent. In addition, the endings of each name can also look similar (-avar vs. -ivam) depending on how they are scripted (see below). Nexavar and Niravam overlap with respect to dosage form (tablet) and route of administration (oral). In addition, both products can overlap with respect to dosing frequency (twice daily) and usual dose if the dose is written in number of tablets (two tablets), which can contribute to potential confusion. However, in order for the dose to be written in terms of number of tablets, a product strength will likely be specified since Niravam is available in more than one strength. Additionally, Nexavar and Niravam do not overlap with regards to product strength (200 mg vs. 0.25 mg, 0.5 mg, 1 mg) or usual dose, if the dose is written out in terms of milligrams (400 mg vs. 0.25 mg to 5 mg). These product characteristics, such as the differing product strengths and numerical usual doses decrease the potential of name confusion between Nexavar and Niravam.

6. Nexavar and Nexium can look similar when scripted. Nexium is a proton-pump inhibitor indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of erosive esophagitis; to maintain symptom resolution and healing of erosive esophagitis, for the treatment of heartburn and other symptoms associated with GERD, and in combination with amoxicillin and clarithromycin for the treatment of *H. pylori* infection and duodenal ulcer disease. Nexavar and Nexium both begin with the letters 'Nex' which is the principal contributor to the look-alike characteristics of each name (see below). However, the endings of each name differ (-avar vs. -ium). Additionally, Nexavar has a longer appearance when scripted than Nexium. Nexavar and Nexium overlap with respect to the route of administration (oral), have similar numerals in their usual dose (400 mg vs. 20 mg to 40 mg), and product strength (200 mg vs. 20 mg and 40 mg). Despite this similarity, Nexavar and Nexium do not overlap with respect to dosing frequency (twice daily vs. once daily), which will most likely be included on a prescription order, and thus help to distinguish the two products from each other. Overall, the orthographic difference along with the differing dosing frequencies decreases the potential for name confusion between Nexavar and Nexium.

7. Nexavar and Narcan can look similar when scripted. Narcan is a detoxification agent indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by opioid including natural and synthetic narcotics and for the diagnosis of suspected acute opioid overdosage. The beginnings (Ne- vs. Na-) and endings (-ar vs. -an) can look similar when scripted which are the principal contributions to the look-alike characteristics of each name (see below). However, the middle portions of each name are orthographically different (-xav- vs. -rc-) which helps to distinguish the names from each other in script. Nexavar and Narcan do not overlap with respect to product characteristics such as route of administration (oral vs. intravenous), dosage form (tablet vs. injection), or product strength (200 mg vs. 0.4 mg/mL). Most importantly, the two products do not overlap with regard to product characteristics such as usual dose (400 mg vs. 0.1 mg to 2 mg) or dosing frequency (twice daily vs. as needed), which are most likely to included in a prescription order. Despite the look-alike similarities, the differing middle portions of each name along with the differing usual dose and dosing frequency decrease the potential for name confusion between Nexavar and Narcan.

8. Nexavar and Norvasc can look similar when scripted. Norvasc is a calcium-channel blocking agent indicated for the treatment of hypertension and angina. Nexavar and Norvasc both begin with the letter 'N,' the letters 'va' appear in the middle of each name, and each name contains seven letters which are the principal contributions to the look-alike characteristics the name pair. However, the letters immediately preceding the letters 'va' in each name (-exa- vs. -vor-) and the last two letters of each name (-ar vs. -sc) are orthographically different which helps to distinguish the two names from each other (see below). Nexavar and Norvasc overlap with respect to product characteristics such as route of administration (oral) and dosage form (tablet). However, the two products do not overlap with respect to usual dose (400 mg vs. 2.5 mg to 10 mg), dosing frequency (twice daily vs. once daily), product strength (200 mg vs. 2.5 mg, 5 mg, and 10 mg), all of which are likely to be included in a prescription order, thereby decreasing the potential for confusion between the two products. Overall, the orthographic differences between Nexavar and Norvasc along with the differing usual doses, dosing frequencies, and product strengths decrease the potential for name confusion between Nexavar and Norvasc.

9. Nexavar and Navane can look similar when scripted. Navane is a thioxanthene derivative antipsychotic agent indicated for the management of schizophrenia. Nexavar and Navane both begin with the letter 'N' and the first four letters are orthographically similar 'Nexa vs. Nava' when scripted. Although the names share the letters 'ava' in each name, the position of the letters 'ava' is different in each name (beginning vs. middle). In addition, the endings of each name differ (-var vs. -ne). Nexavar and Navane overlap with respect to route of administration (oral) and both are solid oral dosage forms (tablet vs. capsule). More importantly, they can overlap with respect to dosing frequency (twice daily) and usual dose if dose is ordered in terms of number of tablets (two tablets), which can increase the potential for confusion between the two products. However, Nexavar and Navane do not overlap with respect to product strength (200 mg vs. 1 mg, 2 mg, 5 mg, 10 mg, and 20 mg). Thus,

although an order may be written for Nexavar or Navane with a direction of "two tablets by mouth twice daily," since Navane is available in more than one strength, the product strength must be specified for Navane, thereby distinguishing the two products from each other. Overall, orthographic differences coupled with different product characteristics such as the strength decrease the potential for name confusion between Nexavar and Navane.

F. INDEPENDENT NAME ANALYSIS

Bayer Pharmaceuticals conducted a name validation study with multiple brand name candidates for this NDA. The research findings indicated that the proposed name, Nexavar, was acceptable as the product trademark. The analysis conducted by Bayer Pharmaceuticals discusses the proprietary names, Nexium and Narcan as potential sound and look-alike names which were also identified by DMETS as potential sound or look-alike products with Nexavar. The Bayer analysis also identified the medication Cozaar, as having sound-alike and or look-alike potential which was not identified by DMETS. Following review of the proprietary name analysis submitted by Bayer Pharmaceuticals, DMETS concurs that Nexium, Narcan, and Cozaar do not pose a significant safety risk from a sound and look-alike perspective.

III. LABEL AND LABELING COMMENTS

A. CONTAINER LABEL

1. We note the strength is based on the active moiety. Thus, we suggest revising the labels and labeling in one of the three following formats.
(Please note that DMETS prefers choice 'a' because this nomenclature is consistent with USP recommendations on "amount of ingredient per dosage unit".)

a.
Nexavar
(Sorafenib Tablets)
200 mg

b.
Nexavar
(Sorafenib Tosylate Tablets)
200 mg*

*Each tablet contains sorafenib tosylate equivalent to 200 mg of sorafenib.

c.
Nexavar
(Sorafenib Tosylate Tablets)
equivalent to 200 mg sorafenib

2. Per CFR 21 201.10(g)(2), increase the prominence of the established name so that it is at least ½ the size of the proprietary name.

3. Relocate the net quantity so that it is not presented in close proximity to the product strength.

4. Revise the "Dosage" statement to read, [redacted]

5. This 120 tablet bottle packaging configuration appears to be unit-of-use. Please ensure that this packaging configuration utilizes a child-resistant closure in accordance with the Poison Prevention Act.

B. INSERT LABELING

1. DOSAGE AND ADMINISTRATION SECTION

   a. *Line 394*: Revise the statement to read [redacted]

   b. [redacted]

2. PATIENT INFORMATION LEAFLET

   See comment 2-a-ii.

V. RECOMMENDATIONS:

A. DMETS has no objection to the use of the proprietary name, Nexavar. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the signature date of this document, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product

C. DDMAC finds the proprietary name Nexavar acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-827-1998.

_____

Kristina C. Arnwine, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur: _____

Linda Kim-Jung, PharmD
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Attachment A

Outpatient Written	Inpatient Written	Verbal
Mixavan	Nexaran	Exobar
Mixavar	Nexaran	Exovar
Mixavar	Nexaran	Exovar
Nexair	Nexaren	Naxovar
Nexavar	Nexarim	Nexavar
Nexavar	Nexaron	Nexavar
Nexavar	Nexavan	Nexavar
Nexavar	Nexaven	Nexovar
Nixavar	Nexaven	Nexovar
Nixavar	Nexaven	Nexovar
Nixavar	Nexavin	
Nixavar		
Uixancu		
Vluxavar		

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/s/

Kristina Arnwine
9/30/2005 04:10:40 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/30/2005 04:12:26 PM
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Carol Holquist
9/30/2005 04:17:57 PM
DRUG SAFETY OFFICE REVIEWER

MEETING MINUTES

MEETING DATE: May 24, 2005 **TIME:** 9:00 a.m. **LOCATION:** WOC2/rm 3004

IND: 60,453

Meeting Request & Briefing Document Submission Date: 4-8-05; sn804
Meeting Request & Briefing Document Submission Date: 4-15-05; sn818

DRUG: Sorafenib (BAY 43-9006)

SPONSOR/APPLICANT: Bayer Pharmaceuticals Corporation

TYPE of MEETING:

