CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201023Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PATENT INFORMATION

Pursuant to 21 CFR 314.53(d)(1) the patent information for this original application is being submitted concurrently herewith by separate letter addressed to the Central Document Room.

Linda Gustavson

Linda Gustavson, PhD, RAC

Director, U.S. Assoc. Therapeutic Axis Head, Oncology

Regulatory Research and Development Portfolio

Corporate Regulatory Affairs

Sanofi-aventis US

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: 7/31/10
See OMB Statement on Page 3.

NDA NUMBER
201023

NAME OF APPLICANT/NDA HOLDER
sanofi-aventis U.S. LLC

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)
JEVTANA®

ACTIVE INGREDIENT(S)	STRENGTH(S)
cabazitaxel	Single dose vials containing 60 mg/1.5mL (40 mg/mL)

DOSAGE FORM
concentrate for solution for infusion

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.

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FDA will not list patent information if you submit 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
5,438,072	August 1, 1995	November 22, 2013

d. Name of Patent Owner	Address *(of Patent Owner)*	FAX Number *(if available)*
Aventis Pharma S.A.	174 Avenue de France	
	City/State: 75013 Paris	
	ZIP Code: FRANCE	
	Telephone Number	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.)*	FAX Number *(if available)*
	1041 Route 202/206	
	City/State: Bridgewater, New Jersey	
	ZIP Code: 08807	(908) 231-2840
Charlotte Barney, Esq.	Telephone Number: (908) 231-4551	E-Mail Address *(if available)*: charlotte.barney@sanofi-aventis.com

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

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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) *(as listed in the patent)*	Does (Do) the patent claim(s) 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 proposed 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
John D. Conway	Feb. 19, 2010

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 John D. Conway	
Address sanofi-aventis U.S. Inc. 1041 Route 202-206	City/State Bridgewater, New Jersey
ZIP Code 08807	Telephone Number (908) 231-5617
FAX Number *(if available)* (908) 231-2626	E-Mail Address *(if available)* john.conway@sanofi-aventis.com

Department of Health and Human Services
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Form Approved: OMB No. 0910-0513
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ACTIVE INGREDIENT(S)	STRENGTH(S)
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DOSAGE FORM
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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,698,582	December 16, 1997	July 3, 2012

d. Name of Patent Owner	Address *(of Patent Owner)*	FAX Number *(if available)*
Aventis Pharma S.A.	174 Avenue de France	
	City/State: 75013 Paris	
	ZIP Code: FRANCE	
	Telephone Number	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.)*	FAX Number *(if available)*
	1041 Route 202/206	
	City/State: Bridgewater, New Jersey	
	ZIP Code: 08807	(908) 231-2840
Charlotte Barney, Esq.	Telephone Number: (908) 231-4551	E-Mail Address *(if available)*: charlotte.barney@sanofi-aventis.com

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

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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) *(as listed in the patent)*	Does (Do) the patent claim(s) 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 proposed 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

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
John D. Conway	Feb 19, 2010

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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 John D. Conway	
Address sanofi-aventis U.S. Inc. 1041 Route 202-206	City/State Bridgewater, New Jersey
ZIP Code 08807	Telephone Number (908) 231-5617
FAX Number *(if available)* (908) 231-2626	E-Mail Address *(if available)* john.conway@sanofi-aventis.com

Department of Health and Human Services
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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,847,170	December 8, 1998	March 26, 2016

d. Name of Patent Owner	Address *(of Patent Owner)*	
Aventis Pharma S.A.	174 Avenue de France	
	City/State: 75013 Paris	
	ZIP Code: FRANCE	FAX Number *(if available)*
	Telephone Number	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.)*	
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Charlotte Barney, Esq.	Telephone Number: (908) 231-4551	E-Mail Address *(if available)*: charlotte.barney@sanofi-aventis.com

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

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**.

Applicant understands Question 2.2 to ask whether the patent claims only a polymorph of the drug substance that is different from that described in the pending NDA. The patent contains claims that encompass any form of the active ingredient, and is submitted for listing on that basis.

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

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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
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☐ 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 John D. Conway	
Address sanofi-aventis U.S. Inc. 1041 Route 202-206	City/State Bridgewater, New Jersey
ZIP Code 08807	Telephone Number (908) 231-5617
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a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,331,635	December 18, 2001	March 26, 2016

d. Name of Patent Owner	Address *(of Patent Owner)*	
Aventis Pharma S.A.	174 Avenue de France	
	City/State: 75013 Paris	
	ZIP Code: FRANCE	FAX Number *(if available)*
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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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) *(as listed in the patent)*	Does (Do) the patent claim(s) 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 proposed 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
John D. Conway	Feb 19, 2010

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 John D. Conway	
Address sanofi-aventis U.S. Inc. 1041 Route 202-206	City/State Bridgewater, New Jersey
ZIP Code 08807	Telephone Number (908) 231-5617
FAX Number *(if available)* (908) 231-2626	E-Mail Address *(if available)* john.conway@sanofi-aventis.com

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

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

NDA NUMBER
201023

NAME OF APPLICANT/NDA HOLDER
sanofi-aventis U.S. LLC

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)
JEVTANA®

ACTIVE INGREDIENT(S)	STRENGTH(S)
cabazitaxel	Single dose vials containing 60 mg/1.5mL (40 mg/mL)

DOSAGE FORM
concentrate for solution for infusion

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 submit 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
6,372,780	April 16, 2002	March 26, 2016

d. Name of Patent Owner	Address *(of Patent Owner)*	FAX Number *(if available)*
Aventis Pharma S.A.	174 Avenue de France City/State: 75013 Paris ZIP Code: FRANCE Telephone Number:	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.)*	FAX Number *(if available)*
Charlotte Barney, Esq.	1041 Route 202/206 City/State: Bridgewater, New Jersey ZIP Code: 08807 Telephone Number: (908) 231-4551	(908) 231-2840 E-Mail Address *(if available)*: charlotte.barney@sanofi-aventis.com

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

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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) *(as listed in the patent)* 1 to 5 and 7 to 14	Does (Do) the patent claim(s) 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 proposed labeling.)* Jevtana (a microtubule inhibitor) in combination with prednisone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing treatment regimen	

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
John D. Conway	Feb 19, 2010

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 John D. Conway	
Address sanofi-aventis U.S. Inc. 1041 Route 202-206	City/State Bridgewater, New Jersey
ZIP Code 08807	Telephone Number (908) 231-5617
FAX Number *(if available)* (908) 231-2626	E-Mail Address *(if available)* john.conway@sanofi-aventis.com

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: 7/31/10
See OMB Statement on Page 3.

NDA NUMBER
201023

NAME OF APPLICANT/NDA HOLDER
sanofi-aventis U.S. LLC

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)
JEVTANA®

ACTIVE INGREDIENT(S)	STRENGTH(S)
cabazitaxel	Single dose vials containing 60 mg/1.5mL (40 mg/mL)

DOSAGE FORM
concentrate for solution for infusion

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.

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FDA will not list patent information if you submit 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
6,387,946	May 14, 2002	March 26, 2016

d. Name of Patent Owner
Aventis Pharma S.A.

Address *(of Patent Owner)*
174 Avenue de France

City/State
75013 Paris

ZIP Code
FRANCE

FAX Number *(if available)*

Telephone Number

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)

Charlotte Barney, Esq.

Address *(of agent or representative named in 1.e.)*
1041 Route 202/206

City/State
Bridgewater, New Jersey

ZIP Code
08807

FAX Number *(if available)*
(908) 231-2840

Telephone Number
(908) 231-4551

E-Mail Address *(if available)*
charlotte.barney@sanofi-aventis.com

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

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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) *(as listed in the patent)* 1, 2, 3, 6, 7, and 8	Does (Do) the patent claim(s) 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 proposed labeling.)*

Jevtana (a microtubule inhibitor) in combination with prednisone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing treatment regimen.

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.***

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
John D. Conway	Feb 19, 2010

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 John D. Conway	
Address sanofi-aventis U.S. Inc. 1041 Route 202-206	City/State Bridgewater, New Jersey
ZIP Code 08807	Telephone Number (908) 231-5617
FAX Number *(if available)* (908) 231-2626	E-Mail Address *(if available)* john.conway@sanofi-aventis.com

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

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

NDA NUMBER
201023

NAME OF APPLICANT/NDA HOLDER
sanofi-aventis U.S. LLC

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)
JEVTANA®

ACTIVE INGREDIENT(S)	STRENGTH(S)
cabazitaxel	Single dose vials containing 60 mg/1.5mL (40 mg/mL)

DOSAGE FORM
concentrate for solution for infusion

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).
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FDA will not list patent information if you submit 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
7,241,907	July 10, 2007	December 10, 2025

d. Name of Patent Owner	Address *(of Patent Owner)*	
Aventis Pharma S.A.	174 Avenue de France	
	City/State: 75013 Paris	
	ZIP Code: FRANCE	FAX Number *(if available)*
	Telephone Number	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.)*	
	1041 Route 202/206	
	City/State: Bridgewater, New Jersey	
	ZIP Code: 08807	FAX Number *(if available)*: (908) 231-2840
Charlotte Barney, Esq.	Telephone Number: (908) 231-4551	E-Mail Address *(if available)*: charlotte.barney@sanofi-aventis.com

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

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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) *(as listed in the patent)*	Does (Do) the patent claim(s) 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 proposed 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.***

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
John D. Conway	Feb 19, 2010

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 John D. Conway	
Address sanofi-aventis U.S. Inc. 1041 Route 202-206	City/State Bridgewater, New Jersey
ZIP Code 08807	Telephone Number (908) 231-5617
FAX Number *(if available)* (908) 231-2626	E-Mail Address *(if available)* john.conway@sanofi-aventis.com

REQUEST FOR EXCLUSIVITY

Pursuant to NDA regulation 21 U.S.C. 355(c)(3)(D)(iv) and under the provisions of NDA regulation 21 CFR 314.108, the applicant hereby claims a period of exclusivity of five (5) years from the date of approval of this new drug application (NDA) for the use of cabazitaxel in combination with prednisone in the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing treatment regimen.

EXCLUSIVITY SUMMARY

NDA # 201023 SUPPL # N/A HFD # 150

Trade Name Jevtana

Generic Name cabazitaxel

Applicant Name sanofi-aventis

Approval Date, If Known June 17, 2010

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 years

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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: Alice Kacuba for Christy Cottrell
Title: CPMS
Date: 6-21-2010

Name of Office/Division Director signing form: Robert L. Justice, M.D., M.S.
Title: Director, Division of Drug Oncology Products

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	Jevtana

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

/s/

ALICE KACUBA
06/21/2010

ROBERT L JUSTICE
06/21/2010

DEBARMENT CERTIFICATION

Sanofi-aventis 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.

Linda Gustavson

Linda Gustavson, PhD, RAC

Director, U.S. Assoc. Therapeutic Axis Head, Oncology

Regulatory Research and Development Portfolio

Corporate Regulatory Affairs

Sanofi-aventis US

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 201023 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Jevtana Established/Proper Name: cabazitaxel Dosage Form: Injection		Applicant: sanofi-aventis Agent for Applicant (if applicable):
RPM: Christy Cottrell		Division: DDOP

NDAs:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ If no listed drug, check box and explain:

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is September 30, 2010	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain ____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): 1

☒ Fast Track
☒ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic 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.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-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.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: 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.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric 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.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• 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).	☐ No paragraph III certification Date patent will expire
• [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 section below (*Summary Reviews*)).*	☐ 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? ☐ Yes ☐ No

  (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)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *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

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

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

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) 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 (b)(2) 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 section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[3]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval dated June 17, 2010
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Included; 6-17-10
• Original applicant-proposed labeling	Included; 3-31-10
• Example of class labeling, if applicable	N/A

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in ttrack-changes format.	Included; 6-17-10
• Original applicant-proposed labeling	Included; 3-31-10
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	Included; 6-17-10
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	 Acceptable; 5/26/10 Review; 5/11/10
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA 5/28/10 ☒ DRISK 6/4/10 ☒ DDMAC 6/15/10 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	6/9/10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

• This application is on the AIP
  ○ If yes, Center Director's Exception for Review memo *(indicate date)*
  ○ If yes, OC clearance for approval *(indicate date of clearance communication)*
	☐ Yes ☒ No
	
	☐ Not an AP action

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 4/21/10 If PeRC review not necessary, explain: _____ • Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	 ☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 2/23/10
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 6/28/06
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	2/24/09
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 6/17/10
Division Director Summary Review *(indicate date for each review)*	☐ None 6/17/10
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 6/17/10
PMR/PMC Development Templates *(indicate total number)*	☐ None 10
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See primary MO review
• Clinical review(s) *(indicate date for each review)*	6/15/10
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See primary MO review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested Included

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None See stat TL memo
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 5/26/10
Statistical Review(s) *(indicate date for each review)*	☐ None 5/26/10
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None See primary CP review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None See primary CP review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 6/2/10
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 6/14/10
• Supervisory Review(s) *(indicate date for each review)*	☐ None 6/3/10
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 6/3/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 6/8/10
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None See primary CMC review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 6/2/10
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 6/8/10
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See primary CMC review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

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

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** 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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/18/2010

From: Cottrell, Christy L.
Sent: Friday, June 11, 2010 11:17 AM
To: 'Linda.Gustavson@sanofi-aventis.com'; Leslie.Aragones@sanofi-aventis.com
Subject: NDA 201023: Carton/container label comments

Importance: High

Linda,

Please refer to your NDA 201023 for cabazitaxel. See below for comments from DMEPA on the carton/container labels.

A. General Comments

As currently presented, the color scheme utilized in the proposed Jevtana container label and carton labeling is identical to the color scheme utilized for your proposed Taxotere label and labeling. We recommend you revise the colors utilized for the Jevtana labels and labeling to allow for more adequate visual differentiation from the Taxotere labels and labeling.

B. Container Label for Jevtana (60 mg/1.5 mL)

1. The container label should provide the following directions for dilution in the event the drug vial is stored out of the carton.

   CAUTION: Reconstitute this vial using the entire contents of the diluent vial (approximately 5.8 mL). Following this first dilution, the resultant solution contains a concentration of 10 mg/mL. Withdraw only the required amount of the first dilution to prepare the final infusion solution prior to administration. See package insert for full dilution information.

   The directions should be prominently displayed and adequately differentiated from all other information on the vial. Please refer to the Taxotere container label for details on the presentation of the dilution directions.

2. The strength expression (b) (4) is currently in a colored box. Revise the label to state "60 mg/1.5 mL Before First Dilution*****" such that Before First Dilution has the same prominence as the strength expression and is located inside the box.

3. Revise the route of administration to read "*****FOR INTRAVENOUS INFUSION ONLY AFTER SECOND DILUTION."

4. In accordance with 21 CFR 201.100(b)(iii), the container label requires the inactive ingredients be listed on the vial. Please include the Statement "Contains 60 mg cabazitaxel and 1.56 mg polysorbate 80" as appears under the description section of the insert labeling. However if inclusion of this statement prohibits the required caution statement then the inactive ingredient statement may be omitted.

C. Container Label for Diluent (5.8 mL)

1. In order to clarify that the vial only contains diluent, we request you revise the label as follows:

   DILUENT
   5.8 mL of 13 % (w/w) ethanol in water injection.
   Use ONLY for dilution of Jevtana.

2. Delete the following statement from the label: (b) (4)

3. We recommend that the drug vial and diluent vial be physically linked to lessen the likelihood that they will become separated. If separated, we are concerned that Jevtana could be administered without dilution or the diluent of Jevtana could be inadvertently administered instead of Jevtana.

4. The storage conditions should be specified on the Diluent label.

D. Carton Labeling

1. As currently presented the carton labeling states Jevtana on the principal display panel and the side panels. This may mislead practitioners to believe the package only contains the drug and no diluent. The carton contains both the drug and diluent. Revise the carton label to read as follows:

   JEVTANA
   (Cabazitaxel) Injection
   60 mg/1.5 mL Before First Dilution*****
   This carton contains: 1 Jevtana vial and 1 Diluent vial

   Please note "60 mg/1.5 mL Before First Dilution*" should have the same prominence as the strength expression.

2. Add a statement: *****Requires two dilutions before administration-See back panel for details before the "FOR INTRAVENOUS INFUSION…" statement.

3. Revise the statement (b) (4)...." to state "FOR INTRAVENOUS INFUSION ONLY AFTER SECOND DILUTION"

4. Revise the directions of dilution on the back panel to state the following:

   Two-step dilution required
   First Dilution: Add **entire** contents of the diluent (approximately 5.8 mL) to Jevtana injection to obtain a concentration of **10 mg/mL**.
   Second Dilution: Withdraw the exact volume required from the 10 mg/mL solution and add to XX mL (Note to Applicant- please fill in specific volume) of 0.9% sodium chloride or 5% dextrose solution.
   For intravenous infusion only after second dilution.
   See package insert……

5. Revise the side panel to state:

   JEVTANA
   (Cabazitaxel) Injection
   60 mg/1.5 mL Before First Dilution*****
   ***** Requires two dilutions before administration
   Contains: 1 Jevtana vial
   1 Diluent vial

6. The entire statement "60 mg/1.5 mL Before First Dilution*****" should have the same prominence as the strength expression.

Feel free to call me with any questions.

Regards,

Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/14/2010

From: Cottrell, Christy L.
Sent: Thursday, June 10, 2010 11:16 AM
To: Linda.Gustavson@sanofi-aventis.com
Subject: NDA 201023 for cabazitaxel: Patient Package Insert labeling edits

Importance: High

Attachments: 6-9-10 PPI edits.doc

Linda,

Attached are the proposed edits to the Patient Package Insert. Please review and provide your counter-proposals by COB tomorrow, Friday, June 11th. As usual, we ask that you accept our revisions and track your counter-proposals.

Let me know if you have any questions.