1. Pre-NDA – follow-up Chemistry, Manufacturing, and Controls and Clinical Pharmacology and Biopharmaceutics

2. **Proposed Indications (from briefing package):** Advanced renal cell carcinoma

FDA PARTICIPANTS:

Hashmukh Patel, Ph.D.	--	Deputy Director, Office of New Drug Chemistry I
Nallaperumal Chidambaram, Ph.D.	--	Chemistry Team Leader
Josephine Jee, M.S.	--	Chemistry Reviewer
Brian Booth, Ph.D.	--	Acting Clinical Pharmacology & Biopharmaceutics Team Leader
Patty Garvey, R.Ph.	--	Regulatory Project Manager
Pre:Carol Noory, Ph.D.	--	Clinical Pharmacology & Biopharmaceutics Reviewer

INDUSTRY PARTICIPANTS:

Olaf Queckenberg, Ph.D.	--	Global Head of Quality Control/Development
Kerstin Pauli	--	Group Leader Dissolution
Werner Heilmann, Ph.D.	--	Manager, Analytical Development, Drug Substance
Kimberly Pharthum, Ph.D.	--	Associate Director, Regulatory Affairs
Aileen Ryan, M.Sc.	--	Director, Global Regulatory Affairs Oncology
Cheryl Anderson	--	Vice President, North America Global Regulatory Affairs
Joseph Scheeren, Pharm.D. (via phone)	--	Senior Vice President, Global Regulatory Affairs
Onyx: Leonard Post, Ph.D.	--	Senior Vice President, Research and Development

MEETING OBJECTIVES (from briefing document):

1. To obtain concurrence from the chemistry and clinical pharmacology & biopharmaceutics review team that the dissolution data to be submitted in the marketing application for sorafenib tosylate tablets are adequate to suppor the changes made in the commercial tablets compared to the tablets used in the Phase 3 clinical/primary stability studies.

2. To discuss the proposal to use [redacted] synthesize the drug substance.

BACKGROUND:

BAY 43-9006/sorafenib is in active global clinical development by Bayer Healthcare Pharmaceuticals Corporation in collaboration with Onyx Pharmaceuticals. Sorafenib is a compound known to target both Raf kinase and VEGFR2 (vascular endothelial growth factor receptor 2) to inhibit two essential mechanisms involved in tumor growth. Raf kinase is a key enzyme in an important growth signaling pathway associated with the proliferation of tumor cells. VEGFR2 is the main receptor of the vascular endothelial growth factor which plays a key role in angiogenesis.

A pre-IND meeting was held between the FDA and the sponsor on May 5, 2000. The sponsor submitted the initial IND on May 30, 2000. An End-of-Phase 1 meeting was held between the FDA and the sponsor on July 2, 2002. The sponsor requested the meeting to discuss the FDA's feedback and comments on the planned Phase 2 program, which is supported by the Phase 1 data and pre-clinical data, accumulated thus far. In addition, the sponsor met with the Office of Clinical Pharmacology & Biopharmaceutics on September 10, 2002 to discuss the clinical pharmacology development plans for BAY 43-9006. An end-of-phase 2 meeting was held between the FDA and the sponsor on August 6, 2003. Sorafenib received orphan drug designation on October 8, 2004 and Fast track status on April 3, 2004 for the metastatic renal cell carcinoma indication.

A multi-national, multi-center Phase III study, Protocol 11213, entitled, "A Phase III randomized study of BAY 43-9006 inpatients with unresectable and or metastatic renal cell cancer", is ongoing. The targeted indication is metastatic renal cell carcinoma (RCC). Interim and final analyses are currently planned. Both of these analyses are event driven with the interim survival analysis occurring when 270 death events have accrued and the final survival analysis at 540 events. The analysis of overall survival will be used to confirm clinical benefit and obtain complete approval. As of November 12, 2004, 581 patients have been randomized in this study. Two hundred fifteen progression events and 27 death events have been reported.

The sponsor was granted fast track designation for metastatic renal cell carcinoma on March 26, 2004. The sponsor was also accepted to participate in the Continuous Marketing Application Pilot 1 program on April 20, 2005. They have submitted the pharmacology/toxicology reviewable unit on April 28, 2005. It is anticipated that the chemistry reviewable unit will be submitted on July 1, 2005 and the final reviewable unit, clinical, will be submitted on August 1, 2005.

QUESTION for DISCUSSION with FDA RESPONSES and DECISIONS REACHED:

Dissolution Date

1. In the absence of an acceptable dissolution procedure, the product sameness can be evaluated by testing the product before the changes and after the changes. Three lots of product before scale up can be tested using the Paddle method with — rpm and the following media:

[ ]

The commercial product (post scale-up) can also be tested using the same procedure and media. The f2 analysis can be made and the comparability of the dissolution profiles can be determined. Once the formulation is finalized, a range for the ingredients will not be accepted.

Discussion:

The sponsor explained their development of the dissolution method. The sponsor also presented the dissolution data (using different media) on production scale lots of 200 mg tablets using [ ] *Refer to attachments for explanation and presentation of dissolution method and data.*

The sponsor will include the dissolution data in their NDA submission.

2. Development of an Acceptable Dissolution Procedure

The following approaches are recommended for setting dissolution specifications for a new chemical entity (see FDA guidance Dissolution Testing of Immediate Release Solid Oral Dosage Forms).

1. Dissolution testing should be carried out under mild test conditions using three batches used in pivotal clinical trials.
2. The Paddle Method at 100 rpm is normally not acceptable. The Paddle Method at 50 rpm and 75 rpm or the Basket method at 100 rpm needs to be evaluated. The basket method provides abrasion which is sometimes beneficial for product with a coating issue causing within lot variability.
3. These tests should be run on individual tablets and the results of 6 – 12 tablets submitted for three pilot batches used in the in vivo studies
4. Single tablets should be tested at 15-minute intervals to generate a dissolution profile.
5. The following media are recommended
    - 0.1N HCL
    - pH 4.5 buffer
    - pH 6.8 buffer
6. The use of surfactants added in incremental amounts such as [ ] and [ ] is acceptable.
7. For slowly dissolving or poorly water soluble drugs (BCS class 2), a two-point dissolution specification, one at 15 minutes to include a dissolution range (a dissolution window) and the other at a later point (30, 45, or 60 minutes) to ensure 85% dissolution, is recommended to characterize the quality of the product.

Proposal of Classification of [ ]

A. Is the information provided on the testing and acceptance criteria of the impurities arising from [ ] and sorafenib tosylate specification sufficient?

FDA: Based on our recommendation, we acknowledge your willingness to classify [ ] Though you have provided multiple batch data [ ] you did not provide release data for sorafenib drug substance batches that were manufactured using [ ] In order for us to evaluate the extent of impurities that are carried over from [ ] we recommend that you submit this data for review. Based on our evaluation, we will provide our comments about acceptability of [ ] acceptance criteria. Please specify the use of lots 505153, 505170, 505171, 515173, and BXROAR9.

Discussion: The acceptance of the final specification will be a review issue.

B. Bayer seeks confirmation from the agency that it is acceptable to use sorafenib tosylate drug substance in the initial commercial distribution that has been produced [ ] which was manufactured with the modifications described in section 4.2.1 and manufactured prior to the completion of the process validation [ ]

FDA: Please provide comparison data for sorafenib drug substance batches prior and after the modifications [ ] to demonstrate the equivalency.

C. If the information in question C is acceptable to the agency, Bayer wishes to understand how this information will be communicated to the inspector performing the pre-approval inspection (PAI).

FDA: When the adequate information is submitted, we will communicate with the Office of Compliance.

ADDITIONAL FDA COMMENT:

Please submit your final composition for BAY 43-9006 in your next submission.

Discussion:

FDA understood that [ ] would be the target and this would meet their need for a fixed composition. The sponsor's proposal for a range in accordance with the concept of design space is a new concept and it requires further discussion within FDA before the sponsor can receive a final response.

ACTION ITEMS:

1. FDA will provide comments to IND 60,453 submission dated May 20, 2005 by June 3, 2005.

2. The sponsor will include the dissolution data presented during the meeting in their NDA submission.

The meeting concluded at 10:10 am. There were no unresolved issues.

/S/

{See appended electronic signature page}

Patty Garvey, R.Ph.
Regulatory Project Manager

Concurrence Chair:

/S/

{See appended electronic signature page}

Nallaperumal Chidambaram, Ph.D.
Chemistry Team Leader

/S/

Brian Booth, Ph.D.
Acting Clinical Pharmacology and Biopharmaceutics Team Leader

ATTACHMENTS: *Sponsor's slides presented during the meeting.*

20 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Nallaperumal Chidambaram
6/3/05 12:06:36 PM

Brian Booth
6/4/05 03:13:10 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 60,453

4/20/05

Bayer Pharmaceuticals Corporation
Attention: Aileen Ryan, M.Sc.
Director, Global Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Ms. Ryan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for Sorafenib (BAY 43-9006).