Regards,
Christy

6-9-10 PPI edits.doc (134 KB)

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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9 pages of draft labeling has been withheld in full immediately following this page as B4 CCI/TS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/14/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201023 **NDA ACKNOWLEDGMENT**

sanofi-aventis U.S., LLC
c/o sanofi-aventis U.S., Inc.
200 Crossing Boulevard, Mailstop: BX2-712B
Bridgewater, NJ 08807

Attention: Linda M. Gustavson
Director, U.S., Associate Therapeutics Head, Oncology

Dear Ms. Gustavson:

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

Name of Drug Product: Jevtana® (cabazitaxel) Injection, 60 mg/1.5 mL

Date of Application: March 31, 2010

Date of Receipt: March 31, 2010

Our Reference Number: NDA 201023

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 May 30, 2010, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/09/2010

From: Cottrell, Christy L.
Sent: Tuesday, June 08, 2010 4:09 PM
To: Linda.Gustavson@sanofi-aventis.com; Leslie.Aragones@sanofi-aventis.com; 'Zareen.Ahmed@sanofi-aventis.com'
Subject: Cabazitaxel CMC PMRs

Importance: High

Linda and team,

We feel that the milestones dates provided for the CMC PMRs are too prolonged. Please provide shorter milestone dates or a justification for why the additional time is needed to complete the PMRs.

Thanks,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov


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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/14/2010

From: Cottrell, Christy L.
Sent: Tuesday, June 08, 2010 2:44 PM
To: Linda.Gustavson@sanofi-aventis.com; Leslie.Aragones@sanofi-aventis.com
Subject: PMR discussion

Linda,

We briefly discussed during the telecon that sanofi would provide assumptions for both studies for the PMRs, including the sample sizes. In the interest of time, please provide this information to us as soon as possible.

Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov


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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

CHRISTY L COTTRELL
06/14/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201023 **FILING COMMUNICATION**

sanofi-aventis U.S., LLC
c/o sanofi-aventis U.S., Inc.
200 Crossing Boulevard, Mailstop: BX2-712B
Bridgewater, NJ 08807

Attention: Linda M. Gustavson
Director, U.S., Associate Therapeutics Head, Oncology

Dear Ms. Gustavson:

Please refer to your New Drug Application (NDA) dated March 31, 2010, received March 31, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Jevtana® (cabazitaxel) Injection, 60 mg/1.5 mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is September 30, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 2, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

REQUIRED PEDIATRIC ASSESSMENTS

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

We reference the waiver granted on April 21, 2010, for the pediatric study requirement for this application.

If you have any questions, call me at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/09/2010

From: Cottrell, Christy L.
Sent: Monday, June 07, 2010 5:03 PM
To: 'Zareen.Ahmed@sanofi-aventis.com'
Cc: Linda.Gustavson@sanofi-aventis.com; Leslie.Aragones@sanofi-aventis.com; Kacuba, Alice
Subject: RE: Cabazitaxel: Telecon needed on Monday

Importance: High
Zareen, Linda and Leslie,

See below for the microbiology deficiency. If you agree to modify the storage time at room temperature to (b) (4), there would be no need for a telecon. Please respond at your earliest convenience.

- Microbiological studies in support of the proposed eight-hour post-constitution storage time at room temperature were not provided. The sponsor should provide a risk assessment report summarizing studies that show adventitious microbial contamination does not grow under these conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. The report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product dilution. It is generally accepted that growth is evident when the population increases more than 0.5 Log10. The test should be run at the label's recommended storage conditions and be conducted for two to three-times the holding period (the total time between initial vial penetration and the completion of patient infusion) and using the label-recommended fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.
- The sponsor should revise the proposed post-reconstitution hold period to (b) (4) at room temperature if it cannot provide supporting data for a longer hold period.

Again, sorry for the confusion regarding today's telecon.

Christy

From: Zareen.Ahmed@sanofi-aventis.com [mailto:Zareen.Ahmed@sanofi-aventis.com]
Sent: Monday, June 07, 2010 3:58 PM
To: Cottrell, Christy L.
Cc: Linda.Gustavson@sanofi-aventis.com; Leslie.Aragones@sanofi-aventis.com
Subject: RE: Cabazitaxel: Telecon needed on Monday

Dear Christy:

I am so very sorry to hear that you were in a car accident this morning. Hope you were not physically hurt, although I know it can be very unsettling and traumatic.

I have not yet received the formal microbiology information request. If you can please forward it to me, we could either respond by email or if needed, discuss during tomorrow's 10:00 am TC.

I hope you feel better.

Thanks,

Zareen

From: Cottrell, Christy L. [mailto:Christy.Cottrell@fda.hhs.gov]
Sent: Monday, June 07, 2010 3:46 PM
To: Ahmed, Zareen R&D/US
Cc: Gustavson, Linda R&D/US; Aragones, Leslie R&D/US
Subject: RE: Cabazitaxel: Telecon needed on Monday

Zareen, Linda, and Leslie-

My apologies about the telecon this morning. I was in a car accident on the way to work today. When I called Alice, I didn't remember that I had scheduled this telecon! (I think I was in shock or something). Did you receive the microbiology information request yet? If so, is another telecon needed?

Christy

From: Zareen.Ahmed@sanofi-aventis.com [mailto:Zareen.Ahmed@sanofi-aventis.com]
Sent: Monday, June 07, 2010 10:09 AM
To: Cottrell, Christy L.
Cc: Linda.Gustavson@sanofi-aventis.com; Leslie.Aragones@sanofi-aventis.com
Subject: RE: Cabazitaxel: Telecon needed on Monday

Dear Christy:

Thank you for arranging this morning's 11:30 am TC to discuss a potential microbiology deficiency for the pending cabazitaxel NDA 201023.

We look forward to a productive discussion.

To help facilitate the discussions, we would really appreciate if there are any additional details that you could share before the TC .

I am also including my work and cell phone numbers in case you need to reach me before the teleconference.

Regards,

Zareen

Work: 908-231-3480
(b) (6)

From: Ahmed, Zareen R&D/US
Sent: Friday, June 04, 2010 7:06 PM
To: 'Cottrell, Christy L.'
Cc: Gustavson, Linda R&D/US; Aragones, Leslie R&D/US
Subject: RE: Cabazitaxel: Telecon needed on Monday

Dear Christy:

The following is the toll free number and access code for our TC on Monday June 7, 2010 at 11:30 am US EST to discuss a potential microbiology deficiency.

We look forward to talking to you and resolving the matter.

Toll free number: 1-877-771-7176

Access code for participants: 304324

Thanks,

Zareen

From: Ahmed, Zareen R&D/US
Sent: Friday, June 04, 2010 4:47 PM
To: 'Cottrell, Christy L.'
Cc: Gustavson, Linda R&D/US; Aragones, Leslie R&D/US
Subject: RE: Cabazitaxel: Telecon needed on Monday

Dear Christy:

Yes, we will be available to have a telecon on Monday, June 7 at 11:30 am to discuss a potential microbiology deficiency.

However, as our microbiology team is based in Europe and have left for the day, it would be helpful if you could please email us the question in advance.

Thanks,

Zareen

From: Cottrell, Christy L. [mailto:Christy.Cottrell@fda.hhs.gov]
Sent: Friday, June 04, 2010 4:14 PM
To: Gustavson, Linda R&D/US; Aragones, Leslie R&D/US; Ahmed, Zareen R&D/US
Subject: Cabazitaxel: Telecon needed on Monday

Leslie and Zareen,

We have identified a potential microbiology deficiency and would like to have a telecon to discuss on Monday at 11:30am (ET). Can you confirm that your CMC/Micro staff can be available at that time to meet?

Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/14/2010

From: Cottrell, Christy L.
Sent: Friday, June 04, 2010 11:40 AM
To: 'Linda.Gustavson@sanofi-aventis.com'; Leslie.Aragones@sanofi-aventis.com
Subject: FW: NDA 201023 for Cabazitaxel: PMRs

Importance: High

Linda/Leslie,

When can we expect to receive your proposed milestone dates for the PMRs listed below? We need them ASAP!

Thanks,
Christy

From: Cottrell, Christy L.
Sent: Wednesday, June 02, 2010 9:36 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Subject: NDA 201023 for Cabazitaxel: PMRs
Importance: High

Linda,

Following our telecon regarding the PMRs for Cabazitaxel, we now need you to submit milestone dates for the three PMRs below (b) (4)

Conduct a drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of cabazitaxel in cancer patients.

Final Protocol Submission:	<<insert date>>
Trial Completion Date:	<<insert date>>
Final Report Submission:	<<insert date>>

Conduct a drug interaction trial to evaluate the effect of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of cabazitaxel in cancer patients.

Final Protocol Submission:	<<insert date>>
Trial Completion Date:	<<insert date>>
Final Report Submission:	<<insert date>>

Submit updates on renal toxicity from the next randomized trial every 6 months for 3 years from the initiation of the clinical trial.

Final Protocol Submission:	<<insert date>>
Trial Completion Date:	<<insert date>>
Final Report Submission:	<<insert date>>

Please submit the dates ASAP.

Thanks,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA

10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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/s/

CHRISTY L COTTRELL
06/14/2010

From: Cottrell, Christy L.
Sent: Wednesday, June 02, 2010 3:09 PM
To: 'Linda.Gustavson@sanofi-aventis.com'; 'Zareen.Ahmed@sanofi-aventis.com'
Subject: NDA 201023 for Cabazitaxel: PMRs

Importance: High

Follow Up Flag: Follow up
Due By: Friday, June 04, 2010 5:00 PM
Flag Status: Flagged

Linda and Zareen,

Below are the two CMC-related PMRs for NDA 201023. We need you to provide the milestone dates **no later than COB on Friday, 6/4**.

Let me know if you have any questions.

Regards,
Christy

PMR #8

To evaluate the potential for a serious risk of intravenous infusion of particulate matter into the blood stream, it is necessary to better understand and characterize the supersaturated pre-mix. Conduct a study to provide data which address particulate nucleation and kinetic factors of precipitation in the pre-mix. Conduct this study using multiple samples drawn from multiple batches so as to more fully support an in-use life of the pre-mix.

Study considerations include (but are not necessarily limited to); interior surface properties of the container closure (e.g., treatments, roughness, scratches, etc.), initial mixing agitation force (vigorous shaking), physical shock on standing (e.g., vigorous shaking during in-use storage), needle sticks, syringe use, temperature (and temperature changes during in-use storage), and additional time point sampling beyond the proposed duration of in-use storage of the pre-mix solution (e.g., 1 to 4 hours).

Collect and provide photographs of the precipitate as it appears in the container and isolated photomicrographs of the particles, as feasible.

Provide by mass balance, the mass of precipitated drug as precipitated mass and as mass percent of the total cabazitaxel content.

Final protocol Submission Date: MM/YR
Study Completion Date: MM/YR
Final Report Submission Date: MM/YR

PMR #9

To evaluate the potential for a serious risk of intravenous infusion of particulate matter into the blood stream, it is necessary to better understand and characterize the supersaturated infusion solution. Conduct a study which addresses particulate nucleation and kinetic factors of precipitation from the infusion solution. Conduct this study using multiple samples drawn for at least three additional batches in the containers (bags and sets) which you propose to label for this use so as to more fully support an in-use life of the infusion solution..

Study factors include (but are not necessarily limited to); interior surface properties of the container (e.g.., treatments, roughness, plasticizers, etc.), initial mixing agitation force (vigorous shaking), physical shock on standing (e.g., vigorous shaking during in-use storage), needle sticks, temperature (and temperature changes during in-use storage), and additional time point sampling beyond the proposed duration of in-use storage of the infusion solution.

Collect and provide photographs of the precipitate as it appears in the container and isolated photomicrographs of the particles, as feasible, for each observed precipitation or evidence of precipitation (e.g., clogged filters, impeded infusion flow, etc.).

Provide by mass balance, the mass of precipitated drug as precipitated mass and as mass percent of the total cabazitaxel content.

Final protocol Submission Date: MM/YR
Study Completion Date: MM/YR
Final Report Submission Date: MM/YR

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/02/2010

From: Cottrell, Christy L.
Sent: Wednesday, June 02, 2010 11:38 AM
To: 'Linda.Gustavson@sanofi-aventis.com'
Subject: NDA 201023 for Cabazitaxel: Telecon

Linda,

We would like to reserve a time for a telecon, if needed, to work out any outstanding labeling or PMR issues for cabazitaxel. Our team is available next Tuesday, 6/8 at 10:00am ET. Can your team be available at that time?

Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/14/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201023 **INFORMATION REQUEST**

Sanofi-aventis U.S. Inc.
Agent for Sanofi-aventis U.S. LLC
Attention: Linda Gustavson, PhD, RAC
Director, U.S. Assoc. Therapeutic Axis Head, Oncology Regulatory Research and Development Portfolio Corporate Regulatory Affairs
200 Crossing Boulevard
Mailstop: BX2-712B
Bridgewater, NJ 08807

Dear Dr. Gustavson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cabazitaxel, 60 mg/1.5 mL, concentrate for solution for infusion.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. Please provide your written response no later than May 30, 2010, in order to continue our evaluation of your NDA.

1. Determine the content of Form B that may be present in the drug substance batches with an (b) (4) of (b) (4)

2. Specify the manufacturing conditions (b) (4) (b) (4) for the mixing and dissolution of drug substance in the drug product manufacturing process. Also, provide data that establishes that the proposed manufacturing process parameters will result in complete dissolution of drug substance with the maximum allowable amount of form B permitted with an (b) (4) content of (b) (4)

3. DMF (b) (4) has been found to be INADEQUATE to support your NDA. Letters dated May 4, 2010, and May 26, 2010, were sent to the DMF holder.

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

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

WILLIAM M ADAMS
05/26/2010
William Adams, acting for Sarah Pope Miksinski

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 201023

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

sanofi-aventis U.S. Inc.
c/o sanofi-aventis U.S. LLC
200 Crossing Boulevard, Mailstop: BX2-712B
Bridgewater, New Jersey 08807

ATTENTION: Linda Gustavson, Ph.D, RAC
Director, U.S. Assoc. Therapeutic Axis Head, Oncology

Dear Dr. Gustavson:

Please refer to your New Drug Application (NDA) submission dated March 30, 2010, received March 31, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cabazitaxel for Injection, 60 mg/1.5 mL.

We also refer to your April 1, 2010, correspondence, received April 1, 2010, requesting review of your proposed proprietary name, Jevtana. We have completed our review of the proposed proprietary name, Jevtana and have concluded that it is acceptable.

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

If **any** of the proposed product characteristics as stated in your April 1, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Simon, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5205. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Christy Cottrell at (301) 796-4256.

Sincerely,

{See appended electronic signature page}
Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CAROL A HOLQUIST
05/26/2010

From: Cottrell, Christy L.
Sent: Tuesday, May 25, 2010 12:28 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Subject: Telecon needed re: PMRs

Linda,

We would like to schedule a telecon for June 1st at 12:30pm (eastern time) to discuss the PMRs for cabazitaxel. Can you confirm your team's availability? We have some CMC PMRs that we will be sending today, so please make sure your CMC team will be available as well.

Thanks,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/14/2010

From: Cottrell, Christy L.
Sent: Friday, May 21, 2010 1:59 PM
To: Linda.Gustavson@sanofi-aventis.com
Cc: 'Leslie.Aragones@sanofi-aventis.com'
Subject: NDA 201023 for Cabazitaxel: CMC comment

Linda,

Please refer to the pending NDA 201023 for cabazitaxel. See below for a comment from the CMC team.

- Revise the drug product criterion for (b) (4) such that it is either below the level qualified in the toxicology studies (b) (4) or the qualification threshold of (b) (4) TDI per ICH Q3B guideline. Based on a maximum clinical dose of 25 mg/m2 and the higher end of body surface area (2.5 m2), we calculate the appropriate limit to be (b) (4) (b) (4)

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov


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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

CHRISTY L COTTRELL
05/21/2010

From: Cottrell, Christy L.
Sent: Wednesday, May 19, 2010 4:09 PM
To: Linda.Gustavson@sanofi-aventis.com
Cc: 'Leslie.Aragones@sanofi-aventis.com'
Subject: NDA 201023 for cabazitaxel: Labeling

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, May 25, 2010 5:00 PM
Flag Status: Flagged

Attachments: 5-19-10 FDA revised labeling sections to sponsor.doc

Linda,

Please refer to your pending NDA 201023 for cabazitaxel. Attached is the division's first round of labeling edits for certain sections of the labeling, specifically:

- **Boxed Warning**
- **Indications**
- **Drug Interactions**
- **Use in Specific Populations**
- **Clinical Pharmacology**
- **Nonclinical Toxicology**
- **Clinical Studies**
- **References**

Please accept all of our revisions in this document and then track your counter-proposals. This will make our review much easier! **We would like to receive your counter-proposals by COB next Tuesday, May 25th.**

Feel free to call me with any questions.

Regards,
Christy

5-19-10 FDA revised labeling s...

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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10 pages of draft labeling has been withheld in full immediately following this page as B4 CCI/ TS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
05/19/2010

From: Cottrell, Christy L.
Sent: Wednesday, May 19, 2010 1:40 PM
To: Linda.Gustavson@sanofi-aventis.com; 'Leslie.Aragones@sanofi-aventis.com'
Subject: NDA 201023 for Cabazitaxel: PMRs

Linda,

Please refer to the pending NDA 201023 for cabazitaxel. See below for a list of PMRs for this NDA. We need you to fill in the dates and any other blanks (such as trial names). **Reply requested by Friday, May 21st.**

PMR #1

Conduct a Phase 3 randomized controlled trial in patients with hormone refractory metastatic prostate cancer comparing docetaxel/prednisone with cabazitaxel 25 mg/m^2/prednisone and cabazitaxel 20 mg/m^2/prednisone as first line therapy. The primary endpoint should be overall survival. The trial should be powered to detect a realistic difference in overall survival. Submit the protocol for agency review prior to commencing the trial.

Final protocol submission Date: MM/YR
Clinical Trial Completion Date: MM/YR
Final Report and Dataset Submission Date: MM/YR

PMR #2

Organize a group of renal experts to review and analyze renal toxicity from all currently available cabazitaxel trials to identify etiologies and to provide recommendations for toxicity mitigation by patient selection or other measures. This group's findings and recommendations should be submitted within 9 months of the cabazitaxel approval date.

Final Report Submission Date: MM/YR

PMR #3

Submit updates on renal toxicity from all active randomized trials <insert trial names> every 6 months for 3 years after the cabazitaxel approval date.

Date of cabazitaxel approval: MM/YR
Dates of interim Reports every 6 month updates:
1. MM/YR
2. MM/YR
3. MM/YR
4. MM/YR
5. MM/YR

Date of Final Report Submission Date: 6. MM/YR

PMR #4

Complete and submit the final report of trial TES10884, along with a thorough review of cardiac safety data, for the potential of cabazitaxel on QTc interval prolongation in patients.

Final protocol submission Date:	MM/YR
Trial Completion Date:	MM/YR
Final Report Submission Date:	MM/YR

PMR #5
Conduct the trial POP6972 to determine the pharmacokinetics and safety of cabazitaxel in patients with hepatic impairment.

Final protocol submission Date: MM/YR
Trial Completion Date: MM/YR
Final Report Submission Date: MM/YR

PMR #6
Conduct a drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of cabazitaxel in cancer patients.

Final protocol submission Date: MM/YR
Trial Completion Date: MM/YR
Final Report Submission Date: MM/YR

PMR #7
Conduct a drug interaction trial to evaluate the effect of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of cabazitaxel in cancer patients.

Final protocol submission Date: MM/YR
Trial Completion Date: MM/YR
Final Report Submission Date: MM/YR

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
05/19/2010

From: Cottrell, Christy L.
Sent: Tuesday, May 18, 2010 3:16 PM
To: Linda.Gustavson@sanofi-aventis.com; 'Leslie.Aragones@sanofi-aventis.com'
Subject: NDA 201023 for Cabazitaxel: Microbiology request for information

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, May 25, 2010 12:00 AM
Flag Status: Flagged

Linda or Leslie,

Please refer to the pending NDA 201023 for cabazitaxel. See below for an information request from the microbiology reviewer.
Please provide your response by May 25, 2010.

Sanofi-aventis is requested to respond to the following. If the information is already in the submission, please indicate the submission location.

(1) For the (b) (4) of the 15 mL glass vials, please provide:
   (i) The (b) (4) manufacturer and model name or number.
   (ii) The temperature and (b) (4) speed used for validation studies.
   (iii) Validation acceptance criteria.
   (iv) The temperature and (b) (4) speed used for production.

(2) For environmental monitoring of the (b) (4), please provide the microbial alert and action limits.

(3) For the endotoxin kinetic-chromogenic testing method described in section 3.2.P.5.3 (Validation of Analytical Procedures), please provide:
   (i) The maximum valid dilution and routine testing dilution for cabazitaxel concentrate.
   (ii) The maximum valid dilution and routine testing dilution for cabazitaxel solvent for dilution.

(4) Please provide a brief description of (b) (4) (b) (4) Include the size, capacity, manufacturer(s), and model name(s) and/or numbers.

(b) (4)

(b) (4)

(6) For (b) (4) of cabazitaxel concentrateand cabazitaxel solvent for dilution, please provide:

(b) (4)

(7) For the microbial filter retention validation studies presented for cabazitaxel concentrate in section 3.2.P.3.5.2.1.2, please provide:
   (i) The growth medium used to prepare the *B. diminuta* challenge inoculum.
   (ii) The volume of bacterial suspension used for challenge and the volume tested for growth after filtration.
   (iii) The time and temperature used for filtrate incubation.
   (iv) A description of the positive and negative controls, and data for these controls.

(b) (4)

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

CHRISTY L COTTRELL
05/18/2010

From: Cottrell, Christy L.
Sent: Monday, May 17, 2010 2:11 PM
To: Linda.Gustavson@sanofi-aventis.com; 'Leslie.Aragones@sanofi-aventis.com'
Subject: NDA 201023 for Cabazitaxel: CMC information request

Importance: High

Linda and Leslie,

Please refer to the pending NDA 201023 for Cabazitaxel. See below for a comment from the CMC team:

- For the preparation of the premix solution, the proposed package insert states that the entire contents of the diluent vial (b) (4) is to be transferred to the cabazitaxel vial (b) (4) to obtain at least 6 mL of a premix solution containing approximately 10 mg/mL cabazitaxel. The cabazitaxel vial is manufactured with a (b) (4) overfill and the diluent vial is manufactured with a (b) (4) overfill. Data provided in tables 6, 7 and 8 (NDA section 3.2.P.2.3 Manufacturing Process Development) describes the variations in concentrations of the premix solutions (b) (4) obtained by three operators. We feel that the presence of the excess diluent and cabazitaxel could result in inaccurate dosing. Revise the drug product by decreasing the fill weight of the cabazitaxel vial to a target fill weight of 60 mg of drug, and revise the fill volume/weight of the diluent to just permit the withdrawal of sufficient excess diluent to enable measurement of an exact volume (b) (4) in the syringe which will be transferred into the cabazitaxel vial thus generating a premix solution with a final concentration of 10.0 mg/mL cabazitaxel.

  The drug product manufacturing procedure and in-process controls, and section 2.5 of the package insert should be revised appropriately to reflect this change in the cabazitaxel vial and the diluent vial. However, there is no need for sanofi-aventis to submit revised wording for the package insert at this time. If you agree with the recommendation above, the Division will work closely with DMEPA to modify the original proposed package insert to reflect this new manufacturing procedure.

Please provide a response by COB on Monday, May 24th. Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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CHRISTY L COTTRELL
05/17/2010

From: Cottrell, Christy L.
Sent: Tuesday, May 11, 2010 11:13 AM
To: Linda.Gustavson@sanofi-aventis.com
Subject: NDA 201023 for cabazitaxel: Microbiology information request

Linda,

See below for an inquiry from the microbiology reviewer for cabazitaxel. Additional inquiries may be forthcoming. As with the other disciplines, you may batch your responses when officially submitting to the NDA.

(1) For the bacterial ingress studies used to validate container-closure integrity, please provide:
(i)The number of vials tested.
(ii)The number of positive controls utilized.
(iii)The number of negative controls utilized.
(iv) The type of bacterial growth medium utilized and data demonstrating that the medium could support growth of the challenge microorganism (*Brevundimonas diminuta*).

(2) Please provide the procedure and validation data for depyrogenation of the grey rubber stoppers used for product closure. If the stoppers are provided ready to sterilize (i.e., already depyrogenated) from the vendor please specify.

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
301.796.4256 (phone) ● 301.796.9845 (fax) | christy.cottrell@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

CHRISTY L COTTRELL
05/11/2010

From: Waxman, Ian
Sent: Friday, May 07, 2010 11:18 AM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: Information request

Hi Linda,

Did patient 710-005-005 have an autopsy performed? If so, can you send the report?

Thanks,
Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/14/2010

From: Waxman, Ian
Sent: Friday, May 07, 2010 5:28 PM
To: 'Leslie.Aragones@sanofi-aventis.com'
Cc: 'Linda.Gustavson@sanofi-aventis.com'; Cottrell, Christy L.
Subject: Neutropenia Analysis request

Hi Leslie and Linda,

Can you send an analysis of rates of grade 1-4 and 3-4 neutropenia in patients who received 20mg/m2 q 3 weekly dosing in the supportive studies? I believe this would include TED6188 (7 patients), TED6190 (20 patients), and ARD6191 (50 patients).

Thank you,
Ian

From: Leslie.Aragones@sanofi-aventis.com [mailto:Leslie.Aragones@sanofi-aventis.com]
Sent: Friday, May 07, 2010 2:17 PM
To: Waxman, Ian
Cc: Cottrell, Christy L.; Linda.Gustavson@sanofi-aventis.com
Subject: RE: Analysis request

Dear Ian,
I am covering for Linda Gustavson, who is out of the office today.

In response to your question, attached is the revised table according to the new categories. The previous conclusion on the effectiveness of G-CSF remains valid.

Best regards,
Leslie

Leslie Aragones
Global Regulatory Affairs, Oncology
P: (908) 231-4142
F: (908) 304-6549
leslie.aragones@sanofi-aventis.com

From: Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]
Sent: Wednesday, May 05, 2010 1:15 PM
To: Gustavson, Linda R&D/US
Cc: Cottrell, Christy L.
Subject: RE: Analysis request

Hi Linda,

Thank you for providing this data.

Regarding Table 1, could this table be organized by neutrophil count cut-offs (perhaps <250, <500, <750, and <1000 instead? It is difficult to interpret clinically in its current form.

Ian

From: Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]
Sent: Tuesday, May 04, 2010 5:07 PM
To: Waxman, Ian
Cc: Cottrell, Christy L.
Subject: RE: Analysis request

Dear Ian,
The team conducted the enclosed analyses to assess the impact of GCSF treatment and dose reductions on neutrophil count in the cabazitaxel arm of the EFC6193 TROPIC protocol. While there are limitations to the analyses, the results seem to support the conclusion that both G-CSF and dose reductions in certain patients have successfully been used to treat neutropenia following cabazitaxel treatment. Treatment with G-CSF increased the neutrophil nadir values when comparing nadir values before and after G-CSF. Use of G-CSF, dose reduction, or both reduced the decline of neutrophil counts and supported the rapid recovery of neutrophil counts from day 8 to day 15 within a cycle.
Regards,
Linda

Linda Gustavson, Ph.D., RAC
Director, R & D Regulatory Affairs
U.S. Head, Oncology
Global Regulatory Affairs
sanofi-aventis US Inc.
Mail code: BX2-712B
200 Crossing Blvd, Bridgewater, NJ 08890-0890
908-304-6221 (work phone)
203-314-2245 (cell phone)
fax: 908-304-6549
email: linda.gustavson@sanofi-aventis.com

From: Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]
Sent: Thursday, April 15, 2010 10:12 AM
To: Gustavson, Linda R&D/US
Cc: Cottrell, Christy L.
Subject: Analysis request

Hi Linda,

I want to analyze differences in degree of neutropenia in patients who received prophylactic G-CSF by comparing counts obtained in cycles before prophylaxis was begun vs. after prophylaxis was begun.

I think one possible way to do this would be to analyze neutrophil nadirs (mean, median, range) in the cycles before prophylactic G-CSF vs. the cycles after prophylactic G-CSF. Can you ask the cabazitaxel team if they think this would be a good way to analyze the effect of G-CSF on actual neutrophil counts, or if they have ideas for alternative analyses that might be useful? I'd be happy to discuss any ideas right after tomorrow's meeting.

Thanks,
Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/14/2010

From: Cottrell, Christy L.
Sent: Friday, May 07, 2010 10:46 AM
To: Linda.Gustavson@sanofi-aventis.com; 'Leslie.Aragones@sanofi-aventis.com'
Subject: NDA 201023 for cabazitaxel: Statistical Information Request

Linda/Leslie,

See below for an information request from the reviewing statistician for NDA 201023 (cabazitaxel):

- For the overall survival analysis in ITT population, there were 242 patients censored for this analysis. Is information on reason of censoring available?
- Where in the submitted data can one locate the 10 patients who were lost to follow-up, as mentioned in your sensitivity analysis for overall survival?

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
05/07/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201023 **INFORMATION REQUEST**

Sanofi-aventis U.S. Inc.
Agent for Sanofi-aventis U.S. LLC
Attention: Linda Gustavson, PhD, RAC
Director, U.S. Assoc. Therapeutic Axis Head, Oncology Regulatory Research and Development Portfolio Corporate Regulatory Affairs
200 Crossing Boulevard
Mailstop: BX2-712B
Bridgewater, NJ 08807

Dear Dr. Gustavson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cabazitaxel, 60mg/1.5mL, concentrate for solution for infusion.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. Please provide your written response no later than May 21, 2010, in order to continue our evaluation of your NDA.

For Drug Substance:

1. Either use the USP<631> Color and Achromicity method for release and stability testing or demonstrate that the USP<631> and Ph. Eur.2.2.2 methods are equivalent.

2. Either use the USP<781> Optical Rotation method for release and stability testing or demonstrate that the USP<781> and Ph. Eur.2.2.7 methods are equivalent.

3. Either use the USP<231> Heavy Metals method for release testing or demonstrate that the USP<231> and Ph. Eur.2.4.8 methods are equivalent.

4. Either use the USP<921> Water Content method for release and stability testing or demonstrate that the USP<921> and Ph. Eur. 2.5.12 or Ph. Eur. 2.5.32 methods are equivalent.

5. Revise the proposed acceptance criterion for (b) (4) (b) (4) to reflect the level observed in the batch release data (b) (4) (b) (4) cabazitaxel drug substance. The therapeutic value of acetone content is (b) (4) based on a (b) (4) molar ratio of cabazitaxel (b) (4) Batch release data for three primary stability batches and three production batches show (b) (4) ranging from (b) (4)

Twelve month primary stability data does not demonstrate any significant change (b) (4) (b) (4) in (b) (4) content when stored at long term storage condition (5 C).

6. Amend the proposed protocol for post-approval stability studies to conduct testing every three months for the first year, every six month for the second year and every 12 month the subsequent years, i.e., 0, 3, 6, 9, 12, 18, 24 and 36 months.

For Drug Product:

7. Provide a justification for the proposed (b) (4) overfill (b) (4). The USP<1151>, Pharmaceutical Dosage Forms, recommendation for viscous liquids is (b) (4) excess volume for 1mL labeled size and (b) (4) excess volume for 2mL labeled size.

8. Provide the results from a study using the proposed concentrated solution and diluent which demonstrates that extractables/leachables in the proposed drug product are at acceptable and safe levels. Alternatively, provide justification that structural differences between cabazitaxel and docetaxel would not affect extractables or leachables from the same container closure system used for both products, and also provide reference to NDA 20,449 (Taxotere®).

9. Either use the USP<791> pH method for release and stability testing or demonstrate that the USP<791> and Ph. Eur.2.2.3 methods are equivalent.

10. Either revise the in-process control limit for residual ethanol to not more than (b) (4) or provide data to justify the currently proposed limit of not more than (b) (4). Data generated on cabazitaxel drug product, including one clinical batch, the three primary stability batches, and one production batch, shows levels below (b) (4) In addition, the proposed in-process control limit exceeds the ICH Q3C recommended maximum limit of not more than (b) (4) using Option 1.

11. Provide a copy of the supplier's certificate of analysis for each packaging component, i.e., the glass vial, elastomeric closure and overseal.

12. Amend the proposed protocol for post-approval stability studies to conduct testing every three months for the first year, every six month for the second year and every 12 month the subsequent years, i.e., 0, 3, 6, 9, 12, 18, 24 and 36 months.

13. Regarding the batch analysis data in the nonclinical study reports (module 4 NDA section 4.2.3.2 under Repeat-Dose Toxicity), the co-eluted impurities in the certificate of analysis (COA) differ from those specified in the drug product specification. In the provided COA, impurities (b) (4) are co-eluted while in the drug product specification and other batch analysis data impurities (b) (4) are co-eluted. Clarify this discrepancy.

14. Revise the drug product specification to include a single criterion for each test. The shelf life acceptance criteria of the drug product specification are considered to be the regulatory specification.

For the Solvent for Dilution:

15. Amend the proposed protocol for post-approval stability protocols for the full scale validation batches and for the annual batches to conduct testing every three month for the first year and every six month for the second year and yearly thereafter , i.e., 0, 3, 6, 9, 12, 18, 24 and 36 months.

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

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

WILLIAM M ADAMS
05/06/2010
William Adams, acting for Sarah Pope Miksinski

From: Cottrell, Christy L.
Sent: Thursday, May 06, 2010 11:25 AM
To: 'Leslie.Aragones@sanofi-aventis.com'
Cc: Linda.Gustavson@sanofi-aventis.com
Subject: RE: NDA 201023 for Cabazitaxel: Statistical information request

Linda/Leslie,

As a follow-up, please provide reason(s) for the discrepancies between CRF and IVRS data on stratification factors.

Thanks,
Christy

From: Leslie.Aragones@sanofi-aventis.com [mailto:Leslie.Aragones@sanofi-aventis.com]
Sent: Friday, April 30, 2010 3:20 PM
To: Cottrell, Christy L.
Cc: Linda.Gustavson@sanofi-aventis.com
Subject: RE: NDA 201023 for Cabazitaxel: Statistical information request

Dear Christy,

Please see sanofi-aventis's response below.

FDA statistical reviewer's question:
According to the submitted EFC6193 study data sets, there appear to be a few randomized patients without ECOG performance status data at baseline. Since baseline ECOG performance status is a stratification factor at randomization for the study, this information should not be missing. Please clarify.

Response:
ECOG performance status and measurable disease were stratification variables and the status of each patient was provided from the site to the IVRS at the time of randomization for all patients. An actual SAS dataset (ivrs.xpt) with this information is attached. The variables in this dataset are described in the following table.

Variable	Label	Type	Codes	Format
USUBJID	Unique Subject Identifier	Text		
SUBJID	Subject Identifier for the Study	Text		
ARM	Description of Planned Arm	Text		
ARMN	Planned Arm Number	Integer		
ITT	Intent-to-treat Population	Text	Y	

TTSTR1	Stratification in IVRS (Num)	Integer		
STRC	Stratification in IVRS (Char)	Text		

The site entered the information on the stratification factors particularly ECOG performance status information in the CRF at visit 0 (Page10 of the CRF). In this dataset indeed 6 patients did not have ECOG status recorded at visit 0. In the analysis we used the entries from visit 1 Day 1 instead, for these patients. This imputation seems appropriate as for those 6 patients the dates of visit 1 were very close to the randomization dates (5 of them within 3 days difference and one within 6 days) and one would not expect any change in performance status in a very short period of time..