We also refer to our March 26, 2004 letter granting fast track designation for Sorafenib (BAY 43-9006) for metastatic renal cell carcinoma (mRCC) and to your April 5, 2005, request for step-wise submission of sections of the New Drug Application (NDA) for this product.

In addition, we also refer to your April 11, 2005 letter requesting participation in the Continuous Marketing Application (CMA) Pilot 1 Program.

We have reviewed your requests and have concluded that the proposed plan for step-wise submission of sections of the NDA and your participation in the CMA Pilot 1 program are acceptable.

If you pursue a clinical development program that does not support use of Sorafenib (BAY 43-9006) for metastatic renal cell carcinoma (mRCC), the application will not be reviewed under the fast track drug development program and submission of sections of the NDA will not be permitted under this program.

If you have any questions, call Patty Garvey, Regulatory Project Manager, at 301-594-5766.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Richard Pazdur
4/20/05 11:43:14 AM

MEETING MINUTES

MEETING DATE: April 6, 2005 **TIME:** 4:30 p.m. **LOCATION:** WOC2/rm 4023

IND: 60,453

DRUG: sorafenib (BAY 43-9006)

SPONSOR/APPLICANT: Bayer Pharmaceuticals Corporation

TYPE of MEETING:

1. Clinical Guidance

2. **Proposed Indications:** Treatment of patients with advanced renal cell carcinoma.

FDA PARTICIPANTS:

Richard Pazdur, M.D.	--	Director, Division of Oncology Drug Products
Ann Farrell, M.D.	--	Medical Team Leader
Robert Kane, M.D.	--	Medical Reviewer
Rajeshwari Sridhara, Ph.D.	--	Statistical Team Leader
Peiling Yang, Ph.D.	--	Statistical Reviewer
Patty Garvey, R.Ph.	--	Regulatory Project Manager
Patty Delaney	--	Cancer Liaison Program, Office of Special Health Issues
JoAnn Minor, M.S.	--	Cancer Liaison Program, OSHI

INDUSTRY PARTICIPANTS:

Susan Kelley, M.D.	--	Vice President, Therapeutic Area, Oncology
Michael Shan, Ph.D.	--	Deputy Director, Statistics
Cheryl Anderson	--	Vice President North America Regulatory Affairs
Aileen Ryan, M.Sc.	--	Director, Global Regulatory Affairs
Brian Schwartz, M.D.	--	Director, Global Clinical Development
Joseph Scheeren, Pharm.D. (via phone)	--	Sr. Vice President, Global Regulatory Affairs
Paul McCarthy, M.D. (via phone)	--	Vice President, Medical Affairs
Onyx: Leonard Post, Ph.D.	--	Sr. Vice President, Research & Development

MEETING OBJECTIVES (from briefing document):

To discuss the Expanded Assess Program, topline results of the Phase 3 trials, and the FDA ethical concern regarding patients on the placebo arm of the trial.

BACKGROUND:

BAY 43-9006/sorafenib is in active global clinical development by Bayer Healthcare Pharmaceuticals Corporation in collaboration with Onyx Pharmaceuticals. Sorafenib is a compound known to target both Raf kinase and VEGFR2 (vascular endothelial growth factor receptor 2) to inhibit two essential mechanisms involved in tumor growth. Raf kinase is a key enzyme in an important growth signaling pathway associated with the proliferation of

tumor cells. VEGFR2 is the main receptor of the vascular endothelial growth factor which plays a key role in angiogenesis.

A multi-national, multi-center Phase III study, Protocol 11213, entitled, "A Phase III randomized study of BAY 43-9006 in patients with unresectable and or metastatic renal cell cancer", is ongoing. The targeted indication is metastatic renal cell carcinoma (RCC). Interim and final analyses are currently planned. Both of these analyses are event driven with the interim survival analysis occurring when 270 death events have accrued and the final survival analysis at 540 events. The analysis of overall survival will be used to confirm clinical benefit and obtain complete approval.

In January 2005, the sponsor reached the number of progression events required to initiate the progression-free survival (PFS) analysis of the data collected from the ongoing Phase 3 study 11213. The independent data monitoring committee has reviewed the safety and efficacy data from this study and has concluded that the trial met its surrogate endpoint – resulting in statistically significant longer progression-free survival in those patients administered BAY 43-9006 versus those patients administered placebo ($p<0.000001$). As a result of the PFS analysis, the sponsor is planning to submit an NDA for BAY 43-9006 by August 1, 2005.

DISCUSSION:

FDA indicted that PFS of this magnitude, if validated on Agency review, would be an acceptable endpoint for approval of the NDA application.

FDA raised ethical concern about the patients that are currently on the placebo arm of the trial. They recommended that the sponsor reconsent the patient if the study is to continue. The study may need to arrange to provide all patients with access to the drug.

The FDA recommended an interim survival analysis plan be formulated now and that the analysis of survival be submitted at the time of NDA submission.

The FDA recommended that the sponsor submit a request to participate in the Continuous Marketing Application (CMA) Pilot 1 Program for their NDA submission.

The sponsor indicated that they would like to work with the Office of Special Health Issues to communicate their findings to patients and advocacy groups in the renal cancer community.

An expanded access protocol will be developed expeditiously.

ACTION ITEMS:

The sponsor will submit a request to participate in the CMA Pilot 1 program.

{See appended electronic signature page}

Patty Garvey, R.Ph.
Project Manager

Concurrence Chair:

{See appended electronic signature page}

Ann Farrell, M.D.
Medical Officer Team Leader

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/s/

Ann Farrell
4/8/05 03:52:56 PM

MEETING MINUTES

MEETING DATE: March 9, 2005 **TIME:** 11:00 a.m. **LOCATION:** WOC2/rm 3004

IND: 60,453

Meeting Request Submission Date: 1-7-05; sn706
Briefing Document Submission Date: 2-4-05; sn741

DRUG: Sorafenib (BAY 43-9006)

SPONSOR/APPLICANT: Bayer Pharmaceuticals Corporation

TYPE of MEETING:

1. Pre-NDA – Chemistry, Manufacturing, and Controls

2. **Proposed Indications (from briefing package):**

   Advanced renal cell carcinoma

FDA PARTICIPANTS:

Nallaperumal Chidambaram, Ph.D.	--	Chemistry Team Leader
Josephine Jee, M.S.	--	Chemistry Reviewer
Patty Garvey, R.Ph.	--	Regulatory Project Manager

INDUSTRY PARTICIPANTS:

Cheryl Anderson	--	Vice President, North America Global Regulatory Affairs
Ed Hugeunel, Ph.D.	--	Global Project Leader
Olaf Queckenberg, Ph.D.	--	Global Head of Quality Control/Development
Aileen Ryan, M.Sc.	--	Director, Global Regulatory Affairs Oncology
Rudolf Schwarz, Ph.D.	--	Head of Pharmaceutical Documentation
Christoph Wessler, Ph.D.	--	Manager, Analytical Development, Drug Product
Onyx: [redacted]	--	Consultant

MEETING OBJECTIVES (from briefing document):

To discuss the content and format of the CMC information to be contained in the marketing application for sorafenib tosylate tablets.

BACKGROUND:

BAY 43-9006/sorafenib is in active global clinical development by Bayer Healthcare Pharmaceuticals Corporation in collaboration with Onyx Pharmaceuticals. Sorafenib is a compound known to target both Raf kinase and VEGFR2 (vascular endothelial growth factor receptor 2) to inhibit two essential mechanisms involved in tumor growth. Raf kinase is a key enzyme in an important growth signaling pathway associated with the proliferation of

tumor cells. VEGFR2 is the main receptor of the vascular endothelial growth factor which plays a key role in angiogenesis.

A pre-IND meeting was held between the FDA and the sponsor on May 5, 2000. The sponsor submitted the initial IND on May 30, 2000. An End-of-Phase 1 meeting was held between the FDA and the sponsor on July 2, 2002. The sponsor requested the meeting to discuss the FDA's feedback and comments on the planned Phase 2 program, which is supported by the Phase 1 data and pre-clinical data, accumulated thus far. In addition, the sponsor met with the Office of Clinical Pharmacology & Biopharmaceutics on September 10, 2002 to discuss the clinical pharmacology development plans for BAY 43-9006. An end-of-phase 2 meeting was held between the FDA and the sponsor on August 6, 2003. Sorafenib received orphan drug designation on October 8, 2004 and Fast track status on April 3, 2004 for the metastatic renal cell carcinoma indication.

A multi-national, multi-center Phase III study, Protocol 11213, entitled, "A Phase III randomized study of BAY 43-9006 inpatients with unresectable and or metastatic renal cell cancer", is ongoing. The targeted indication is metastatic renal cell carcinoma (RCC). Interim and final analyses are currently planned. Both of these analyses are event driven with the interim survival analysis occurring when 270 death events have accrued and the final survival analysis at 540 events. The analysis of overall survival will be used to confirm clinical benefit and obtain complete approval. As of November 12, 2004, 581 patients have been randomized in this study. Two hundred fifteen progression events and 27 death events have been reported.