The comparison of the stratification factors as recorded by the IVRS versus the CRF data showed that for 111 patients (50 patients in the cabazitaxel group and 61 patients in the mitoxantrone group) the classification on the stratification factors in both sources differed. (see attached document ecogdiff_i.rtf). Most of the differences were in the assessment of measurable disease. ECOG performance status was different between IVRS and CRF in 6 patients in the cabazitaxel arm and 4 patients in the mitoxantrone arm.

The primary analysis for Overall Survival as submitted, used as stratification variables the information recorded in the CRF. The sensitivity analysis using the stratification variables from the IVRS provided similar results compared to the primary analysis as presented in the attached document dp41diff_i.rtf (p<0.0001, HR=0.67 (0.57 - 0.80).

Best regards,

Leslie

Leslie Aragones
Global Regulatory Affairs, Oncology
P: (908) 231-4142
F: (908) 304-6549
leslie.aragones@sanofi-aventis.com

From: Cottrell, Christy L. [mailto:Christy.Cottrell@fda.hhs.gov]
Sent: Friday, April 30, 2010 2:29 PM
To: Gustavson, Linda R&D/US; Aragones, Leslie R&D/US
Subject: FW: NDA 201023 for Cabazitaxel: Statistical information request
Importance: High

Linda/Leslie,

Can you let me know when you will be responding to this inquiry? (I hope you haven't already responded and I missed it!)

Christy

From: Cottrell, Christy L.
Sent: Monday, April 26, 2010 10:21 AM
To: 'Linda.Gustavson@sanofi-aventis.com'
Subject: NDA 201023 for Cabazitaxel: Statistical information request
Importance: High

Linda,

Please refer to the pending NDA 201023 for cabazitaxel. See below for an inquiry from the statistical reviewer.

- According to the submitted EFC6193 study data sets, there appear to be a few randomized patients without ECOG performance status data at baseline. Since baseline ECOG performance status is a stratification factor at randomization for the study, this information should not be missing. Please clarify.

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
301.796.4256 (phone) • 301.796.9845 (fax) | christy.cottrell@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/14/2010

From: Waxman, Ian
Sent: Wednesday, May 05, 2010 1:15 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: RE: Analysis request

Hi Linda,

Thank you for providing this data.

Regarding Table 1, could this table be organized by neutrophil count cut-offs (perhaps <250, <500, <750, and <1000 instead? It is difficult to interpret clinically in its current form.

Ian

From: Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]
Sent: Tuesday, May 04, 2010 5:07 PM
To: Waxman, Ian
Cc: Cottrell, Christy L.
Subject: RE: Analysis request

Dear Ian,
The team conducted the enclosed analyses to assess the impact of GCSF treatment and dose reductions on neutrophil count in the cabazitaxel arm of the EFC6193 TROPIC protocol. While there are limitations to the analyses, the results seem to support the conclusion that both G-CSF and dose reductions in certain patients have successfully been used to treat neutropenia following cabazitaxel treatment. Treatment with G-CSF increased the neutrophil nadir values when comparing nadir values before and after G-CSF. Use of G-CSF, dose reduction, or both reduced the decline of neutrophil counts and supported the rapid recovery of neutrophil counts from day 8 to day 15 within a cycle.
Regards,
Linda

Linda Gustavson, Ph.D., RAC
Director, R & D Regulatory Affairs
U.S. Head, Oncology
Global Regulatory Affairs
sanofi-aventis US Inc.
Mail code: BX2-712B
200 Crossing Blvd, Bridgewater, NJ 08890-0890
908-304-6221 (work phone)
203-314-2245 (cell phone)
fax: 908-304-6549
email: linda.gustavson@sanofi-aventis.com

From: Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]
Sent: Thursday, April 15, 2010 10:12 AM
To: Gustavson, Linda R&D/US
Cc: Cottrell, Christy L.
Subject: Analysis request

Hi Linda,

I want to analyze differences in degree of neutropenia in patients who received prophylactic G-CSF by comparing counts obtained in cycles before prophylaxis was begun vs. after prophylaxis was begun.

I think one possible way to do this would be to analyze neutrophil nadirs (mean, median, range) in the cycles before prophylactic G-CSF vs. the cycles after prophylactic G-CSF. Can you ask the cabazitaxel team if they think this would be a good way to analyze the effect of G-CSF on actual neutrophil counts, or if they have ideas for alternative analyses that might be useful? I'd be happy to discuss any ideas right after tomorrow's meeting.

Thanks,
Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/14/2010

From: Cottrell, Christy L.
Sent: Friday, April 30, 2010 2:24 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Subject: NDA 201023 Cabazitaxel: Information Request

Importance: High

Linda,

See below for an information request from the statistical reviewer:

The statistical reviewer is not able to verify this variable DPLASTDT: the last date of alive or dead. Please specify the source data sets and provide the program used for this variable derivation.

Feel free to call me with any questions.

Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov


consider the environment before printing this e-mail

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
06/14/2010

From: Waxman, Ian
Sent: Wednesday, April 28, 2010 3:39 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: Question regarding dose delays and interruptions

Hi Linda,

Can you clarify the difference between a dose delay and a dose interruption? The ADAE dataset includes both terms.

Thanks again,
Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

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NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
05/07/2010

From: Waxman, Ian
Sent: Wednesday, April 28, 2010 12:53 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: Information Request - Discontinuations

Hi Linda,

Can you clarify the reasons for 2 treatment discontinuations on the cabazitaxel arm?

1) Patient 380-004-003: medical decision not safety related. Is there any additional information available?

2) Patient 826-005-014: abnormal LFTs. LFTs appear relatively unchanged from baseline at time of treatment discontinuation. Is there any additional information available?

Thanks,
Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

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/s/

CHRISTY L COTTRELL
05/07/2010

From: Cottrell, Christy L.
Sent: Tuesday, April 27, 2010 10:50 AM
To: 'Linda.Gustavson@sanofi-aventis.com'
Subject: Cabazitaxel request (not related to the pending NDA)

Linda,

The information below is not related to the pending NDA for cabazitaxel- just coincidental timing. Please respond.

FDA plans on holding a meeting of the Pediatric Oncology Subcommittee of ODAC in October or November 2010 to focus on optimizing the development of oncology and hematology drugs for pediatric use. The products that will be the focus of this meeting will be those recently approved or those products currently in phase 3 development for adults. We are seeking advice from the subcommittee regarding the potential role of these drugs in pediatric cancers and hematological disorders. In addition, we will seek the Committee's input regarding the optimal design of future clinical studies that may serve as part of a Pediatric Written Request.

We would like to invite Sanofi-Aventis to make a brief presentation at the meeting to provide background information on cabazitaxel to serve as a basis for this discussion. The presentation should be limited to 20 minutes, and include a brief, high-level summary of the following:

1. Regulatory History
2. Preclinical data supporting clinical studies
3. Clinical trial experience in adults (Phase 1, 2, and 3 trials as appropriate)
4. Other clinical trials that are ongoing or completed after approval
5. Post marketing experience
6. Current drug development plan for other indications in adults
7. EMA PIP and any ongoing clinical trials in pediatrics
8. Current or potential challenges that have been identified regarding clinical trials in children (e.g., pediatric formulation issues).

If you agree to participate in the Fall 2010 meeting, we request that you submit a description of the PIP and any ongoing pediatric clinical trials of cabazitaxel outside of the U.S. for our review. We anticipate that one or more planning teleconferences between FDA staff & company representatives may be necessary prior to the meeting. Additional logistical details, including information about the need for an AC briefing document, will follow as planning progresses. The usual timelines for advisory committee meeting preparation will apply to the ODAC Pediatric Subcommittee meeting.

If you have any questions, please do not hesitate to contact Amy McKee at (301)796-3909 or amy.mckee@fda.hhs.gov, or Dianne Spillman, Oncology Program Lead Project Manager, at (301) 796-1467 or dianne.spillman@fda.hhs.gov.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
04/27/2010

From: Waxman, Ian
Sent: Monday, April 26, 2010 3:06 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: Blood and Lymphatic Analysis Clarifications

Hi Linda,

I have a few questions and clarifications.

1. I believe that 356-001-010 (cabazitaxel arm) should have been coded as having grade 3 or grade 4 febrile neutropenia. The patient experienced grade 4 neutropenia on 5/16/08 followed by grade 1 pyrexia (38.3 C) on 5/17/08. The neutropenia was reported as unresolved at the time of death. Please explain why an AE of febrile neutropenia was not captured for this patient. If you agree that such an AE should have been captured, would it be grade 3 or grade 4?

2. I have identified 3 additional patients on the cabazitaxel arm with grade 3 anemia based on CTCAE grading: 203-003-001, 840-008-008, and 840-026-001. Each of these patients is included in your analysis under the grade 2 anemia category. However, each of these 3 required a transfusion and should have been considered to have had a grade 3 event. Please justify your exclusion of these 3 grade 3 anemia patients from the grade 3/4 analysis. It is not appropriate to use strict lab values for grade 3/4 anemia, as CTCAE grading clearly states that transfusion alone is a free-standing criteria for grade 3. It is appropriate to use strict lab values for other hematologic parameters since CTCAE grading is based solely on lab values and does not include a clinical component.

3. Table 2 of your proposed label uses a denominator of 371 patients for adverse events of neutropenia, leukopenia, and thrombocytopenia. However, fewer patients had post-baseline labs drawn. Please explain why you have chosen to use a denominator of 371 for these 3 adverse events.

Thanks,
Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

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/s/

CHRISTY L COTTRELL
05/07/2010

From: Cottrell, Christy L.
Sent: Monday, April 26, 2010 10:21 AM
To: 'Linda.Gustavson@sanofi-aventis.com'
Subject: NDA 201023 for Cabazitaxel: Statistical information request

Importance: High

Linda,

Please refer to the pending NDA 201023 for cabazitaxel. See below for an inquiry from the statistical reviewer.

- According to the submitted EFC6193 study data sets, there appear to be a few randomized patients without ECOG performance status data at baseline. Since baseline ECOG performance status is a stratification factor at randomization for the study, this information should not be missing. Please clarify.

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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/s/

CHRISTY L COTTRELL
04/26/2010

From: Waxman, Ian
Sent: Friday, April 23, 2010 3:35 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: Narrative/CRF Request

Hi Linda,

Can you provide a narrative and CRF for patient 152-005-004 from the TROPIC study?

Thanks,
Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
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/s/

CHRISTY L COTTRELL
05/07/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR Patient Reported Outcomes (PRO) ENDPOINTS CONSULTATION

TO: Study Endpoints and Labeling Development (SEALD)
CDER/OND-IO White Oak Bldg 22, Mail Drop 6411
SEALD.ENDPOINTS@FDA.HHS.GOV

FROM: Review Division: Division of Drug Oncology Products
Medical Reviewer: Amy McKee
Project Manager: Christy Cottrell

DATE OF CONSULT REQUEST	Application# IND/NDA/BLA#	LETTER # OR SUBMISSION #	TYPE OF DOCUMENT (Meeting; Protocol/SPA; PDUFA Product Review)	REQUESTED SEALD COMPLETION DATE*
April 22, 2010	**NDA 201023**	Original submission	New NME NDA	**May 21, 2010**

DRUG ESTABLISHED NAME	DRUG TRADE NAME	NAME OF SPONSOR	SPONSOR SUBMIT DATE
Cabazitaxel	**Jevtana**	Sanofi-aventis	**March 31, 2010**

DEVELOPMENT PHASE (E.G., pre-IND/NDA/BLA; IND/BB-IND Phase 1, 2, 3; NDA/BLA): NDA

GOAL DATE (if NDA/BLA./SPA): **June 11, 2010 (expedited high priority review)**

ELECTRONIC LINK (if applicable): EDR Location: \\CDSESUB1\EVSPROD\NDA201023\0005
Gateway Location: \\fdswa132\cderesub\inbound\ectd\ci1270144878267.282096@llnap03 te

BACKGROUND PACKAGE (deliver PAPER to CDER SEALD Endpoints mailbox in Bldg 22, Rm 6411): N/A

MEETINGS (if applicable) (please send invite to **SEALD.ENDPOINTS@FDA.HHS.GOV)**

Internal mid-cycle meeting on 5/7; Labeling meetings on 5/11, 5/18, 5/19, 5/24, 5/26, 6/1; Wrap-up meeting on 6/2

PLEASE make certain the background-briefing package is included with this consult. It should contain the following applicable information needed to start Study Endpoints Review: Protocol or Study ID; Endpoint Concept(s); Instrument(s); Indication(s); Study population(s); Prior related reviews. Division PM, please provide the following specific information on this consult form:

Instrument(s):

Indication(s): Metastatic hormone refractory prostate cancer

Specific Questions/Comments for SEALD: DDOP would like SEALD to review the secondary pain assessment/endpoints for this NDA.

Please confirm whether you can meet the expedited review timeline with a requested completion date of May 21, 2010. You may contact Amy McKee, MD, (clinical reviewer) at 6-3909 for more information/details.

Requester	
Christy Cottrell, RPM	
Name/Phone number/email address/office location	301-796-4256/christy.cottrell@fda.hhs.gov/WO22 Room 2122

Glossary:
Concept: The specific goal of a measurement (i.e. the *thing* that is to be measured by a PRO instrument).
Instrument: A means to capture data (e.g. questionnaire, diary) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results.
*For voluminous study endpoint submissions (e.g. PRO "dossier" or content validity documentation greater than 50 pages), SEALD requests 60 days after receiving the background/briefing package document to complete the review.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
04/22/2010

From: Waxman, Ian
Sent: Wednesday, April 21, 2010 10:07 AM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: Information Request: AE Data

Hi Linda,

Regarding Table 2 (Adverse Reactions) in your proposed label for cabazitaxel:

Please clarify the definition of "all grades"; is this grade 1-4 or grade 1-5?

Also, please clarify whether the grade 3/4 column also includes grade 5 events. Based on our calculations, it appears to include grade 5 events. Discrepancies based on your possible inclusion of grade 5 events are noted for vomiting, abdominal pain, renal failure acute, and dyspnea on the cabazitaxel arm and hematuria and dyspnea on the mitoxantrone arm.

Thanks,
Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
05/07/2010

From: Waxman, Ian
Sent: Tuesday, April 20, 2010 11:18 AM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: RE: Information Request

I am referring to CSR Table 56. I used all lab data (ADLB dataset) collected during from lab day 2 until end of treatment.

Ian

From: Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]
Sent: Tuesday, April 20, 2010 11:13 AM
To: Waxman, Ian
Cc: Cottrell, Christy L.
Subject: Re: Information Request

Hi Ian,
Question: I am trying to reconcile the blood and lymphatic disorder AE numbers. My numbers do not match for cabazitaxel arm grade 3-4 anemia and grade 1-4 thrombocytopenia. I am also off for mitoxantrone arm gr 1-4 anemia, leukopenia, and thrombocytopenia. Can you tell me which patients are included in your lab data analyses? Is it all patients who received at least one dose of drug?

Answer: Please provide us the Table number and the name of the report that you were unable to reconcile, so that we can better assist you.

Here is a general answer to your question. In some tables, we used laboratory data and in some tables we used ae data. When lab data were used, we used only lab tests which were done after Day1 Cycle 1 until 30 days after last treatment infusion. When ae data were used, we used treatment emergent AE (flag aetrtem='T'). These selection criteria were used to include the records that showed the results while patients were under study treatment. In the safety section, only patients who received at least one dose of drug were included in the analysis (371 patients each in either group).

Regards,
Linda

Linda Gustavson, Ph.D., RAC
Director, R & D Regulatory Affairs
U.S. Head, Oncology
Global Regulatory Affairs
sanofi-aventis US Inc.
Mail code: BX2-712B
200 Crossing Blvd, Bridgewater, NJ 08890-0890
908-304-6221 (work phone)
203-314-2245 (cell phone)
fax: 908-304-6549
email: linda.gustavson@sanofi-aventis.com

From: Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]
Sent: Monday, April 19, 2010 5:24 PM
To: Gustavson, Linda R&D/US
Cc: Cottrell, Christy L.

Subject: Information Request

Hi Linda,
I am trying to reconcile the blood and lymphatic disorder AE numbers. My numbers do not match for cabazitaxel arm grade 3-4 anemia and grade 1-4 thrombocytopenia. I am also off for mitoxantrone arm gr 1-4 anemia, leukopenia, and thrombocytopenia.

Can you tell me which patients are included in your lab data analyses? Is it all patients who received at least one dose of drug?

Thanks,
Ian
Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993
Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
05/07/2010

From: Waxman, Ian
Sent: Monday, April 19, 2010 5:24 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: Information Request

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Can you tell me which patients are included in your lab data analyses? Is it all patients who received at least one dose of drug?

Thanks,
Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

CHRISTY L COTTRELL
05/07/2010

From: Waxman, Ian
Sent: Friday, April 16, 2010 4:05 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: G-CSF analysis

Hi Linda,

Another way to explore whether patients received prophylactic G-CSF is to separate patients into 2 groups: those who received G-CSF before first onset of neutropenia and those who received G-CSF only after first onset of neutropenia. This may be a more clear approximation of who received truly prophylactic G-CSF, rather than the arbitrary 3 day cut-off. An analysis using this definition of prophylaxis would be useful.

Let me know if questions arise.

Thanks,
Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
05/07/2010

From: Waxman, Ian
Sent: Thursday, April 15, 2010 10:12 AM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: Analysis request

Hi Linda,

I want to analyze differences in degree of neutropenia in patients who received prophylactic G-CSF by comparing counts obtained in cycles before prophylaxis was begun vs. after prophylaxis was begun.