Bayer is planning to submit the New Drug Application of for sorafenib in August 2005. They are considering requesting a rolling submission or participation into the Continuous Marketing Application Pilot 1 program. They were granted fast track designation for metastatic renal cell carcinoma on March 26, 2004.

QUESTION for DISCUSSION with FDA RESPONSES and DECISIONS REACHED:

NDA format

1. Bayer plans on submitting the NDA for sorafenib tosylate tablets as an electronic NDA in CTD format. The Chemistry, Manufacturing and Controls information will be provided electronically only. Please confirm that this will be acceptable.

   FDA: Your proposal to submit an electronic NDA in CTD format is acceptable.

2. As outlined in the Introduction section, the sections of the Quality Module will be comprised of various individual Technical Registration Documents (TRDs). Is there any additional information that Bayer can provide to aid in the review of this section?

   FDA: We recommend that the stability data be submitted in tabular format.

Discussion: The tabular format outlined by the sponsor (see attachment) together with graphical presentation for assay, dissolution, impurities and water content across batches will be provided in the application.

Drug Product

3. In Table 2.6 of the stability portion of Section D, Chapter 2.6, we have outlined the primary stability studies as well as when data from additional timepoints will be available. We are currently planning to submit the NDA in August 2005 and are intending to request a priority review. We are also considering a rolling NDA submission and/or requesting acceptance into the Pilot 1 program, in which case one of the reviewable units may be the CMC section of the application. Please confirm that, if either of these submission plans are agreed by the Division, the current stability data would be sufficient for filing and additional data could be added at the times listed in the table in the stability section to support the expiration dating period.

   FDA: We are willing to accept a chemistry submission with the primary stability data outlined in your submission. Your proposal to submit chemistry as a rolling submission is also acceptable provided it is submitted as a complete package. We will be willing to accept a one time update to stability data during the review of your NDA. This should be submitted at least two/three months before the goal date.

4. Is the stability data, as outlined in section D, Chapter 2.6, in this submission sufficient to support the proposed initial shelf-life claim [ ]

   FDA: We cannot comment on your proposal for granting [ ] of shelf-life at this time as it is a review issue. Generally, shelf-life will be determined based on real time stability data from primary stability batches. A reasonable extrapolation may be considered based on the strength and quality of your primary and supportive stability data.

5. Process modifications (classified as minor changes according to SUPAC guidelines) have been introduced during scale up from pilot to commercial scale to ensure a robust manufacturing process of the drug product in commercial scale. The proposed modifications are described in detail in Section D, chapter 2.2.4 of the briefing package. Additional data (e.g. dissolution, stability), as described in Table 2-3 of Section D will be provided at the time of submission to support these changes. Does the agency agree that the proposed data are appropriate to support these changes?

   FDA: Please clarify what you mean by [ ]" and [ ]. It is our expectation that you will finalize the formulation by the time you initiate pivotal clinical trials.

Discussion: The sponsor clarified [redacted] *in their presentation (see attachments). FDA understands the clarification.*

The sponsor will provide in the initial NDA submission [redacted] *of stability data from pilot scale batches (45 ml bottle),* [redacted] *of data from pilot scale batches (90 ml bottle) without embossing and* [redacted] *and* [redacted] *accelerated and long term data on the commercial scale with* [redacted]

A one time update including data from above batches will be provided in the NDA.

The comparative dissolution data between clinical and commercial batches will be submitted for review and comment under IND 60,453 sorafenib.

6. A revised drug product specification is proposed for the commercial product. The intended modifications and their rationale are described in detail in Section D, chapter 2.4 of the briefing package. Does the agency agree that the proposed rationale is appropriate to support these changes?

FDA: In general, your proposed drug product specification appears reasonable to support filing of an NDA. However, we recommend that you should identify and qualify any unspecified degradants above identification and qualification threshold.

Your proposal for [redacted] **is not acceptable at this time because your product** [redacted] **In addition, you do not have enough manufacturing history** [redacted] **Hence, we recommend that you propose acceptance criteria for** [redacted] **. Please note that if you will be using compendial methods other than USP, you will need to demonstrate equivalence of the other compendial method to USP.**

Your proposal to perform [redacted] **for** [redacted] **appears to be acceptable. We recommend that you perform** [redacted] **testing at release and future stability studies annually there after rather than at release,** [redacted] **as indicated in your stability protocol for NDA primary stability batches.**

Discussion: The sponsor will be providing long term stability data in the NDA from pilot scale batches to support the proposal for [redacted]

Based on the discussion and the rationale that dissolution will capture any changes to [redacted] *it is acceptable to eliminate testing* [redacted]

7. At the time of a possible pre-approval inspection, Bayer HealthCare will have available a written and approved validation plan for the commercial manufacturing process. The validation itself however may not be completed at this time. Is there a

requirement or an expectation to have process validation completed at the time of the pre-approval inspection?

FDA: We recommend that you have your process validation completed and available at the time of your submission (the pre-approval inspection). We recommend that you contact the district for any additional questions you may have related to inspection.

Drug Substance

8. Bayer HealthCare intends to make a post approval change [

] We plan to include a comparability protocol in the NDA submission and would like to have this change implemented as a post approval change using a Changes Being Effected in 30 Days (CBE-30) supplement. An outline of the rationale for this change as well as the supporting documentation to be included in the comparability protocol is included in section E of this documentation. Does the Agency agree that this change can be filed as a CBE-30 supplement if the acceptance criteria and the prerequisites defined in the outline of the protocol are fulfilled?

FDA: Yes, your proposal for a post approval change appears to be acceptable.

GENERAL DISCUSSION:

The FDA suggested that based on the draft drug substance guidance from January 2004, [ ] be considered [ ]

The synthesis of the drug substance is [ ] hence we need to have tight control regarding carry over of impurities.

The sponsor states that it has been progressing in development including process validation under the agreement reached at the EOP2 meeting. The sponsor will request a teleconference to discuss the extent of documentation to be provided in order to address the concerns raised by the FDA.

ACTION ITEMS: The comparative dissolution data between clinical and commercial batches will be submitted for review and comment under IND 60,453 sorafenib.

The meeting concluded at 12:30 pm. There were no unresolved issues.

{See appended electronic signature page}

Patty Garvey, R.Ph.
Project Manager

Concurrence Chair:

{See appended electronic signature page}

Nallaperumal Chidambaram, Ph.D.
Chemistry Team Leader

ATTACHMENTS: Bayer's overheads presented during the meeting.

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Nallaperumal Chidambaram
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TELECONFERENCE MINUTES

TELECON DATE: December 14, 2004

IND: 60,453

Meeting Request Submission Date: 9-21-04; sn611
Briefing Document Submission Date: 11-16-04; sn673

DRUG: sorafenib (BAY 43-9006)

SPONSOR/APPLICANT: Bayer Pharmaceuticals Corporation

TYPE of MEETING:

1. Pre-NDA

2. **Proposed Indications (from briefing package):**

   Treatment of patients with renal cell carcinoma

FDA INTERNAL PARTICIPANTS:

Richard Pazdur, M.D.	--	Director, Division of Oncology Drug Products (DODP)
Grant William, M.D.	--	Deputy Director, DODP
Ann Farrell, M.D.	--	Medical Team Leader
Robert Kane, M.D.	--	Medical Reviewer
David Morse, Ph.D.	--	Pharmacology/Toxicology Team Leader
Rajeshwari Sridhara, Ph.D.	--	Statistical Team Leader
Patty Garvey, R.Ph.	--	Regulatory Project Manager

SPONSOR: Aileen Ryan -- Director, Global Regulatory Affairs

MEETING OBJECTIVES (from briefing document):

1. Format and content of the non-clinical section of the filing. An outline of these sections of the NDA are provided in Appendix E.

2. Format and content of the clinical section of the filing including the following:

   - Plan for the analysis of the Phase III data. While the Statistical Analysis Plan (SAP) will have been provided separately to the IND for a detailed review, a summary of the study design is provided in Appendix B. We are also providing an update on the ongoing validation of the Patient Reported Outcome (PRO) tool used in this study, FACT Kidney Symptom Index (FKSI) in Appendix C.

   - Plans for pooling of studies in the safety analyses.

3. Our plan to request inclusion in the Pilot 1 program as well as the proposed contents and availability of the reviewable units.

BACKGROUND:

BAY 43-9006/sorafenib is in active global clinical development by Bayer Healthcare Pharmaceuticals Corporation in collaboration with Onyx Pharmaceuticals. Sorafenib is a compound known to target both Raf kinase and VEGFR2 (vascular endothelial growth factor receptor 2) to inhibit two essential mechanisms involved in tumor growth. Raf kinase is a key enzyme in an important growth signaling pathway associated with the proliferation of tumor cells. VEGFR2 is the main receptor of the vascular endothelial growth factor which plays a key role in angiogenesis.

A pre-IND meeting was held between the FDA and the sponsor on May 5, 2000. The sponsor submitted the initial IND on May 30, 2000. An End-of-Phase 1 meeting was held between the FDA and the sponsor on July 2, 2002. The sponsor requested the meeting to discuss the FDA's feedback and comments on the planned Phase 2 program, which is supported by the Phase 1 data and pre-clinical data, accumulated thus far. In addition, the sponsor met with the Office of Clinical Pharmacology & Biopharmaceutics on September 10, 2002 to discuss the clinical pharmacology development plans for BAY 43-9006. An end-of-phase 2 meeting was held between the FDA and the sponsor on August 6, 2003. Sorafenib received orphan drug designation on October 8, 2004 and Fast track status on April 3, 2004 for the metastatic renal cell carcinoma indication.

A multi-national, multi-center Phase III study, Protocol 11213, entitled, "A Phase III randomized study of BAY 43-9006 inpatients with unresectable and or metastatic renal cell cancer", is ongoing. The targeted indication is metastatic renal cell carcinoma (RCC). Interim and final analyses are currently planned. Both of these analyses are event driven with the interim survival analysis occurring when 270 death events have accrued and the final survival analysis at 540 events. The analysis of overall survival will be used to confirm clinical benefit and obtain complete approval. As of November 12, 2004, 581 patients have been randomized in this study. Two hundred fifteen progression events and 27 death events have been reported.

After the internal FDA meeting, draft responses were faxed to the sponsor on December 14, 2004. During the subsequent telecon, it was confirmed that the responses were clear and that a face-to-face meeting scheduled for December 17, 2004 was not needed.

QUESTION for DISCUSSION with FDA RESPONSES and DECISIONS REACHED:

Nonclinical

A. Bayer has submitted the nonclinical reports (a list reports is included in Appendix E) as IND amendments and will submit them with the NDA CTD in PDF-format. Since these reports constitute legacy data the PDF files will not be in a searchable format.

Please confirm that this is acceptable.

FDA: Yes, this format is acceptable.

B. A comprehensive nonclinical program has been conducted to characterize the toxicological and toxicokinetic profile of sorafenib, tested as tosylate salt BAY 54-9085. Administration was by the oral route, consistent with the clinical use of the drug candidate. Single-dose toxicity / tolerance studies were conducted in the rat, mouse and dog. Repeat-dose toxicity was covered by studies with daily treatment up to 6 months in rats, 3 months in mice, and up to 12 months in dogs.

Please confirm that this package is acceptable to support marketing approval.

FDA: Yes, the proposed nonclinical package appears acceptable.

Clinical

C. For studies that are completed, Bayer is planning to submit complete reports. For the combination study with irinotecan (10981), Bayer is planning to provide an interim report with data up to a cut-off date of May 31, 2004. For the remaining studies, summary data with a cut off of December 31, 2004 will be included in the ISS. The interim report will contain the same level of detail as in the complete reports. The level of detail provided in the summary data will be similar to that included in an IND annual report. A list of sorafenib clinical studies is included in Appendix A together with the type of data we plan to include in the NDA.

Please confirm that this is acceptable.

FDA: This is acceptable.

Integrated Summary of Safety – Proposed analyses

D. Bayer intends to include three major analyses (2 pooled datasets and the data from the Phase III study) in the integrated safety of data from studies in cancer patients as outlined below;

- Completed uncontrolled single agent Phase 1 pool exploring the maximum tolerated dose (MTD) using different dosing schedules. The following studies will be included:

  - 100283 Single dose once a week
  - 10164 – Part 1 21 days treatment/7 days off
  - 100277 28 days treatment/7 days off
  - 100342 1 week treatment/1 week off
  - 100313 1 week treatment/3 weeks off
  - 10658 Continuous treatment in Japanese patients
  - 10922 Extension study

- Phase II Completed Single Agent Pool

  - This pool consists of two trials: the Phase II single arm trial in HCC Patients (Study 11213) in RCC patients (single agent sorafenib vs. placebo) is a placebo controlled study and the Phase II studies are uncontrolled, data from this study will not be pooled with the Phase II data.

As the Phase III study (Study 11213) in RCC patients (single agent sorafenib vs. placebo) is a placebo controlled study and the Phase II studies are uncontrolled, data from this study will not be pooled with the Phase II data.

Please confirm that this is acceptable.

FDA: This is acceptable.

E. In Section 6, we have provided an outline of the analyses we intend to include on the data pools for safety.

Please confirm that they are sufficient and/or provide suggestions for additional analyses.

FDA: This is acceptable.

Integrated Summary of Efficacy

F. Bayer is currently planning to provide the Integrated Summary of Efficacy and Section 2.7.3 of Module 2 as exact copies.

Please confirm that this is acceptable.

FDA: This is acceptable.

Submission Logistics

PDUFA Fee Exemption

G. Bayer received Orphan Drug Designation for sorafenib on October 8, 2004 Therefore, under section 526 of the Federal Food, Drug, and Cosmetic Act, BAY 43-9006 is exempt from the PDUFA application fees.

Does the Agency require any further documentation concerning the Sponsor's exemption from this requirement?

FDA: Not at this time.

Case Report Forms

H. Bayer is intending to submit CRFs in electronic format only, in accordance with FDA guidance on electronic submissions, and to include CRFs for only those patients who either withdrew or died during the course of the study, or who discontinued from the study due to an adverse event.

Please confirm that this is acceptable.

FDA: This is acceptable. CRFs are expected for all deaths within 28 days of last treatment also.

Electronic Datasets

I. Bayer is planning to submit all applicable electronic datasets as SAS system Transport Format (Version 5 SAS transport Format) files in accordance with the 1999 FDA guidance on electronic format.

FDA: This is acceptable.

J. Bayer intends to provide the NDA/CTD in electronic format in accordance with eNDA specification guidance. Does the Division agree that the review and archival copy of the NDA can be provided in electronic format?

FDA: Yes.

Patients Reported Outcomes

K. A separate validation study (Appendix C – [redacted] is being conducted with the [redacted] A final validation report based on 148 patients is expected in December 2004. We are considering conducting an analysis of the — endpoint at the time of the analysis of PFS. We would be happy to work with the study endpoint group to obtain agreement with the planned analyses to be developed based on the validation study.

Please confirm that this is acceptable.

FDA: This can be evaluated after the review of the principal study endpoint, if the study appears to have a positive result.

We will refer this question to the Agency's PRO team.

Pilot 1 Program Request

L. Bayer is currently planning to request admittance to the Pilot program for submission of a CMA. The contents and timing of the availability of the proposed reviewable units are provided in Section 7.

Would the Division support admittance of sorafenib, for this indication, to the Pilot 1 program?

FDA: At the time of the final PFS analysis, please resubmit this question to us.

{See appended electronic signature page}

/S/

Patty Garvey, R.Ph.
Regulatory Project Manager

Concurrence Chair:

{See appended electronic signature page}

/S/

Ann Farrell, M.D.
Medical Team Leader

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/s/

Ann Farrell
1/6/05 10:24:01 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

October 8, 2004

Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, Connecticut 06516

Attention: Vivienne Arasai, M.D.
Deputy Director, Global Regulatory Affairs

Re: Designation Request

Dear Dr. Arasai:

Reference is made to your request for the orphan-drug designation dated February 27, 2004, of sorafenib for the "treatment of renal cell carcinoma." Please also refer to our letters of March 3 and June 1, 2004 and to your submission dated August 25, 2004.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan drug designation of sorafenib is granted for the *treatment of renal cell carcinoma.* Please be advised that it is sorafenib and not the formulation of the drug that is designated.

Please note that if the above drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (*see* 21 C.F.R. 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the drug's designated use.

If you need further assistance in the clinical development of your drug, please feel free to contact Tan T. Nguyen, M.D., Ph.D., at (301) 827-3666. Please refer to this letter as official notification. Congratulations on obtaining your orphan-drug designation.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

3/26/04

IND 60,453

Bayer Corporation
Attention: Vivienne Arasi, M.D.
Deputy Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Dr. Arasi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for BAY 43-9006 (sorafenib).

We also refer to your February 10, 2004, request for fast track designation and for step-wise submission of sections of a New Drug Application supplemental new drug application under section 506 of the Act.

We have reviewed your request and have concluded that it meets the criteria for fast track designation. Therefore, we are designating BAY 43-9006 for the treatment of metastatic renal cell carcinoma (mRCC) as a fast track product.

We are granting fast track designation for the following reasons:

1. Metastatic renal cell carcinoma is a serious and life-threatening disease.

2. Existing therapy provides only a small therapeutic benefit at the expense of considerable toxicity. As suggested by your early phase 2 results in metastatic renal cell carcinoma, your drug may have the potential to provide a new, possibly less toxic, alternative. Your randomized phase 3 trial, study 11213, has the potential to demonstrate an effect on a serious or life-threatening aspect of this condition.