I think one possible way to do this would be to analyze neutrophil nadirs (mean, median, range) in the cycles before prophylactic G-CSF vs. the cycles after prophylactic G-CSF. Can you ask the cabazitaxel team if they think this would be a good way to analyze the effect of G-CSF on actual neutrophil counts, or if they have ideas for alternative analyses that might be useful? I'd be happy to discuss any ideas right after tomorrow's meeting.

Thanks,
Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

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/s/

CHRISTY L COTTRELL
04/15/2010

From: Waxman, Ian
Sent: Thursday, April 15, 2010 10:24 AM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.; Mehrotra, Nitin
Subject: RE: Information Request

Linda,

Can you send the program and final composite dataset that was used to calculate the table for G-CSF/Neutropenia by cycle?

Ian

From: Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]
Sent: Wednesday, April 14, 2010 8:45 AM
To: Waxman, Ian
Cc: Cottrell, Christy L.
Subject: RE: Information Request

Hi Ian,
Here is the table of neutropenia/GCSF by cycle. As discussed with you and Liji Shen (s-a biostats) on the phone yesterday, we will follow up on your additional request for information regarding the number of missing dates of GCSF administration by cycle.
Regards,
Linda

Linda Gustavson, Ph.D., RAC
Director, R & D Regulatory Affairs
U.S. Head, Oncology
Global Regulatory Affairs
sanofi-aventis US Inc.
Mail code: BX2-712B
200 Crossing Blvd, Bridgewater, NJ 08890-0890
908-304-6221 (work phone)
203-314-2245 (cell phone)
fax: 908-304-6549
email: linda.gustavson@sanofi-aventis.com

From: Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]
Sent: Tuesday, April 13, 2010 9:03 AM
To: Gustavson, Linda R&D/US
Cc: Cottrell, Christy L.
Subject: RE: Information Request

Hi Linda,

Can you ask your team to provide the neutropenia/G-CSF information provided in Table 47 of the Summary of Clinical Safety by each cycle, rather than by cycle 1 vs. cycle 2 to 10?

Thank you,

Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
05/07/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: QT IRT			FROM (*Name, Office/Division, and Phone Number of Requestor)*: Division of Drug Oncology Products Christy Cottrell, RPM	
DATE April 14, 2010	IND NO.	NDA NO. 201023	TYPE OF DOCUMENT New NME NDA	DATE OF DOCUMENT March 31, 2010
NAME OF DRUG Cabazitaxel	PRIORITY CONSIDERATION High		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE May 18, 2010

NAME OF FIRM: sanofi-aventis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☒ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DDOP is requesting an IRT consult for NDA 201023 (cabazitaxel) for the treatment of patients with metastatic hormone-refractory prostate cancer who progressed after docetaxel. This application includes one randomized study of cabazitaxel + prednisone vs. mitoxantrone + prednisone, with a safety population of 371 patients per arm. This consult request is for evaluation for QTc abnormalities in patients who received cabazitaxel. The applicant has submitted only one ECG dataset with their NDA submission (ADEG.XPT). This dataset contains only qualitative information. Please note that the applicant is planning to conduct a separate QT study (TES10884¬). This QT protocol was submitted on Jan 7, 2010, and was subsequently reviewed by IRT (Dr. Monic Fiszman) and entered into DARRTS on Feb 24, 2010. Please be aware that this NDA is receiving an expedited review and discussion of QT-related portions of the labeling is scheduled to occur at a meeting on May 18, 2010. Links to the submission are:
EDR Location: \\CDSESUB1\EVSPROD\NDA201023\201023.enx
Letter Date: 04/01/2010; Stamp Date: 4/1/2010
EDR Location: \\CDSESUB1\EVSPROD\NDA201023\0005
Gateway Location: \\fdswa132\cderesub\inbound\ectd\ci1270144878267.282096@llnap03_te

Please contact Dr. Ian Waxman (MO for safety) at 6-5123 to discuss the expedited timeline for this NDA review and any outstanding questions pertaining to this request. PM=Christy Cottrell	
SIGNATURE OF REQUESTOR Christy Cottrell	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
04/14/2010

From: Waxman, Ian
Sent: Tuesday, April 13, 2010 9:03 AM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: RE: Information Request

Hi Linda,

Can you ask your team to provide the neutropenia/G-CSF information provided in Table 47 of the Summary of Clinical Safety by each cycle, rather than by cycle 1 vs. cycle 2 to 10?

Thank you,

Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

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/s/

CHRISTY L COTTRELL
05/07/2010

Baird, Amy

From: Baird, Amy
Sent: Tuesday, April 13, 2010 1:58 PM
To: 'linda.gustavson@sanofi-aventis.com'
Subject: NDA 201-023 Cabazitaxel..Request for QT data

Linda,

I am a Regulatory Project Manager in the Division of Drug Oncology Products acting for Christy Cottrell today.

Per the request of the FDA Cabazitaxel review team, please submit all clinical and non-clinical QT data collected to date and a summary of your analyses for QT risk evaluation. In addition, please update the status of Study TES10884.

Regards,
Amy

Amy Baird
Regulatory Project Manager
Division of Oncology Drug Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	GI-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

AMY C BAIRD
04/13/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: QT IRT

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Division of Drug Oncology Products
Christy Cottrell, RPM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 14, 2010		201023	New NME NDA	March 31, 2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cabazitaxel	High		May 18, 2010

NAME OF FIRM: sanofi-aventis

REASON FOR REQUEST

I. GENERAL

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- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
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- ☒ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

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- ☐ BIOPHARMACEUTICS
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- ☐ BIOAVAILABILTY STUDIES
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V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DDOP is requesting an IRT consult for NDA 201023 (cabazitaxel) for the treatment of patients with metastatic hormone-refractory prostate cancer who progressed after docetaxel. This application includes one randomized study of cabazitaxel + prednisone vs. mitoxantrone + prednisone, with a safety population of 371 patients per arm. This consult request is for evaluation for QTc abnormalities in patients who received cabazitaxel. The applicant has submitted only one ECG dataset with their NDA submission (ADEG.XPT). This dataset contains only qualitative information. Please note that the applicant is planning to conduct a separate QT study (TES10884¬). This QT protocol was submitted on Jan 7, 2010, and was subsequently reviewed by IRT (Dr. Monic Fiszman) and entered into DARRTS on Feb 24, 2010. Please be aware that this NDA is receiving an expedited review and discussion of QT-related portions of the labeling is scheduled to occur at a meeting on May 18, 2010. Links to the submission are:
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Letter Date: 04/01/2010; Stamp Date: 4/1/2010
EDR Location: \\CDSESUB1\EVSPROD\NDA201023\0005
Gateway Location: \\fdswa132\cderesub\inbound\ectd\ci1270144878267.282096@llnap03_te

Please contact Dr. Ian Waxman (MO for safety) at 6-5123 to discuss the expedited timeline for this NDA review and any outstanding questions pertaining to this request. PM=Christy Cottrell	
SIGNATURE OF REQUESTOR Christy Cottrell	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
04/14/2010

From: Mesmer, Deborah
Sent: Friday, April 09, 2010 10:55 AM
To: 'Linda.Gustavson@sanofi-aventis.com'
Subject: NDA 201023 : CMC IR 4/9/10

From: Deborah Mesmer, Regulatory Health Project Manager
FDA/CDER
Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment III and Manufacturing Science

To: Linda Gustavson, PhD, RAC

RE: NDA 201023

Please refer to your NDA for Cabazitaxel, 60mg/1.5mL, (b) (4) for solution for infusion.

We have the following request for information.

> As soon as feasible, provide a **placebo** sample of the to-be-marketed package, including a full-color sample of the proposed commercial labeling for the drug product.

Ship samples to the following address:

Deborah Mesmer
Food and Drug Administration
10903 New Hampshire Avenue
Building 21, Room 1627, Mail Stop 21-1603
Silver Spring, MD 20993

Please submit a copy of the cover letter for your sample shipment to your NDA.

Please acknowledge receipt of this message.

If you have any questions, please call Deborah Mesmer, Project Manager for Quality at (301) 796- 4023.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

DEBORAH M MESMER
04/09/2010

From: Cottrell, Christy L.
Sent: Thursday, April 08, 2010 12:38 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Subject: NDA 201023: Clinical pharmacology request for information

Linda,

See below for a request for information from the clinical pharmacology team regarding NDA 201023 (Cabazitaxel).

Please address the following data request by 12 April 2010:

Study TED6188 and TED6190:

- We note that the exploratory PK-PD analysis was performed for these two studies for safety endpoints (Neutrophils, WBCs) using WinNonlin. Refer to Section 3.6, 10 and 10.4 of summary of Clinical Pharmacology studies, TED6188 and TED6190, respectively. Please submit the combined PK-PD datasets associated with these analyses. The PK-PD datasets should include demographic factors and all the relevant covariates for each individual. A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Please also submit details of WinNonlin models and outputs wherever applicable.

Study ARD6191:

- Please submit the report, datasets and programs for the PK study of ARD6191. The datasets should include demographic factors and all the relevant covariates for each individual. A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Please also submit details of WinNonlin models and outputs where applicable.

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
04/08/2010

From: Waxman, Ian
Sent: Thursday, April 08, 2010 10:06 AM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: RE: Information Request

Hi Linda,

I need a bit more clarification regarding your response.

There were 9 deaths on the mitoxantrone arm within 30 days of last dose. Based on what you wrote below, any death within 30 days, regardless of cause, is considered a TEAE. However, in table 38, only 5 of these 9 deaths are considered TEAEs, though all occurred within 30 days of last dose. In table 38 (section: death during treatment phase), why did you include the patients with 840014006 and 250004018 in the TEAE subset rather than the Progression subset of mitoxantrone-treated patients who died within 30 days of last dose?

Thanks,

Ian

From: Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]
Sent: Thursday, April 08, 2010 9:01 AM
To: Waxman, Ian
Cc: Cottrell, Christy L.
Subject: RE: Information Request

Hi Ian,
You are correct that in table 38 of the Clinical Study Report (CSR), 4 deaths are due to disease progression and 5 deaths were TEAE, i.e., deaths during the treatment phase (within 30 days) on the mitoxantrone arm.

The patient ID's for the 5 patients with death due to TEAE and the cause of death are as below:

1. 250001027 – Pneumococcal sepsis {PT: Pneumococcal Sepsis}
2. 380003014 – Motor vehicle accident {PT: Multiple fractures}
3. 724004005 – Disease Progression with Pleural Effusion {PT: Pleural Effusion}
4. 840014006 – Disease Progression due to metastatic prostate cancer {PT: Prostate cancer metastatic}
5. 250004018 – Metastasis to the meninges {PT: Metastases to meninges}

These patient ID's with hyperlinks to either narratives (250001027; 380003014; 724004005; 840014006) or case report forms (250004018) are provided in Table 41 of the CSR.

The last 3 patients, although they died of disease progression, were coded as deaths due to TEAE following the Sponsor's data recording conventions because the event occurred within 30 days of last study drug administration. Narratives for patients 840014006 – Disease Progression due to metastatic prostate cancer, and 250004018 – Metastasis to the meninges, were provided on April 7, 2010. As defined in the statistical analysis plan, a treatment emergent adverse event is an event that is new or worsened during the treatment period, regardless of the causes or

relationship to the drug . Therefore, a fatal AE due to the motor vehicle accident or PD will be considered TEAE as long as they are new or meet the criteria for a TEAE.

Regards,
Linda

Linda Gustavson, Ph.D., RAC
Director, R & D Regulatory Affairs
U.S. Head, Oncology
Global Regulatory Affairs
sanofi-aventis US Inc.
Mail code: BX2-712B
200 Crossing Blvd, Bridgewater, NJ 08890-0890
908-304-6221 (work phone)
203-314-2245 (cell phone)
fax: 908-304-6549
email: linda.gustavson@sanofi-aventis.com

From: Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]
Sent: Wednesday, April 07, 2010 5:24 PM
To: Gustavson, Linda R&D/US
Cc: Cottrell, Christy L.
Subject: RE: Information Request

Hi Linda,

According to the CSR (Table 38), there were 4 disease progression deaths and 5 TEAE deaths during the treatment phase on the mitoxantrone arm.

Can you tell me which 5 mitoxantrone arm deaths within 30 days of last dose were considered to be secondary to TEAEs? It seems that patients 250-004-018 and 840-014-006 were included among these 5 deaths, but as you mentioned in your email earlier today, these deaths should have been considered to be secondary to progressive disease.

Thanks for your clarification.

Ian

From: Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]
Sent: Wednesday, April 07, 2010 1:45 PM
To: Waxman, Ian
Cc: Cottrell, Christy L.
Subject: RE: Information Request

Dear Dr. Waxman,

We will submit to the NDA the CRF's for all patients who died within 30 days due to progressive disease. These were not originally submitted in the dossier based on FDA recommendation provided at the preNDA meeting below, to submit deaths within 30 days of last treatment, unless due to progressive disease.

Patient 250004018 died due to an event reported as metastases to the meninges (outcome death). The death was considered progressive disease. There is a mini narrative for this patient on page 119 of the EFC6193 Clinical Study Report (CSR). No narrative or CRFs for this patient was included as they were considered death due to PD.

Patient 840014006 died due to an event reported as metastatic prostate cancer (outcome death). The death was considered progressive disease. This patient had a narrative because the patient had an SAE of confusional state starting on 23 Oct 2007. The patient died on (b) (4) due to the prostate cancer metastatic. CRFs should be currently available for this patient as well. A mini narrative for this patient is on page 120 of the EFC6193 CSR with the hyperlink to the narrative that was included in the submission made on March 31, 2010.

Narratives for both of the patients are attached. Both of these patients were on the mitoxantrone plus prednisone arm of Study EFC6193.

Regards,

Linda

Linda Gustavson, Ph.D., RAC
Director, R & D Regulatory Affairs
U.S. Head, Oncology
Global Regulatory Affairs
sanofi-aventis US Inc.
Mail code: BX2-712B
200 Crossing Blvd, Bridgewater, NJ 08890-0890
908-304-6221 (work phone)
203-314-2245 (cell phone)
fax: 908-304-6549
email: linda.gustavson@sanofi-aventis.com

5. Does the Agency agree with the proposed electronic data submission proposed in the electronic data submission planning template?

FDA response: Please provide patient narratives and CRFs for all patients in both treatment groups of study EFC6193 who:

- **Died within 30 days of last treatment, unless due to progressive disease**
- **Discontinued study drug due to an AE**
- ***Experienced SAEs**
- **Experienced "events of special interest"**

From: Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]
Sent: Tuesday, April 06, 2010 5:52 PM
To: Gustavson, Linda R&D/US
Cc: Cottrell, Christy L.
Subject: Information Request

Hi Linda,

For EFC6193, can you please provide CRFs for all patients who died within 30 days of the last dose of treatment, regardless of causality?

Also, narratives were supposed to have been provided for all patients who experienced a treatment-emergent adverse event leading to death, but I can't find narratives for 250-004-018 and 840-014-006. Both of these patients were included in the CSR as deaths due to TEAEs, rather than as deaths due to progression, and should therefore have narratives. Can you please send these 2 narratives as well?

Thanks,

Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

immediately at ian.waxman@fda.hhs.gov and delete this e-mail communication from your computer.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
04/08/2010

Memorandum of Teleconference

NDA 201023/ Cabazitaxel/Sanofi Aventis

TCON date: April 7, 2010
Topics of Discussion: Environmental assessment submission timing
Redundant DMF and associated review completion impact

FDA Attendees: Richard Lostritto, Sarah Pope Miksinski, Deborah Mesmer

Sanofi Aventis Attendees:
Peter Wilson: Environmental Assessment, Manager
Zareen Ahmed: Regulatory CMC Development, Associate Director
Leslie Aragones: Regulatory Affairs Oncology, Regulatory Coordinator
Mark Moyer: VP Regulatory Affairs Oncology, VP Global Regulatory Affairs
Gail Owens: Regulatory CMC Development, Director
Linda Gustavson: Regulatory Affairs Oncology, US Head
Gopi Vudathala: Regulatory Affairs Interface CMC, Associate VP
James Boyd: VP CM
Yvette Gohee: Sanofi-Chimie Regulatory Development
Jacqueline Caniglia: Project Direction

Agreements reached:
Sanofi will submit justification in the form of references to their previous applications to support their claim for categorical exclusion from the environmental assessment. They will submit the references by email to Deborah Mesmer.

Sanofi will consider if they can remove one of the DMFs (and associated manufacturing establishment) for the (b) (4) They will respond by the week of April 12, 2010, whether they can do this. FDA requested that if Sanofi removes a site, that they provide specific information as to what is in the NDA for the two remaining sites. (That is, FDA doesn't want to review information that would be remaining in the application from a third site that had been removed.)

FDA mentioned that if one site is removed, Sanofi can amend post-approval to add the third site for manufacture of (b) (4)

Refer also to information request below

From: Mesmer, Deborah
Sent: Wednesday, April 07, 2010 12:50 PM
To: 'Linda.Gustavson@sanofi-aventis.com'

Cc: Cottrell, Christy L.
Subject: NDA 201023 TCON - April 7,2010
Importance: High

Dear Dr. Gustavson,

Thank you for agreeing to the TCON for NDA 201023 this afternoon at 3:30 p.m. I have received your call-in number of:

866-680-0168
Participant 786065

The topics of discussion will be:

1) Environmental assessment submission timing

2) Redundant DMF and associated review completion impact

With regard to the environmental assessment, we have the following request:

> Indicate the earliest date by which you can provide an environmental assessment for the drug substance that includes for the yew plants the harvesting practices and permits (if applicable) as well as a certification statement that the harvest is not harmful to the environment. Note that the lack of this information in the original submission is a potential refuse-to-file issue. Environmental assessemnt information is an integral part of the multidisciplinary CMC review and the necessary process by which we conduct CMC reviews is delayed until we have this information. We recommend that we receive this information within two weeks of this communication.