When formulating your plans for submitting your NDA, please submit a plan for your rolling submission and a formal request for rolling review.

If you pursue a clinical development program that does not support use of BAY 43-9006 for the treatment of metastatic renal cell carcinoma (mRCC), we will not review the application or accept step-wise submission of sections of an NDA a supplemental new drug application under the fast track program.

If you have any questions, call Patty Garvey, Regulatory Project Manager, at 301-594-5766.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Richard Pazdur
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INDUSTRY MEETING MINUTES

MEETING DATE: January 13, 2004 **TIME:** 9:30am **LOCATION:** G

IND/NDA IND 60,453

Meeting Request Submission Date: 11-17-03
Briefing Document Submission Date: 12-11-03
Additional Submission Dates:

DRUG: BAY 43-9006 (Sorafenib)

SPONSOR/APPLICANT: Bayer HealthCare Pharmaceuticals

TYPE OF MEETING:

1. End-Of-Phase 2.

2. **Proposed Indication:** treatment of metastatic renal cell carcinoma.

BACKGROUND: Bayer Pharmaceuticals held an End-of-Phase 2 meeting with the Division in August of 2003 to discuss the Phase 2 Randomized Discontinuation trial (Study 100391). Bayer has now requested a follow-up End-of-Phase 2 meeting to provide clinical data from 65 patients with renal cell carcinoma from the study 100391. Bayer wishes to discuss the significance of the data gathered thus far and the impact on the current development plan.

FDA PARTICIPANTS:

Richard Pazdur, M.D., Director, DODP
Grant Williams, M.D., Deputy Director, DODP
Ann Farrell, M.D., Clinical Team Leader, DODP
Robert Kane, M.D., Clinical Reviewer, DODP
Rajeshwari Sridhara, Ph.D., Acting Statistical Team Leader, DODP
Yong-Cheng Wang, Ph.D., Statistical Reviewer
Brian Booth, Ph.D., Biopharmaceutical Reviewer, DODP
Amy Baird, Consumer Safety Officer, DODP

INDUSTRY PARTICIPANTS:

Vivienne Arasi, M.D., Deputy Director, Regulatory Affairs
Paul MacCarthy, M.D., VP, Medical Sciences
Scott Freeman, M.D., VP, Clin. Development, Onyx Pharmaceuticals
Adriaan Fruijtier, M.Sc., Dir. Oncology, Global Regulatory Affairs
[ ] Medical Consultant, Onyx Pharmaceuticals
Ed Huguenel, Ph.D., Global Project Leader
Susan Kelley, M.D., VP, Oncology Therapeutic Area
Chetan Lathia, Ph.D., Deputy Director, Medical Sciences II
Richard Lee, M.D., Assoc. Director, Medical Sciences II
Kemal Malik, M.D., Head, Global Product Development
[ ] Consultant to Onyx Pharmaceuticals
Len Post, Ph.D., Senior VP, Research & Development, Onyx
Joseph Scheeren, Ph.D., Senior VP, Head of Global Reg. Affairs
Brian Schwartz, M.D., Director, Global Clinical Development
Minghua Shan, Ph.D., Deputy Director, Biometry

MEETING OBJECTIVES: Discuss sponsor's briefing package dated December 11, 2003.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. **Intravenous high dose IL-2 is the only approved modality of treatment for the first-line metastatic RCC patients. However, due to its severe toxicity profile, and stringent administration criteria, only a small fraction of eligible RCC patients receive this treatment. In general, its use has been recommended for patients in the intensive care setting with a good performance status, normal cardiac status, and good pulmonary function tests. Hence, many patients receive alternative first-line treatment for metastatic RCC. Also, there is no other approved therapy for patients who fail first-line treatment. Therefore, does the agency agree that this constitutes a patient population with an unmet medical need?**

   FDA Response:

   - Yes.

2. **In the sorafenib Phase II RD trial, of the first 65 patients, 86% of metastatic RCC patients failed at least one prior therapy and 42% failed more than one prior therapy. Interleukin-2 (all dose schedules) and Interferon were administered as a prior therapy in 56% and 54% of the patients, respectively. Does the Agency agree that this metastatic RCC patient population in the RD trial represents an appropriate patient population, with an unmet medical need, to evaluate the clinical benefit of sorafenib?**

   FDA Response:

   - Yes.

3. **Does the Agency agree that the following criteria are reasonably likely to predict clinical benefit for patients with metastatic RCC assuming all are met in the data set of approximately 150 metastatic RCC patients currently enrolled in the Study 100391, Phase II RD trial?**

Criteria:

a. **an observed partial response rate of 8-10%, and, (for PR rates of 8% and 10%, the lower bounds of 95% CI are 4.2% and 5.7% respectively)?**

FDA Response:

- No. FDA does not prospectively define a response rate that would be adequate for accelerated approval. This is a review issue that requires confirmation of response duration and location of response, number of CR and PR. We believe that this drug appears to be promising with demonstration of preliminary modest activity in this disease. Therefore, we encourage you to develop a larger database to bring greater clarity to the effectiveness of this drug. Response should be defined as CRs plus PRs (determined by traditional methods such as 50% decrease in sum of cross-products or by RECIST) confirmed after an additional month and verified by an independent review process. In determining adequacy to support accelerated approval, we consider duration and overall risk benefit relationship. Note, we do not consider stable disease and minimal responders part of the response rate.

- The sponsor needs to clarify the definition of partial response (PR) reported in the protocol in terms of standard criteria. WHO response criteria for PR require a 50% decrease in the sum of perpendicular diameters. Duration of response and evidence of symptom improvement are also relevant to assessing the potential for clinical benefit.

b. **an overall disease control demonstrating that patients with stable disease or better (PR + MR + SD) have median time to treatment failure of at least 18 weeks?**

FDA Response:

- No. Median time to treatment failure is not interpretable in a single arm study and has not generally been used by FDA in regulatory assessments.

c. **a trend in progression free rate at week 24 (12 weeks after randomization) in favor of sorafenib in the randomized portion of the study where patients with stable disease at 12 weeks are randomized to either placebo or sorafenib (the blind has not been broken by Bayer on any patients on this portion of the study)?**

FDA Response:

- No, a trend in progression free rate at week 24 in the randomized portion of the study is not acceptable as a criterion. Furthermore, there will be only approximately 35 patients on the randomized portion of the trial.

d. **safety data that continues to demonstrate that sorafenib is well tolerated.**

FDA Response:

- A sufficient number of patients are required at the dose level of interest and for a duration consistent with the intended use of the product to allow labeling. Generally, in a refractory life threatening disease, the number of patients needed is dictated by efficacy requirements.

4. **If the Agency would consider granting an accelerated approval, does the Agency agree that the current Phase III study design might need to be modified and that modified study could serve as a Phase IV commitment?**

FDA Response:

- No. At this time we do not think you have sufficient data for accelerated approval. Accelerated approval requires further study to verify clinical benefit. Confirmatory studies are expected to be underway at the time of an accelerated approval such that an approval action would not jeopardize completion of definitive studies. Your current phase 3 trial as planned may provide strong confirmation if results are positive.

Discussion: There is no objection to the current randomized discontinuation phase 2 trial as a potential support for accelerated approval depending upon results of response rate, response duration, toxicity and number of patients enrolled. Whether 150 patients will suffice will depend upon the results after review by independent evaluation and review by the FDA.

5. **If data from the Phase II RD trial are found to constitute clinical benefit for patients with metastatic RCC, an NDA submission based on the RD Phase II efficacy data, may occur as early as the third quarter of 2004. This is approximately one year sooner than time to progression data that would be**

available from the ongoing Phase III trial for filing. In this context, does the Agency agree that it would be appropriate to file an NDA for accelerated approval based on these Phase II data, if the data meet the criteria outlined in question 3 above?

FDA Response:

- See above responses. Your data appear insufficient at this time.

6. **The proposed NDA package for accelerated approval will include safety data from 400 patients in the RD trial and over 1000 patients exposed to sorafenib on all trials at the 400 mg bid dose. There will also be efficacy and safety information on approximately 150 patients with metastatic RCC for response rate, time to progression, and overall survival. In addition, there will be approximately 35 patients on the randomized portion of the trial. Is this an acceptable NDA package?**

   FDA Response:

   - See previous FDA responses.

The meeting was concluded at 10:30am.