Sincerely,

Debbie Mesmer

Deborah Mesmer
Regulatory Health Project Manager
FDA/CDER
Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment III and Manufacturing Science
301-796-4023
deborah.mesmer@fda.hhs.gov

_____

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

DEBORAH M MESMER
04/09/2010

From: Waxman, Ian
Sent: Wednesday, April 07, 2010 5:24 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: RE: Information Request

Hi Linda,

According to the CSR (Table 38), there were 4 disease progression deaths and 5 TEAE deaths during the treatment phase on the mitoxantrone arm.

Can you tell me which 5 mitoxantrone arm deaths within 30 days of last dose were considered to be secondary to TEAEs? It seems that patients 250-004-018 and 840-014-006 were included among these 5 deaths, but as you mentioned in your email earlier today, these deaths should have been considered to be secondary to progressive disease.

Thanks for your clarification.

Ian

From: Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]
Sent: Wednesday, April 07, 2010 1:45 PM
To: Waxman, Ian
Cc: Cottrell, Christy L.
Subject: RE: Information Request

Dear Dr. Waxman,

We will submit to the NDA the CRF's for all patients who died within 30 days due to progressive disease. These were not originally submitted in the dossier based on FDA recommendation provided at the preNDA meeting below, to submit deaths within 30 days of last treatment, unless due to progressive disease.

Patient 250004018 died due to an event reported as metastases to the meninges (outcome death). The death was considered progressive disease. There is a mini narrative for this patient on page 119 of the EFC6193 Clinical Study Report (CSR). No narrative or CRFs for this patient was included as they were considered death due to PD.

Patient 840014006 died due to an event reported as metastatic prostate cancer (outcome death). The death was considered progressive disease. This patient had a narrative because the patient had an SAE of confusional state starting on 23 Oct 2007. The patient died on (b) (4) due to the prostate cancer metastatic. CRFs should be currently available for this patient as well. A mini narrative for this patient is on page 120 of the EFC6193 CSR with the hyperlink to the narrative that was included in the submission made on March 31, 2010.

Narratives for both of the patients are attached. Both of these patients were on the mitoxantrone plus prednisone arm of Study EFC6193.

Regards,

Linda

Linda Gustavson, Ph.D., RAC
Director, R & D Regulatory Affairs
U.S. Head, Oncology
Global Regulatory Affairs
sanofi-aventis US Inc.
Mail code: BX2-712B
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fax: 908-304-6549
email: linda.gustavson@sanofi-aventis.com

5. Does the Agency agree with the proposed electronic data submission proposed in the electronic data submission planning template?

FDA response: Please provide patient narratives and CRFs for all patients in both treatment groups of study EFC6193 who:

- **Died within 30 days of last treatment, unless due to progressive disease**
- **Discontinued study drug due to an AE**
- ***Experienced SAEs**
- **Experienced "events of special interest"**

From: Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]
Sent: Tuesday, April 06, 2010 5:52 PM
To: Gustavson, Linda R&D/US
Cc: Cottrell, Christy L.
Subject: Information Request

Hi Linda,

For EFC6193, can you please provide CRFs for all patients who died within 30 days of the last dose of treatment, regardless of causality?

Also, narratives were supposed to have been provided for all patients who experienced a treatment-emergent adverse event leading to death, but I can't find narratives for 250-004-018 and 840-014-006. Both of these patients were included in the CSR as deaths due to TEAEs, rather than as deaths due to progression, and should therefore have narratives. Can you please send these 2 narratives as well?

Thanks,

Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
04/08/2010

From: McKee, Amy
Sent: Wednesday, April 07, 2010 2:51 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: Cabazitaxel information request

Linda,

I am conducting the efficacy review for NDA 201023 and am hoping you can point me in the right direction. Which dataset contains the raw data which were used for the analysis of the primary efficacy endpoint of overall survival? Thank you for your help.

Amy

Amy E. McKee, M.D.
Medical Officer
FDA/CDER/OND/OODP/DDOP
White Oak, Building 22 Room 5232
10903 New Hampshire Avenue
Silver Spring, MD 20993
(P) 301-796-3909
(F) 301-796-9849
amy.mckee@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
04/08/2010

From: Waxman, Ian
Sent: Tuesday, April 06, 2010 5:52 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: Information Request

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

CHRISTY L COTTRELL
04/08/2010

From: Waxman, Ian
Sent: Tuesday, April 06, 2010 5:52 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: Information Request

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Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
04/07/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Drug Oncology Products Christy Cottrell, RPM

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
April 6, 2010		NDA 201023	New NME NDA

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Cabazitaxel	High priority		May 15, 2010

NAME OF FIRM:	
Sanofi-aventis	PDUFA Date: October 1, 2010

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
X PACKAGE INSERT (PI)
X PATIENT PACKAGE INSERT (PPI)
X CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
X ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
X INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission: EDR Location: \\CDSESUB1\EVSPROD\NDA201023\0005
Gateway Location: \\fdswa132\cderesub\inbound\ectd\ci1270144878267.282096@llnap03 te

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS: DDOP is planning an expedited 8-week review of this high priority NDA. Target goal date is May 26, 2010.

Mid-Cycle Meeting: May 7, 2010

Labeling Meetings: May 11 at 3:00pm, May 18 at 1:00pm, May 19, at 2:30pm, May 24 at 2:00pm, May 26 at 1:00pm, and June 1 at 1:00pm

Wrap-Up Meeting: June 2 at 1:00pm

SIGNATURE OF REQUESTER
Christy Cottrell

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) X eMAIL ☐ HAND

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
04/06/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **OSE**
Attention: Sarah Simon

FROM: Division of Drug Oncology Products
Christy Cottrell, RPM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 6, 2010		NDA 201023	New NME NDA	March 31, 2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cabazitaxel	High priority		May 15, 2010

NAME OF FIRM: sanofi-aventis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ✓ OTHER *(SPECIFY BELOW)*: New NME NDA

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: As previously discussed during planning meetings, DDOP is planning an expedited 8-week review of this application. Requesting OSE review of package insert, carton/container labels and attendance at labeling meetings. Links to the submission are below:
EDR Location: \\CDSESUB1\EVSPROD\NDA201023\0005
Gateway Location: \\fdswa132\cderesub\inbound\ectd\ci1270144878267.282096@llnap03_te

PDUFA date is October 1, 2010. Target action date is May 26, 2010. Requesting completed OSE review by May 15, 2010.
DMEPA reviewer already assigned: Lubna Najam
Awaiting DRISK reviewer assignment.

DDOP MO: Ian Waxman/Amy McKee
DDOP RPM: Christy Cottrell

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)	
Christy Cottrell	X DARRTS	☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
04/06/2010

From: Waxman, Ian
Sent: Monday, April 05, 2010 12:12 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: RE: Cabazitaxel review question

Hi Linda,

I am trying to locate a CRF for patient 840-071-004 (EFC6193), but cannot seem to find one. Can you tell me if this CRF was submitted? Were CRFs submitted for all patients? If not, which ones are missing?

Thanks,

Ian

From: Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]
Sent: Friday, April 02, 2010 2:27 PM
To: Waxman, Ian
Subject: RE: Cabazitaxel review question

Before Amendment 1, the dose and schedules of investigational products were:
• Arm A: XRP6258, 20 mg/m2, as a 1-hour iv infusion, every 3 weeks.
• Arm B: XRP6258, 10 mg/m2, as a weekly 1-hour iv infusion (Days 1, 8, 15, 22), every 5 weeks.
• Arm C: XRP9881, 90 mg/m2, as a 1-hour iv infusion, every 3 weeks.

From: Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]
Sent: Friday, April 02, 2010 2:21 PM
To: Gustavson, Linda R&D/US
Subject: RE: Cabazitaxel review question

Can you also tell me what the weekly dose was?

From: Linda.Gustavson@sanofi-aventis.com [mailto:Linda.Gustavson@sanofi-aventis.com]
Sent: Friday, April 02, 2010 2:17 PM
To: Waxman, Ian
Cc: Cottrell, Christy L.
Subject: RE: Cabazitaxel review question

Dear Dr. Waxman,

Study ARD6191 was originally planned to compare cabazitaxel q3 weekly, cabazitaxel q1 weekly and another taxane larotaxel (XRP9881). Due to low enrollment the protocol was amended and subsequently patients were only further enrolled in the cabazitaxel q3 weekly arm.

In total 71 patients were treated with the q3 weekly regimen. There were 13 patients who had been treated in the cabazitaxel q1 weekly arm. The study report does not provide a comprehensive analysis on safety for these 13 patients but presents individual patient profiles in Appendix C 4.2 of the study report and the SAE narratives of those patients in section 14.5 of the

study report. However, the data from these 14 patients were included in the integrated summary of safety and are described together with data from another weekly study TED6189 in the Summary of Clinical Safety in section 2.7.4 of the submission. Therefore, the data from those 13 patients were included in the electronic datasets.

Regards,
Linda

Linda Gustavson, Ph.D., RAC
Director, R & D Regulatory Affairs
U.S. Head, Oncology
Global Regulatory Affairs
sanofi-aventis US Inc.
Mail code: BX2-712B
200 Crossing Blvd, Bridgewater, NJ 08890-0890
908-304-6221 (work phone)
203-314-2245 (cell phone)
fax: 908-304-6549
email: linda.gustavson@sanofi-aventis.com

From: Waxman, Ian [mailto:Ian.Waxman@fda.hhs.gov]
Sent: Friday, April 02, 2010 11:41 AM
To: Gustavson, Linda R&D/US
Cc: Cottrell, Christy L.
Subject: Cabazitaxel review question

Hi Linda,

I am conducting a safety review for NDA 201023 and am having difficulty reconciling patient numbers for supportive study ARD6191.

The study synopsis includes 71 treated patients, all of whom received q3 weekly dosing. The dataset, however, contains an additional 13 patients who received weekly dosing. Are these additional 13 patients documented anywhere in the study report synopsis? Was the protocol design changed?

Thanks,
Ian

Ian Waxman, MD
Medical Officer
FDA/CDER/OND/OODP/DDOP
WO Bldg 22, Rm 2115
10903 New Hampshire Avenue
Silver Spring, MD 20993

Email: ian.waxman@fda.hhs.gov
Phone: 301-796-5123
Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
04/05/2010

From: Waxman, Ian
Sent: Friday, April 02, 2010 11:41 AM
To: 'linda.gustavson@sanofi-aventis.com'
Cc: Cottrell, Christy L.
Subject: Cabazitaxel review question

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Ian Waxman, MD
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/s/

CHRISTY L COTTRELL
04/05/2010

From: Cottrell, Christy L.
Sent: Thursday, April 01, 2010 12:51 PM
To: 'Linda.Gustavson@sanofi-aventis.com'
Subject: NDA 201023 for Cabazitaxel: Information Request

Linda,

See below for a request from one of the clinical reviewers regarding NDA 201023 for Cabazitaxel.

- Please add an "event within 30 days of last dose" variable to the AE datasets submitted on 3/31/10.

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
301.796.4256 (phone) • 301.796.9845 (fax) | christy.cottrell@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	GI-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
04/01/2010

From: Cottrell, Christy L.
Sent: Tuesday, March 23, 2010 10:35 AM
To: 'Mark.Moyer@sanofi-aventis.com'; 'Linda.Gustavson@sanofi-aventis.com'
Subject: NDA 201023: PK request

Mark and Linda,

See below for a PK request for information to be submitted with the NDA.

In your NDA submission, please submit the pharmacokinetic dataset including individual concentration vs. time and corresponding pharmacokinetic parameters by patient as SAS transport files. The following are the general expectations for submitting pharmacometric data and models:

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

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

Let me know if you have any questions.

Regards,
Christy Cottrell

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHRISTY L COTTRELL
03/23/2010

MEMORANDUM OF MEETING MINUTES

Meeting Date: February 23, 2010
Time: 4-5 PM
Location: FDA, White Oak Building/Room 1309

Application: IND 56,999

Type of Meeting: Pre-NDA meeting

Meeting Chair: V. Ellen Maher, M.D.

Meeting Recorder: Alice Kacuba

FDA Attendees, Titles, and Office/Division:

Division of Drug Oncology Products (HFD-150)

Robert Justice, M.D., M.S., Director DDOP
Anthony Murgo, M.D., M.S., FACP, Associate Director OODP IO, Acting Deputy Director DDOP
V. Ellen Maher, M.D., Clinical Team Leader
Nancy Scher, M.D., Medical Officer
Y. Max Ning, M.D., Ph.D., Medical Officer
Haleh Saber, Ph.D., Supervisory Pharmacologist
Gene Williams, Ph.D., Senior Clinical Pharmacology Reviewer, DCP5
Shenqhui Tang, Ph.D., Acting Team Leader, DB
Chia-Wen (Kiki) Ko, Ph.D., Mathematical Statistician, DB 5
Alice Kacuba, MSN, R.N., RAC, Chief, Project Management Staff

External Constituent Attendees and Titles:

Sanofi-aventis
Jacqueline Caniglia, MBA, MPPA, Project Direction
Sunil Gupta, M.D., Sr. Director, Clinical Oncology
Linda Gustavson, Ph.D., RAC, Director, Regulatory Affairs, Oncology
Mark Moyer, MS, Vice President, Regulatory Affairs
Steven Neibart, M.D., Global Safety Officer, Global Pharmacovigilance and Epidemiology
Martin Roessner, MS, Sr. Director, Clinical Biostatistics
Debasish Roychowdhury, M.D., Head of Oncology Business Division
Dorothee Semiond, Ph.D., Drug Metabolism and Pharmacokinetics
Liji Shen, Ph.D., Assoc. Director, Clinical Biostatistics

Background: IND 56,999 is being investigated for use in combination with prednisone or prednisolone in metastatic cancer patients who progressed during or after docetaxel-based therapies. Sanofi-aventis submitted a Meeting Request and Background Package on November 9, 2009 and a subsequent Part 2 Background package on January 29, 2010. In preparation fot he

meeting, the FA communicated our preliminary responses to the sponsor ahead of time.

Discussion Points (bullet format):
Clinical/Statistics

1. At the EOP2 and through SPA, FDA agreed that the patient population targeted for inclusion in TROPIC was appropriate for a registration study. The demonstration of a survival benefit in TROPIC provides a therapeutic option for patients with no available therapy.
   Does the Agency agree that the TROPIC study evaluates the treatment of an unmet medical need population?

FDA Response: We concur that there is no approved therapy for hormone resistant patients who have progressed on or after docetaxel therapy.

2. The safety information will be based on 6 studies: the Phase III TROPIC study together with 5 supportive studies. Does FDA agree with the statistical approach for the safety summary analysis? (See slides 55-57 Integrated Analysis Plan)?

FDA Response: This seems acceptable. We agree with not integrating the data from the combination study with capecitabine in breast cancer, TCD6945, although the data may be presented separately. Also, see response to question 6.

3. Does the Agency agree that the data provided from the Phase III TROPIC study together with the supportive studies will allow an assessment of the risk/benefit of Cabazitaxel for a potential indication in metastatic prostate cancer patients who have progressed on or after docetaxel therapy?

FDA Response: This will be a review issue.

4. Does the Agency recommend any additional analyses/data displays to enable an assessment of the risk/benefit profile?

We have some recommendations for the TROPIC study report:

- **For primary and key secondary endpoints, please make sure that the definition of the endpoints, assessment schedule, as well as amount of missing data are specified in the report.**
- **Consider sensitivity analyses for evaluation of results robustness, to assess if there is an imbalance in missing assessments between the two treatment arms.**
- **Consider a subgroup analysis of overall survival based on types of disease progression at enrollment (radiologic progression vs. PSA progression).**

Meeting discussion: The sponsor indicated that they collected information on whether patients progressed but not on the criteria used to determine progression.

5. Does the Agency agree with the proposed electronic data submission proposed in the electronic data submission planning template?

FDA response: Please provide patient narratives and CRFs for all patients in both treatment groups of study EFC6193 who:

- **Died within 30 days of last treatment, unless due to progressive disease**
- **Discontinued study drug due to an AE**
- ***Experienced SAEs**
- **Experienced "events of special interest"**

The narratives and CRFs should be indexed and grouped according to category (e.g., died, discontinued, etc.), with hyperlinks.

Meeting discussion: According to the sponsor, there are narratives for all categories requested and that indexing in CSR is based on: deaths within 30 days excluding deaths due to progressive disease, discontinuations due to an AE and SAE's as categories with hyperlink to narratives. As well as, within the CSR and the safety summary text, there is hyperlinking.

6. The data pooling strategy on slide 57 has studies pooled together for <25 and ≥ 25 mg/m^2 which includes a Phase II study in breast cancer. Does the Agency agree that these should be pooled together as presented in the table or does the Agency recommend that the breast cancer be presented as a separate column to assess potential gender effect?

FDA Response: We suggest you follow the pooling strategy outlined on slide 57 for the primary analysis, but also provide a separate analysis by gender (and dose). Demographic analysis for efficacy and safety are required for gender (when appropriate), age and race as part of the NDA submission.

Meeting Discussion: According to the sponsor, the interpretability of gender analysis is limited by indication, age and small number of patients. To address the gender effect, we propose to assess safety on the individual study, ARD6191
Study report will be submitted
Safety table from ARD6191 will be included as part of safety summary
The Division found this acceptable.

7. Does the Agency have any additional comments on the CTD?

FDA Response: Regarding the clinical pharmacology portion of the submission:

- **all raw concentration-time data, pharmacodynamic data, and accompanying demographic data, should be submitted in SAS transport format**

- **for each analyte, please submit the validation of the bioanalytical assay, the results of the actual analytical runs (all values: standards, samples, blanks, QC samples, dilutions, re-assays, and incurred sample analysis), and the chronology of the actual analytical runs (all values: standards, samples, blanks, QC samples, dilutions, re-assays, and incurred sample analysis).**

Clinical/Pharmacology

8. The sponsor's proposed action plan to address the FDA End-of-Phase 2 meeting pharmacology comments is provided in the back-up slides 60-65. Studies to assess drug-drug interactions, hepatic impairment are planned or on-going, as shown in the table below. The sponsor proposes to address the potential for drug-drug interactions and hepatic impairment through appropriate language in the label. The sponsor proposes to provide the results from the drug-drug interaction, hepatic impairment as post-marketing requirements.