/S/

Amy Baird
Consumer Safety Officer
Minutes Preparer

/S/

Concurrence Chair: _____
Robert Kane, M.D.
Clinical Reviewer

11 Page(s) Withheld

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/s/

Amy Baird
2/4/04 11:08:29 AM

Robert Kane
2/4/04 12:21:12 PM

MEETING MINUTES

MEETING DATE: August 6, 2003 **TIME:** 11:00 a.m. **LOCATION:** WOC2/r 6002

IND: 60,453

Meeting Request Submission Date: 5-13-03; sn 231
FDA Response Date: 5-22-03
Briefing Document Submission Date: 7-3-03; sn 256
Additional Submission Date: 7-10-03; sn 263

DRUG: BAY 43-9006 (Raf Kinase Inhibitor)

SPONSOR/APPLICANT: Bayer Pharmaceuticals Corporation

TYPE of MEETING:

1. End-of-Phase 2

2. **Proposed Indications (from briefing package):**

   Unresectable and/or metastatic renal cell carcinoma

FDA PARTICIPANTS:

	Richard Pazdur, M.D.	--	Director, Division of Oncology Drug Products
	Grant William, M.D.	--	Deputy Director, DODP
	Lilia Talarico, M.D.	--	Associate Director, DODP
	Ann Farrell, M.D.	--	Medical Team Leader
	Robert Kane, M.D.	--	Medical Reviewer
	Steven Hirschfeld, M.D., Ph.D.	--	Medical Reviewer
	Kevin Ridenhour, M.D.	--	Medical Reviewer
	Atiqur Rahman, Ph.D.	--	Clinical Pharmacology & Biopharmaceutics Team Leader
	Sophia Abraham, Ph.D.	--	Clinical Pharmacology & Biopharmaceutics Reviewer
	Brian Booth, Ph.D.	--	Clinical Pharmacology & Biopharmaceutics Reviewer
	Peter Lee, Ph.D.	--	Clinical Pharmacology & Biopharmaceutics Fellow
	Ning Li, Ph.D.	--	Acting Statistical Team Leader
	Dotti Pease for Patty Garvey	--	Chief Project Management
at pre-meeting:	Patty Garvey, R.Ph.	--	Project Manager

INDUSTRY PARTICIPANTS:

Vivienne Arasi, M.D.	--	Deputy Director, Global Regulatory Affairs
Christopher Carter, Ph.D.	--	Principal Research Scientist, Dept. of Cancer Research
Adriann Fruijtier, M.Sc.	--	Global Regulatory Strategist Oncology, Global RA
Edward Huguenel, Ph.D.	--	Global Project Leader, Oncology
Susan Kelley, M.D.	--	Vice President, Therapeutic Area Head, Oncology
Chetan Lathia, Ph.D.	--	Deputy Director, Clinical Pharmacology
Richard Lee, M.D.	--	Associate Director, Medical Science
Wolfgang Rossberg, M.D.	--	Research Fellow
Brian Schwartz, M.D.	--	Director, Global Clinical Development
Michael Shan, Ph.D.	--	Deputy Director, Biometry
Mary Taylor, M.P.H	--	Vice President, Regulatory Affairs North America
Terry Taylor, M.D.	--	Vice President, Global Clinical Development North America
Friederick Jekat, M.D.	--	Director, Drug Safety Evaluation

Kathleen Gondek, Ph.D.	--	Head, Global Health Economics & Outcomes Research
Lisa Murray	--	Operations Coordinator
Hans Scholl, Ph.D.	--	Director, Regulatory CMC
Onyx: [ ]	--	Medical Consultant

MEETING OBJECTIVES (from briefing document):

To discuss proposed clinical trial for renal cell carcinoma and respond to sponsor's questions.

BACKGROUND:

BAY 43-9006, a raf kinase inhibitor, is in active global clinical development by Bayer Pharmaceuticals Corporation in collaboration with Onyx Pharmaceuticals. A pre-IND meeting was held between the FDA and Bayer on May 5, 2000. Bayer submitted the initial IND on May 30, 2000. An End-of-Phase 1 meeting was held between the FDA and Bayer on July 2, 2002. Bayer request the meeting to discuss the FDA's feedback and comments on the planned Phase 2 program, which is supported by the Phase 1 data and pre-clinical data, accumulated thus far. In addition, Bayer met with the Office of Clinical Pharmacology & Biopharmaceutics on September 10, 2002 to clinical pharmacology development plans for BAY 43-9006.

QUESTION for DISCUSSION with FDA RESPONSES and DECISIONS REACHED:

NOTE: Bayer received the Division's comments via facsimile on July 31, 2003.

During the course of the meeting, there were additional agreements between the Division and Bayer. These agreements are *italicized* under the Discussion heading in these minutes.

Regulatory

1. a) Does the Agency agree that an overall type I error rate of 0.025 (one-sided) based on this final TTP analysis in the single Phase III pivotal study in RCC with the additional supportive data outlined above would be acceptable for accelerated approval? In this case, the post-approval commitment would be the final analysis of overall survival from this single Phase III RCC study.

FDA: You refer to a randomized discontinuation study (study 100391?). Please describe this study and present the results and/or a study report so that we may determine the relevance of this study to your proposal.

As stated in the FDA Efficacy Guidance, a single phase 3 study that is well conducted, internally consistent, and demonstrates a compelling survival benefit could be persuasive for full approval. Your study could potentially provide such evidence, but such a determination is a review issue.

Because separate analyses of TTP and survival could each support approval (accelerated approval and regular approval, respectively), and hence provide two possible chances for a positive result (favorable FDA action), the overall experimental type I error should be controlled: we suggest you use 0.01 for the TTP and 0.04 for the survival analysis.

b) Does the Agency agree that an overall type I error rate of 0.025 (one-sided) for the overall survival endpoint in this single Phase III pivotal study in RCC with the additional supportive data outlined above would be acceptable for full regulatory approval?

FDA: The error rate is acceptable. Please also refer to the response to question # 1(a).

2. Does the Agency agree with our expectation that this HCC protocol could qualify for a Special Protocol Assessment?

FDA: Yes. Please submit a Special Protocol Assessment after an EOP2 meeting for HCC.

3. We propose that the NDA package for RCC will contain only adult patient information. Does the Agency agree with this approach?

FDA: Yes; however, we do encourage you to consider pediatric studies and remind you that such studies may qualify for pediatric exclusivity if done in response to an FDA written request.

4. Does the Agency agree that BAY 43-9006 meets the criteria necessary for the fast track designation?

FDA: Please submit a separate request for the fast track program.

Preclinical Toxicology

Does the Agency agree that the program conducted and the results seen are sufficient to support the clinical program outlined in this submission and to support marketing approval?

FDA: The proposed toxicological program is sufficient to support the NDA filing for BAY 43-9006.

Clinical Pharmacology

1. A QTc study has been proposed in the updated clinical pharmacology development plan presented in this submission. This evaluation, along with a preclinical evaluation, is considered comprehensive for an anticancer agent. Will this QTc study be sufficient with respect to QTc evaluations for the approval of the BAY 43-9006 NDA?

   FDA: Generally, the design of the study appears to be adequate. However, you should address the following issues

   Patient numbers: You described enrolling 30-50 patients, but the rationale for this number was not explained. You should enroll a statistically sufficient number of patients to address the question of QTc prolongation.

   Doses: The dose and dosing regimen have not been described. When choosing the dose/dosing regimen(s), you should consider the proposed labeled dosing for BAY 43-9006, and the potential for excessive drug exposure in cases of organ dysfunction or drug-drug interactions.

   Sampling: You have described QTc and pharmacokinetic sampling, at steady state out to 6 hours. However, you should consider sampling over a period of 4 half-lives of BAY 43-9006 following the last dose, to capture any potential lag in the drug effect.

   Discussion: The FDA strongly encourage Bayer to do a QTc study based on a valid rationale, but the QTc study would not necessarily be required for NDA filing, especially for Accelerated Approval. The plans submitted seem reasonable – the FDA would like to review the detailed protocol.

2. Is our proposal for population pharmacokinetic evaluations in the proposed Phase III trial adequate for characterizing BAY 43-9006 pharmacokinetics in RCC patients?

   FDA: Too little information is provided in the synopsis you supplied to adequately assess your population pharmacokinetic plan. Specially, you should

   a. **Describe the process for building and validating the population pharmacokinetic model.**
   b. **Describe the analysis plan for the data generated.**
   c. **Describe how the pharmacokinetics will be correlated with safety and efficacy endpoints.**

With regard to assessing the effect of renal impairment on the pharmacokinetics of BAY 43-9006, you should ensure that an adequate number of patients with varying degrees of renal impairment are included in the study to assess a meaningful change in C_{max} and AUC.

3. Instead, BAY 43-9006 pharmacokinetics will be evaluated in the Phase III RCC patients, some of whom may be renally impaired, using the population pharmacokinetic methods described above (question 2). Is our proposal to evaluate BAY 43-9006 pharmacokinetics in RCC patients acceptable?

   FDA: Yes, this is acceptable. However, for proper comparison, you should include in the population PK database an adequate number of cancer patients with normal renal function (from other Phase 1-2 studies) in addition to mild-to-moderate RCC patients' data from your Phase 3 study.

   How do you plan to address the issue of the use of this product in the severely renal impaired (Ccr < 30 cc/min) patients?

   Discussion: If severely renally impaired (<30 creatinine clearance) patients are excluded form the phase 3 study, FDA would expect a separate study to be done in renally impaired patients.