Drug Effect	Study	Status
Drug-Drug Interaction with moderate CYP3A4 inhibitor	Interaction with aprepitant Study TCD10870 (in combination with cis-platin)	On-going
Drug-drug interaction to assess inhibitory effect on CYP3A substrate	CYP3A probe, oral midazolam Study TCD11068 (in combination with gemcitabine)	On-going
Hepatic impairment	Study POP6792	Planned
QT interval	Study TES10884	Planned

8a) Does the Agency agree with the sponsor proposal to address the potential for drug-drug interactions and hepatic impairment through appropriate language in the label?

FDA Response: We do not agree that package insert information from *in vivo* studies of drug-drug interactions and hepatic impairment is appropriately postponed until the post-marketing period. Whether the NDA will be filed will be a review issue made in the context of the efficacy and safety data, and other NDA data.

8b) Does the Agency agree with the provision of the results from drug-drug interaction studies, hepatic impairment assessment as post-marketing requirements?

FDA Response: We do not agree, see response to 8a.

9. Urinary excretion is 3.7%. The sponsor is of the opinion that the data on urinary excretion is sufficient to assess the product for approval and labeling.
   Does the Agency agree based on this initial information, a specific renal impairment study would be unlikely required and would be subject to full dossier review?

FDA Response: Yes, with the proviso that we cannot answer definitively until we have conducted preliminary review of the relevant completed study reports.

10. In non-clinical studies, cabazitaxel did not show a potential to affect QT interval (slide 64). A thorough review of the clinical safety data including cardiac safety will be provided in the eCTD to determine the current safety profile (slide 65). The sponsor is of the opinion that the data on QT is sufficient to assess the product for approval and labeling.
    Does the Agency agree a specific QT study would be unlikely required and would be subject to full dossier review.

FDA Response: Per the ICH E-14 guidelines, a dedicated QT assessment is required to characterize drug effects on cardiac repolarization. The proposed QT study TES10884 along with a thorough review of cardiac safety data would be acceptable to fulfill this requirement.

Administrative

11. Does FDA agree with the proposed rolling submission schedule?
    - Non-Clinical (Module 4, 2.4, and 2.6 December 18, 2009
    - Quality (Module 3 and 2.3) late February or within March 2010 final submission
    - Complete submission March 2010

FDA Response: Yes.

12. The sponsor proposes to start an expanded access program after the eCTD is filed and before cabazitaxel is approved as described in slide 12. Does FDA agree that based on the Phase III TROPIC results, an expanded access protocol is appropriate?

FDA Response: Yes. Please clarify whether this will be submitted as a treatment protocol or an intermediate size expanded access protocol and provide the protocol for review. Please state whether any of this safety information will be included in the 120 day safety update.

<u>Additional Clinical Comment:</u>

Regarding the subset analysis for the primary endpoint, please explain:

- **HR=1 for the subset of patients who are not Europe and not US (Slide 33)**
- **HR=1 for the subset of patients who received prior Taxotere total dose less than 225 mg/m^2 (Slide 34)**

There were a disproportionate number of deaths due to an AE in the carbazitaxel arm (18 vs. 7). Please provide the causes of deaths in each arm.

Appears This Way On Original

Additional Comments:

1. **Please indicate the type of approval you plan to request when submitting your NDA submission, either full approval or accelerated approval. It is expected that you will be able to discuss your requested approval plan during the scheduled meeting with us.**

2. **Please complete the following table for Study X and submit this with your NDA.**

Site Address Point of Contact	# Enrolled	Efficacy Measure	# Gr 3-4 AEs	# Major Protocol Violations

3. **NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.**

   The following comments, based on our experience with other applications, are intended to help you plan and prepare for submitting a quality application. This list is not inclusive of all issues you need to consider in preparing an application, but highlights areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application we encourage you to provide justification and discuss it with us.

Clinical:

1) **Submit copies of the original versions of all protocols, statistical analysis plans, DSMB and adjudication committee charters, and all amendments.**
2) **Submit copies of minutes of all DSMB, and adjudication committee meetings.**
3) **If investigator instructions were produced in addition to the protocol and investigator brochure, submit copies of all such instructions.**
4) **Submit copies (in SAS transport format) of randomization lists and, if used, IVRS datasets.**
5) **Submit copies (in SAS transport format) of all datasets used to track adjudications.**

6) **Clinical study report(s) should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf).**
7) **For each of the completed Phase 3 clinical trials, submit a table with the following columns:**
   a) **Site number**
   b) **Principle investigator**
   c) **Location: City State, Country**
   d) **Number of subjects screened**
   e) **Number of subjects randomized**
   f) **Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites**
   g) **Number of protocol violations (Major, minor, definition)**
8) **Prepare integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:**
   a) **Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf)**
   b) **Cancer Drug and Biological Products-Clinical Data in Marketing Applications (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf)**
9) **Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).**
10) **Safety Analysis Plan. In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. At a minimum the Safety Analysis Plan should address the following components:**
    a) **Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).**
    b) **Safety endpoints for Adverse Events of Special Interest (AERI)**
    c) **Definition of Treatment Emergent Adverse Event (TEAE)**
    d) **Expert adjudication process (Expert Clinical Committee Charter)**
    e) **Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)**
    f) **Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.**

g) When unanticipated safety issues are identified the QSAP may be amended.

11) Provide detailed information, including a narrative, for all patients terminating study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision.

12) Narrative summaries should contain the following components:
   a) subject age and gender
   b) signs and symptoms related to the adverse event being discussed
   c) an assessment of the relationship of exposure duration to the development of the adverse event
   d) pertinent medical history
   e) concomitant medications with start dates relative to the adverse event
   f) pertinent physical exam findings
   g) pertinent test results (for example: lab data, ECG data, biopsy data)
   h) discussion of the diagnosis as supported by available clinical data
   i) a list of the differential diagnoses, for events without a definitive diagnosis
   j) treatment provided
   k) re-challenge results (if performed)
   l) outcomes and follow-up information
   m) an informed discussion of the case, allowing a better understanding of what the subject experienced.

13) Provide complete CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs upon request.

14) For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

15) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm).

16) Pediatric Studies. 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 exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request including supporting data. A request

for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

17) **Regulations require that the safety and effectiveness data be presented for subgroups including "by gender, age, and racial subgroups". Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis.**

18) **In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.**

19) **The NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:**

   a) **Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.**
   b) **Exposure-Response Relationships – important exposure-response assessments.**
   c) **Less common adverse events (between 0.1% and 1%).**
   d) **Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.**
   e) **Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.**
   f) **Marked outliers and dropouts for laboratory abnormalities.**
   g) **Analysis of vital signs focused on measures of central tendencies.**
   h) **Analysis of vital signs focused on outliers or shifts from normal to abnormal.**
   i) **Marked outliers for vital signs and dropouts for vital sign abnormalities.**
   j) **A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all Aes coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.**
   k) **Overview of ECG testing in the development program, including a brief review of the nonclinical results.**
   l) **Standard analyses and explorations of ECG data.**
   m) **Overdose experience.**
   n) **Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.**
   o) **Explorations for:**

i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
ii) Dose dependency for adverse findings
iii) Provide summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
iv) Time dependency for adverse finding
v) Provide data summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
vi) Drug-demographic interactions
vii) Drug-disease interactions
viii) Drug-drug interactions

p) Dosing considerations for important drug-drug interactions.
q) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

Datasets and Programs:

20) The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included. If the SAS programs use any macro programs, please provide all necessary macro programs.
21) Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every value proposed to be included in the label.
22) The SAS transport files should be created by a procedure which allows the file to be easily read by the JMP software.
23) Data Format:
    a) *We strongly encourage that data be supplied in CDISC format.* The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org).
        i) Study Data Tabulation Model (SDTM) Issues:
            (1) The current published SDTM and SDTM Implementation Guide (SDTMIG) should be followed carefully. Refer to the SDTMIG section on Conformance (3.2.3)
            (2) Domains
            (3) There are additional domains listed below that are not included in the current DTMIG. Information on these domains may be obtained at www.cdisc.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.
                (a) (DV) Protocol deviations
                (b) (DA) Drug Accountability
                (c) (PC, PP) Pharmacokinetics
                (d) (MB, MS) Microbiology
                (e) (CF) Clinical Findings
            (4) The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.

(a) Tumor information
(b) Imaging Data
(c) Complex Inclusion/Exclusion Criteria

(5) Variables
(a) All required variables are to be included.
(b) All expected variables should be included in all SDTM datasets.
(c) Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.
(d) A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.
(e) A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.
(f) Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.

(6) Specific issues of note:
(a) SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.
(b) Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy should be placed in the SUPPQUAL dataset or an ADaM dataset.
(c) These issues can be addressed through the request for ADaM datasets

ii) Analysis Data Model (ADaM) Issues:
(1) Specify which ADaM datasets you intend to submit.
(2) Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.
(3) Discuss the structure of the datasets with the reviewing division and specify in the QSAP.
(4) Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.
(5) Indicate which core variables will be replicated across the different datasets, if any.
(6) SDTM and ADaM datasets should use the unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.

iii) General Items:
(1) Controlled terminology issue:
(a) Use a single version of MedDRA for a submission. Does not have to be the most recent version
(b) We recommend that the WHO drug dictionary be used for concomitant medications.
(c) Refer to the CDISC terminology for lab test names.
(d) Issues regarding ranges for laboratory measurements should be addressed.

(2) **Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.**

(3) **Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.**

b) **If you submit non-CDISC Datasets, we request the following:**

i) **All datasets should contain the following variables/fields (in the same format and coding)**

(1) **Each subject should have one unique ID across the entire NDA**
(2) **Study number**
(3) **Treatment assignment**
(4) **Demographic characteristics (age, race, gender, etc.)**

ii) **The safety dataset that should include the following fields/variables:**

(1) **A unique patient identifier**
(2) **Study/protocol number**
(3) **Patient's treatment assignment**
(4) **Demographic characteristics, including gender, chronological age (not date of birth), and race**
(5) **Dosing at time of adverse event**
(6) **Dosing prior to event (if different)**
(7) **Start and stop dates for adverse events**
(8) **Days on study drug at time of event**
(9) **Outcome of event (e.g. ongoing, resolved, led to discontinuation)**
(10) **Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).**
(11) **Marker for serious adverse events**
(12) **Verbatim term**

iii) **The adverse event dataset should include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset should also include the Verbatim term taken from the case report form. Ensure that mapping of a preferred term to the primary MSSO defined SOC level is not changed.**

iv) **See the attached mock adverse event data set in Figure 1 that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables should appear and does not address other content that is usually contained in the adverse event data set.**

v) **In the adverse event data set, please provide a variable that gives the numeric MedDRA code for each lower level term.**

vi) **The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.**

vii) **Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.**

viii) **The spelling and capitalization of MedDRA terms should match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.**

ix) **The concomitant medication dataset should use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.**

x) **Ensure that laboratory data are organized in the data sets in a standardized manner with consistent units and a single reference range for each laboratory variable. Include a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result should be in numeric format. Define the range(s), with supporting documentation, that are used to identify severe toxicity.**

xi) **Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.**

xii) **In every dataset, all dates should be formatted as ISO date format.**

xiii) **Across all datasets, the same coding should be used for common variables, e.g. "PBO" for the placebo group. Datasets should not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable should be included in the datasets.**

xiv) **A single combined analysis dataset including variables from a number of separate data sets can sometimes be useful to the medical review officer and may avoid data set errors caused be joining these variables together using JMP. Provide a dataset (SAS Transport file), including one record per subject screened, that includes the following variables.**

(1) **Study Information: Subject ID, subject enrolled (Y/N), subject in efficacy population (Y/N), subject in safety population (Y/N), intent-to-treat population (Y/N), per-protocol population (Y/N), evaluable patient population (Y/N), date/time of randomization and date of the first study treatment, etc.**

(2) **Demographics: Sex, race/ethnicity, age, weight, BMI, location U.S. (Y/N), region (e.g., North America, Eastern Europe, Western Europe, etc.)**

(3) Study Medications: Treatment assignment (for efficacy analyses), treatment designation for safety analyses ("as treated"), date/time of initial dose, date/time of last dose, total days of treatment, total dose received. In addition, provide the study medication lot numbers used for each dose administered.

(4) Baseline Disease Characteristics: e.g. Performance status, previous treatment regimens or procedures, and other prognostic factors as deemed necessary

(5) Non-protocol specified anti-cancer therapy (systemic medication/surgery/radiotherapy, etc) : e.g. indicators for such procedures, date of such procedures and type or reasons for the procedures, etc

(6) Outcomes: For time-to-event type of endpoints, please provide for each subject the censoring status, the time-to-event, the date of the event and which event type occurred (when an event occurs), the reasons for censoring if censored and the data-cut-off date. Information for individual component of the primary endpoint should also be provided. The variables used for sensitivity analyses for the primary and key secondary efficacy endpoints should be included. The important time variables, usually used for deriving variables for sensitivity analyses, such as the last disease assessment time, last disease assessment time before > 1 missing assessment, last assessment time prior to non-protocol specified anti-cancer therapy and last contact time, etc., should be included. For laboratory results include a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result should be in numeric format. Define the range(s), with supporting documentation, that are used to identify severe toxicity

(7) Necessary data documentation, for example, algorithm for variable derivation, source of the data (i.e. corresponding CRF pages), decoding of the data values (i.e. data format), indication of data structure (one record per subject or one record per visit per subject), etc., should be included

(8) Other: Please provide a Y/N variable for potential conflict of interest, i.e., subjects enrolled at sites where an investigator has reported a potential conflict of interest(s) should receive a "yes" flag

Physician's Labeling:

24) Highlights:

a) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]

b) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

c) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]

d) **The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]**

e) **The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to 21 CFR 201.57(a)(4) and to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).**

f) **For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).**

g) **The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:**

"(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

h) **Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.**

i) **Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).**

j) **A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].**

k) **Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights.**

l) **The Patient Counseling Information statement must appear in Highlights and must read "See 17 for PATIENT COUNSELING INFORMATION." [See 21 CFR 201.57(a)(14)]**

m) **A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.**

n) **A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]**

25) **Table of Contents:**

a) **The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]**

b) **The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]**

c) **Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.**

d) **Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.**

e) **When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d)(1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:**

8.1 Pregnancy
8.3 Nursing Mothers *(not 8.2)*
8.4 Pediatric Use *(not 8.3)*
8.5 Geriatric Use *(not 8.4)*

f) **When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents:**

"*Sections or subsections omitted from the Full Prescribing Information are not listed."

26) Full Prescribing Information (FPI):

a) **Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).**

b) **Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.**

c) **Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format" (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf).**

d) **The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf]**

e) **Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]**

f) **Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]**

g) **The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-**

Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

h) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.

i) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.

j) If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.

k) Refer to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format.

l) Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

Electronic Common Technical Document (eCTD):

27) Relating sequences properly allows reviewers to easily navigate the application's original and supplemental submissions. By relating sequences correctly a reviewer can focus on the data at hand without wondering "what is missing" or "what are the reasons for this disorganized submission?" Delays in your review are also avoided.

a) First-level submission types should not use related sequence

i) First-level submission types are

(1) "original-application"
(2) "annual-report"
(3) "efficacy-supplement"
(4) "labeling-supplement"
(5) "chemistry-manufacturing-controls-supplement"
(6) "other"

b) Second-level submission types should use a single related sequence

i) The related sequence should always be a first-level submission type

ii) Second-level submission types are:

(1) "amendment"
(2) "resubmission"

iii) Related Sequences are indicated in the us-regional.xml file:

Submission Type	Level	Related Sequence

Original	**Primary**	**NO**
Annual Report	**Primary**	**NO**
Efficacy Supplement	**Primary**	**NO**
Labeling Supplement	**Primary**	**NO**
CMC Supplement	**Primary**	**NO**
Other	**Primary**	**NO**
Amendment	**Secondary**	**YES**
Resubmission	**Secondary**	**YES**

c) **See Appendix 1 for examples of correct usregional.xml file submission code. Contact ESUB@fda.hhs.gov with any questions.**

Other Issues:

28) **The application should include a statement that the manufacturing facilities are ready for inspection upon submission of the application.**

29) **The application should contain a table that list all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).**

30) **Review of an application can be facilitated by including a chronology of prior substantive communications with FDA and copies of official meeting/telecon minutes.**

Figure 1:

Please note that the HLGT and HLT level terms in this table are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data that is typically found in an adverse event data set.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

Appendix 1. **Code snippet examples of correct usregional.xml file submissions:**

An usregional.xml file for a First Level Submission
NOTE because this is a primary submission type there is NO related sequence:

```
<?xml version="1.0" standalone="no"?>
<?xml-stylesheet type="text/xsl" href="../../util/style/us-regional.xsl" ?>
<!DOCTYPE fda-regional:fda-regional SYSTEM "../../util/dtd/us-regional-v2-01.dtd">
<fda-regional:fda-regional xmlns:fda-regional="http://www.ich.org/fda"
xmlns:xlink="http://www.w3c.org/1999/xlink" dtd-version="2.01">
        <admin>
                <applicant-info>
                        <company-name> Pharma USA</company-name>
                        <date-of-submission>
                                <date format="yyyymmdd">20080601</date>
                        </date-of-submission>
                </applicant-info>
                <product-description>
                        <application-number>999999</application-number>
                        <prod-name type="established">Fixitol</prod-name>
                </product-description>
                <application-information application-type="nda">
                        <submission submission-type="labeling supplement">
                                <sequence-number>0010</sequence-number>
                                </submission>
                </application-information>
        </admin>
```

In the example above the sponsor is sending in a labeling supplement and it will not have a related sequence.