4. A clinical pharmacology development plan was presented and agreed upon with the FDA in September 2002. An updated clinical pharmacology development plan is presented in this submission. Is the updated clinical pharmacology development plan acceptable in terms of the clinical pharmacology package for approval of the BAY 43-9006 NDA?

   FDA: Yes, the clinical pharmacology development plan appears adequate.

Clinical

1. With reference to the inclusion criteria of the Phase III RCC protocol (protocol section 4.2.1) and the primary efficacy analysis in the statistical plan (protocol section 6.1.1), the current plans for stratification is based on 1) the key prognostic features characterized by the Motzer criteria; 2) by country. The stratification by prognostic factors will include the "low risk" versus the "intermediate risk" groups. Does the Agency agree with the strategy of stratification by country?

FDA: Please estimate how many countries will enter patients in your study and your rationale for stratifying by country. Please consider the total number of strata. If you anticipate entering patients from many countries, stratifying by region may be more appropriate. Please discuss your rationale for this stratification by country. Do you anticipate differences in prior therapy, or other factors (such as nephrectomy for stage 4 presentations)?

2. Rare histological* variants of RCC have differing prognoses. Hence, Bayer plans to exclude from the pivotal Phase III trial patients whose tumor biopsy cell types include: collecting duct or medullary cells, sarcomatoid, granular, papillary, chromophobe, small cell carcinoma, cystic RCC, rhabdoid variant of RCC, and transitional cell cancer of the renal pelvis. How would these exclusions be reflected in the product labeling?

FDA: In general, the population treated in the study is the population described in the label for therapy.

3. a) Overall survival is the primary endpoint of the study. Patients will be followed until death. A total of 513 deaths are expected by the end of this study. Bayer is planning on providing narratives on deaths within 30 days of administration of study drug that were not related to disease progression. Does the Agency agree?

FDA: Yes.

b) Given the oncology patient population with multiple medical conditions, Bayer is planning to provide narratives only on SAEs that were considered drug related. Does the Agency agree?

FDA: Please plan to provide narratives on all patients with serious or severe (grade 3 or 4) AEs.

Discussion: Bayer should make a proposal regarding specific events, which would not be reported, i.e. clearly define prospectively what constitutes "drug related."

4. There are no validated HRQoL instruments for advanced RCC. Therefore, Bayer has worked closely with investigators to construct a RCC (FACT-RCC) HRQoL instrument to be tested in the Phase III RCC protocol. A total of 80 blinded valid subjects who complete the FACT-RCC at baseline and at least three cycles will be examined to validate the instrument. After validation, if statistical significant improvement in the HRQoL is observed at the final analysis, could this be used as an indicator of clinical benefit? (Please see Appendix in Section 5.17.1 of the Clinical Summary for details.)

FDA: Please submit the HRQoL plan for review. Comments will follow after our review of the HRQoL plan.

Discussion: The FDA will look at Bayer's proposal and consult Dr. Laurie Burke. The FDA will provide comments after the consult has been completed.

5. Bayer is planning to collect adverse event data using the NCI-CTC version 3.0. This new version can be readily mapped to MedDRA. Bayer's intention is to report toxicity data using this new NCI-CTC version 3.0 in the label. However, the information can be provided in both formats. Does the Agency have a preference for a specific format?

FDA: CTCAE version 3 is acceptable.

ADDITIONAL FDA COMMENTS:

Clinical

Note: The following comments were conveyed immediately following the meeting and therefore not discussed at the meeting.

Deficiencies:

1. Please clarify your definition of "clinical" in the definition of TTP (pages 41 and 42). Do you mean a quantitative change in a tumor measured clinically? The determination of TTP is based on determining "progression." This should be as objective as possible. If you plan to include symptomatic changes, please describe them in sufficient detail to provide consistency in application to all patients.
2. Please add a term, objective response rate, to indicate the sum of the CR and PR rates, to your efficacy variables (pages 43) just before the entry "Disease Control Rate."

Comments:

1. For clarification for the study sites:
   Routine CT to determine if a lesion is measurable uses 20 mm cuts.
   Spiral CT for determining if a lesion is measurable uses 10 mm.
   Spiral CT for assessing response using RECIST should use 5 mm reconstructions.
2. Page 21 refers to dose modifications in section 5.5.5.1; we think you mean 4.5.5.1.
3. Plan to retain the images (CT/MRI) and local written radiographic reports for all responding patients for all critical timepoints (initial exam, exam showing response, confirmatory exam, exam showing progression) for later FDA review if you plan to make an efficacy claim related to response.
4. Please submit the FACT-RCC scale and validation when available
5. Please submit a sample annotated case report form (CRF) as soon as possible.
6. Please indicate in the protocol the nomenclature you will use to describe the AEs in the CRFs? NCI-CTC or MedDRA, etc?

7. Please consider and propose a plan to evaluate the hypertension AE during this study.
8. Please include an explicit statement prohibiting the use of G- or GM-CSFs during the study.

Regulatory

1. Final Protocol

   Please refer to the December 1999 DRAFT "Guidance for Industry - Special Protocol Assessment" (posted on the Internet 2/8/ 2000) and submit final protocol(s) to the IND for FDA review as a REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA) in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical) and include a reference to this EOP2 meeting. 10 desk copies of this SPA should be submitted directly to the project manager. Since we would like to use our ODAC consultant for this protocol review, and their clearance takes several weeks, we would appreciate any lead- in time you could give us as to when the SPA will be submitted. You should also be aware that our using a consultant extends the due date on these Spas till 45 days after we receive the consultant's written comments.

2. Submission of Clinical Trials to NIH Public Access Data Base

   Section 113 of the Food and Drug Modernization Act (Modernization Act) amends 42 U. S. C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life- threatening diseases conducted under FDA's Investigation New Drug (IND) regulations (21 CFR part 312). The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Modernization Act.

   FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information to the Clinical Trials Data Bank. The guidance entitled " Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at http://www.fda.gov/cder/guidance/4856fnl.htm

   The clinical trial information for the Clinical Trials Data Bank should include the purpose of the trial, the patient eligibility criteria, the location of the trial sites and, a contact for patients wanting to enroll in the trial. The data fields and their definitions are available in the Protocol Registration System at http://prsinfo.clinicaltrials.gov/. Protocols listed in this system by will be made available to the public on the Internet at http://clinicaltrials.gov.

   If you have any questions, contact Theresa Togo at (301) 827-4460 or 113trials@oc. fda.gov.

4. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "Guidance for Industry: Financial Disclosure By Clinical Investigators" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

5. Pediatric Final Rule

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

6. Pediatric Exclusivity

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a " Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

7. Demographics

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for

presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG
Gender	Males		All Females		Females >50	
Age:	0-≤1 Mo.		>1 Mo.-≤ 2Year		>2-≤12	
	12-16		17-64		≥65	
Race:	White		Black		Asian	
	Other					

8. Chemistry

   Prior to initiating pivotal clinical studies, we request a complete, updated submission of chemistry, manufacturing and controls (CMC). Please refer to the appropriate CDER guidelines for assistance in preparing this submission. At the time of this submission, we strongly urge you to request a meeting to discuss CMC issues, e. g., impurity profile, stability protocols, approaches to specifications, and attributes, packages, etc.

ACTION ITEMS:

1. Regarding Clinical question #1, FDA will get back to Bayer regarding stratification by country.

2. The FDA will consult Laurie Burke and get back to Bayer regarding QOL.

3. Bayer will submit overhead material as an official submission.

4. Bayer will submit a Fast Track/Rolling request and a SPA for HCC and possibly also for RCC.

There were no unresolved issues. The meeting concluded at 10:45 a.m.

ADDENDUM:

Regarding to the clinical question #1, Bayer's strategy for stratification by country is acceptable to the FDA.

{See appended electronic signature page}

/S/

Patty Garvey, R.Ph.
Project Manager

Concurrence Chair:

{See appended electronic signature page}

/S/

Robert Kane, M.D.
Medical Officer

ATTACHMENTS: Bayer's overheads presented during the meeting.

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_____ § 552(b)(5) Draft Labeling

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/s/

Robert Kane
8/27/03 03:33:14 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-923/RU-001

Bayer Pharmaceuticals Corporation
Attention: Aileen Ryan
Director, Global Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Ms. Ryan:

We have received a reviewable unit (RU) of your new drug application (NDA) submitted under the Continuous Marketing Application (CMA)-Pilot 1 program for the following:

Name of Drug Product:	NEXAVAR (sorafenib tosylate) Tablets 200 mg
Date of Submission:	April 28, 2005
Date of Receipt:	April 29, 2005
Our Reference Number:	NDA 21-923
Reviewable Unit:	RU-001

Unless we notify you otherwise within 60 days of the above receipt date, we will accept this presubmission as an RU. The user fee goal date for us to complete our review of this RU will be October 29, 2005.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submission to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Document Room 3106
1451 Rockville Pike
Rockville, Maryland 20854

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 594-5779.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
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/

Amy Baird
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for Dotti Pease