In the example below the sponsor has been asked to provide some additional data to support their labeling supplement. Because it is an amendment it will need to designate a related sequence.

```
<?xml version="1.0" standalone="no"?>
<?xml-stylesheet type="text/xsl" href="../../util/style/us-regional.xsl" ?>
<!DOCTYPE fda-regional:fda-regional SYSTEM "../../util/dtd/us-regional-v2-01.dtd">
<fda-regional:fda-regional xmlns:fda-regional="http://www.ich.org/fda"
xmlns:xlink="http://www.w3c.org/1999/xlink" dtd-version="2.01">
        <admin>
                <applicant-info>
                        <company-name> Pharma USA</company-name>
                        <date-of-submission>
                                <date format="yyyymmdd">20080705</date>
                        </date-of-submission>
                </applicant-info>
                <product-description>
                        <application-number>999999</application-number>
                        <prod-name type="established">Fixitol</prod-name>
                </product-description>
                <application-information application-type="nda">
                        <submission submission-type="amendment">
                        <sequence-number>0012</sequence-number>
                          <related-sequence-number>0010</related-sequence-number>
                        </submission>
```

</application-information>
</admin>

Minutes Preparer: Alice Kacuba

Chair Concurrence: V. Ellen Maher, M.D.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-56999	GI-1	SANOFI-AVENTIS U S INC	RPR 116258A INJECTION CONCENTRATE

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/s/

ALICE KACUBA
06/01/2010

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

Sponsor Name:	Sanofi-aventis U.S. Inc.
Application Number:	IND 56,999
Product Name:	Cabazitaxel (XRP6258)
Meeting Type:	Type C
Meeting Category:	Chemistry, Manufacturing and Controls, Guidance Meeting
Meeting Date and Time:	Tuesday, February 24, 2009, 13:00 – 14:00 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	January 22, 2009

The following consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled as a **FACE-TO-FACE MEETING** on **TUESDAY, FEBRUARY 24, 2009**, between **13:00–14:00 ET** between **SANOFI-AVENTIS U.S. INC.** and the Center for Drug Evaluation and Research/Office of New Drug Quality Assessment. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Deborah Mesmer, Regulatory Health Project Manager for Quality, (301) 796-4023). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. **Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting**. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager for Quality to discuss the possibility of including these for discussion at the meeting.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-56999	GI-1	SANOFI-AVENTIS U S INC	RPR 116258A INJECTION CONCENTRATE

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/s/

ALICE KACUBA
06/01/2010

1.0 BACKGROUND

Cabazitaxel (XRP6258, RPR116258A) is being developed by Sanofi-aventis U.S. Inc. for the treatment of advanced prostate cancer. An End-of-Phase 2 meeting was held with FDA clinical division on June 28, 2006. Cabazitaxel is undergoing phase III study in second line hormone refractory prostate cancer in combination with prednisome. A Type C meeting request was submitted on December 16, 2008, and received on December 18, 2008, for a CMC Guidance meeting to discuss the common development plans for this drug and (b) (4) A meeting was granted on January 8, 2009, to discuss both drugs jointly in a face-to-face meeting to be held on February 24, 2009. The meeting briefing package was received on January 22, 2009. The purpose of this document is to provide preliminary responses to the questions contained in the meeting briefing package. These responses are being archived and shared with Sanofi-aventis U.S. to promote an efficient discussion at the meeting scheduled for February 24, 2009.

2.0 SPONSOR QUESTIONS AND FDA PRELIMINARY RESPONSES

2.1 DRUG SUBSTANCE

Question 1: **Does the Agency agree with the designation of (b) (4)) as a starting material for the synthesis of (b) (4) ?**

(b) (4)

A final determination of acceptability will be made at the time of NDA review.

2.2 DRUG PRODUCT

Question 2: **Does the Agency agree with the proposed concurrent drug product process validation strategy and the suitability of the process validation data package intended to be provided in the NDA**

FDA Response: Your approach is reasonable from a review perspective. However, you may wish to also contact the Office of Compliance to confirm acceptability of your approach. Ensure that validation information relating to the adequacy and efficacy of any sterilization process (e.g., drug product, packaging components) is submitted in section 3.2.P.3.5.

Question 3: **Considering the proposed approach to define in-use stability and compatibility with infusion (b) (4) and sets with different product contact materials (representative of what is widely used in hospitals):**

a. Does the Agency agree that the test design is adequate to determine in-use stability and compatibility with the proposed materials to be tested?

FDA Response: The approach to determine in-use stability and compatibility with the proposed modeling approach appears reasonable. However, in order to support this proposed approach please consider providing the following information at the time of NDA submission:

- The scientific rationale for choosing the 2 factor interaction linear model as the optimality criteria for the D-optimal model.
- Data to show that the chosen model is optimum for all the responses being evaluated e.g. appearance, assay, particulate matter, impurity levels, for both compatibility study as well as in-use study
- Verification of proposed DOE model. For example comparing model prediction with analytical data at conditions that were not used to derive the model
- Statistical analysis of DOE data.
- Plans for continual improvement of the model.

The acceptance criteria for the compatibility study with (b) (4) (Table 13, page 41) are not adequate. Revise the acceptance criteria for cabazitaxel assay and impurity (b) (4) to be within the drug product specification. Include impurity

profiles (not only (b) (4), but also any other impurities and total impurities) in the compatibility study.

(b) (4)

c. Does the Agency agree that it is not necessary to recommend the use of an (b) (4) for product administration if particulate matter testing meet the acceptance criteria for solution for injection in experiments carried out without (b) (4) ?

FDA Response:. It is premature to discuss this proposal at this time. The use of an (b) (4) is recommended in light of the fact that the infusion solution is a supersaturated solution. Any proposal to eliminate the use of an (b) (4) needs to include a full supporting data package.

3.0 ADDITIONAL COMMENTS

1. We recommend you to submit Drug Substance information in the NDA instead of a DMF unless there is some compelling reason (for example, the drug substance is manufactured by an outside firm). It is noted that the drug substance and intermediates (b) (4) are to be manufactured by Sanofi facilities. Therefore, we encourage you to submit CMC information regarding drug substance and the intermediates in the NDA.
2. Impurities which exceed ICH Q3B(R) limits need to be adequately qualified. Certificates of Analyses for drug batches, including limits of individual qualified impurities, must be included with study reports.

4.0 CONCURRENCE:

{See appended electronic signature page}

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

{See appended electronic signature page}

Richard T. Lostritto, Ph.D.
Division Director
Division of Pre-Marketing Assessment III and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name / Subject
IND 56999	SANOFI-AVENTIS U S INC	RPR 116258A INJECTION CONCENTRATE

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/s/

DEBORAH M MESMER
02/18/2009

RICHARD T LOSTRITTO
02/19/2009

TELECON MEETING MINUTES

MEETING DATE: June 28, 2006

IND/NDA: (b) (4); **56,999**
Meeting Request Submission Date: May 1, 2006 (N215); May 5, 2006 (N085)
Briefing Document Submission Date: May 23, 2006(N219); May 25, 2006 (N086)

DRUG: RPR9881A and XRP6258

SPONSOR/APPLICANT: Sanofi-Aventis Pharmaceuticals

TYPE of MEETING/TELECON:

1. End of phase 2

2. Proposed Indication: Treatment of HRPC previously treated with a Taxotere containing regimen; (b) (4)

FDA PARTICIPANTS:
Robert Justice, MD, Director, Division of Drug Oncology Products
Ann Farrell, MD, Acting Deputy Director
John Johnson, M.D., Medical Team Leader
Martin Cohen, M.D., Medical Reviewer
Adrian Senderowicz, MD, Medical Reviewer
Raji Sridhara, PhD, Statistics Team Leader
Hun Ke, PhD, Statistician
Brian Booth, PhD, Acting Clinical Pharmacology Reviewer (internal meeting only)
Gene Williams, PhD, Clinical Pharmacology Reviewer
Laurie Burke, Study Endpoints and Labeling Development
Bill Pierce, Study Endpoints and Labeling Development (internal meeting only)
Sharon Hertz, MD, Deputy Director, Division of Analgesia, Anesthesia and Rheumatology (internal meeting only)
Ann Staten, RD, Project Manager
Patricia DeLaney, Office of Special Health Issues
Joann Minor, Office of Special Health Issues
Eugene Kazmierczak, PhD, HRPC Patient Representative
Jennifer Wells, Pancreatic Cancer Patient Representative

INDUSTRY PARTICIPANTS:

Hichem Chakroun, Ph.D., Director, Project Direction
Avinash Desai, M.D., Director, Clinical Development
Sunil Gupta, M.D., Senior Director, Clinical Oncology
Linda Gustavson, Ph.D., Associate Director Regulatory Development, Oncology
Mark Moyer, Vice President, Regulatory Development
Martin Roessner, U.S. Head of Biostatistics, Acting Head Statistics Oncology
Dorothee Semiond, Ph.D, Pharm. D., Director, Global Metabolism and Pharmacokinetics
Zhenming Shun, Ph.D., Director, Biostatistics, Oncology
Sophie Jourdan, Pharm. D., Senior Manager, Global Health Outcomes and Market Access, Oncology

BACKGROUND: Following the FDA internal meetings, responses to the sponsor's questions were sent via e-mail (see attachments). On June 26, 2006, the sponsor requested that both meetings be combined into one and requested a teleconference. The discussion points are identified in italics below.

MEETING/TELECON OBJECTIVES:

To discuss the development plan for the treatment of HRPC previously treated with a Taxotere containing regimen (b) (4) (b) (4)

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Sanofi-Aventis: We agree to have overall survival as the single, primary endpoint for both Phase III registration trials, for XRP9881 and for XRP6258. We seek clarification from FDA on the following issues:

1. We appreciate the FDA's detailed guidance or (b) (4)t

   Discussion: If the study fails on survival, there will be no approval. If you win on survival, any secondary endpoints would have to be convincing to be included in the label. Given the unblinded nature of the trial, these secondary endpoints are unlikely to be included in the label.

2. We appreciate the FDA's comments on the pain endpoint in the XRP6258 response #5. We wish to gain any additional recommendations FDA has that would help maximize the potential for labeling statements for our secondary clinical endpoint of pain response

endpoint using a similar approach as used for approval of mitoxantrone for treatment of HRPC?

Discussion: See our response to question #1.

3. In reference to XRP6258 response #4 on PFS, what advice can the FDA provide to strengthen the PFS endpoint that would allow this endpoint to be considered a secondary endpoint supportive of labeling statements versus an exploratory endpoint?

   Discussion: See our response to question #1 and there are two problems with PFS as an endpoint: PSA inclusion and measuring progression in bone only disease.

4. We acknowledge the FDA comments on XRP6258 response #7 and propose to request a separate meeting with FDA to discuss the adequacy of the overall planned PK program and address the questions raised by the FDA. However, at this time, we wish to obtain FDA agreement with our proposed pharmacokinetic strategy for our Phase III clinical protocol in HRPC patients. We propose to implement sparse sampling in as many patients as possible at cycle 1 in the Phase III protocol, EFC6193, in order to assess the PK profile in this population, assuming no effect of the first dose of prednisone on PK, of XRP6258 and to investigate PK/PD relationships for safety and efficacy. In addition, 25 patients will be sampled at cycle 2 in order to assess the effect of repeated administrations of prednisone on the PK of XRP6258. Does the FDA agree with this proposal for our Phase III HRPC protocol?

   FDA Response: Yes

ACTION ITEMS:

Sanofi-Aventis will respond in writing to the FDA responses sent June 22, 2006.

_____ Concurrence Chair:_____

Ann Staten, Project Manager

John Johnson, MD
Medical Team Leader Team

Attachment: FDA responses to sponsor's questions
Regulatory Bullets

IND 56,999 XRP6258
EOP2 meeting minutes
HRPC

Questions

1. Does the FDA agree that the proposed patient population for study EFC6193 is adequately defined and suitable for a comparator-controlled Phase III study with marketing approval intent?

   FDA Response: Yes. However, please clarify the following inclusion criteria found on page 2/11 of the briefing book "Previously irradiated lesions, primary prostate lesion and bone lesions are excluded".

2. Does the FDA agree that mitoxantrone in combination with prednisone is an appropriate comparator for this Phase III, randomized, comparator controlled trial?

   FDA Response: Yes. However, M/P therapy can be administered for 12 cycles (cumulative dose ~ 140 mg/m^2). The dose proposed for the pivotal study (6 cycles of 12 mg/m2, total 72 mg/m2) represents half the total dose permitted for mitoxantrone.

3. Does the FDA agree that one Phase III trial, EFC6193, is adequate to support a marketing application for full approval provided this trial demonstrates a clear benefit in survival for XRP6258 in combination with prednisone compared to mitoxantrone in combination with prednisone?

   FDA Response: Possibly depending on the results. For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. If an improvement in survival is demonstrated, a single trial may be adequate. However, if the regulatory endpoint is pain improvement then a second controlled study would be required.

4. Does the FDA agree with the definition of the composite secondary endpoint, PFS, defined as meeting at least one of the criteria below?
   - Tumor progression as defined by RECIST
   - PSA Progression that is 25% increased over baseline or over nadir
   - Death due to any cause

   FDA Response: We consider this endpoint to be exploratory and will not be considered supportive for an approval or for labeling.

5. Does the FDA agree that the protocol defined pain response provides supportive evidence of clinical benefit and supportive evidence for potential labeling?

   FDA Response: No.

   1. We recommend that you submit the final version of the PPI and the AS in the exact format it is administered in your protocol with instructions on how the instrument will be administered, directions explaining how scores will be derived, and how the statistical analyses will be applied.
   2. Open-label data are only appropriate for labeling if results are convincing and conclusive.
   3. Pain intensity should be assessed at screening, and then continued eligibility by pain score should be verified at baseline (i.e. before randomization/dosing).
   4. Pain intensity should then be recorded daily, over the duration of the trial. There should also be evidence of efficacy over the entire duration of treatment.
   5. Pain relief and "rate of pain relief" are not accepted efficacy endpoints in analgesic trials intended to support marketing of a product.
   6. Assessment of the "worst pain" will provide more reliable results than "average pain" over 24 hours.
   7. Use of a known analgesic for rescue is acceptable (and recommended to reduce the number of placebo dropouts). The maximum amount of rescue should be pre-specified. The statistical analysis plan should describe how the use of rescue medication will be incorporated into the primary analysis.
   8. Evidence that a palliative pain response defined as > 2 point reduction from baseline with no increase in analgesic score or a reduction of at least 50% in the analgesic score with no increase in the pain score must be provided to use this endpoint to support labeling or promotional claims.
   9. Additional documentation of the development and validity of the PRO instrument designed for HRMPC (e.g., for a "TTSW" or "improvement in tumor related symptoms" claim) will be required for this type of claim to be included in labeling. *(See Draft Guidance for Industry- Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims).*

6. If XRP6258 does not demonstrate a survival benefit but demonstrates superior clinical benefit in pain response defined as a two point or greater reduction from baseline median PPI with no concomitant increase in analgesic score OR a reduction of at least 50% in analgesic use from baseline mean AS with no concomitant increase in pain, does the FDA agree that demonstration of superior pain response could support the potential marketing approval of XRP6258? (If FDA agrees, sponsor will consider power calculation and sample size accordingly)

   FDA Response: No. If you want to claim benefit based on pain relief then you have to design the study with pain intensity as a co-primary endpoint with survival and adequate allocation of alpha. In addition, a second study would be required to support a pain intensity claim. Any improvement in pain will be weighed against toxicity. We

discourage you from attempting to salvage a failed survival study based on pain intensity in an open label study and for reasons listed in our response to question #5.

7. Does the FDA agree that the completed pharmacokinetics and the proposed population pharmacokinetic analysis are adequate to support a marketing application for the proposed indication: treatment of hormone refractory prostate cancer patients who have relapsed during or following Taxotere based therapy?

FDA Response: In order to maximize the ability to discern exposure-response relationships, we recommend that you perform pharmacokinetics sampling in all patients, rather than the planned subset of patients, in the efficacy and safety studies.

We cannot comment on the overall adequacy of the planned program, as we lack answers to the numbered questions, below. These questions assume that FDA review of the preliminary data presented in the submission would agree with the conclusions of the Sponsor.

1. For pathways that contribute more than 25% of the clearance, we recommend that studies of the ability of inhibitors and inducers (if applicable) to alter the pharmacokinetics of the new drug be performed. Do you plan to perform *in vivo* drug interaction studies of the ability of a CYP3A4 inhibitor, a CYP3A4 inducer, and a CYP2C8 inhibitor to alter XPR6258 concentrations?

2. Based on *in vitro* data, are CYPs 1A2, 2C9, 2C19, and 2D6 likely each responsible for less than 25% of the *in vivo* elimination of XPR6258? If no, do you plan to perform *in vivo* drug interaction studies of the ability of inhibitors and inducers to alter XPR6258 concentrations? If yes, what are the designs of the planned studies?

3. Given that I/Ki for *in vitro* inhibition of CYP3A4 by XPR6258 exceeds 0.1, do you plan to perform an *in vivo* drug interaction study of the ability of XPR6258 to change concentrations of a reference CYP3A4 substrate? If yes, what is the design of the planned study?

4. Is I/Ki for *in vitro* inhibition of CYPs 1A2, 2C8 and 2C19 by XPR6258 less than 0.1? If no, do you plan to perform one or more *in vivo* studies of the ability of XPR6258 to alter concentrations of the relevant reference CYP substrates? If yes, what are the designs of the planned studies?

5. Does XPR6258 act as a CYP inducer *in vitro*? If yes, do you plan to perform one or more *in vivo* studies of the ability of XPR6258 to alter concentrations of reference CYP substrates? If yes, what are the designs of the planned studies?

6. Does XPR6258 act as a substrate or inhibitor of transporters *in vitro*? If yes, do you plan to perform *in vivo* studies with inhibitors or substrates? If yes, what are the designs of the planned studies?

7. If the results of the mass balance study show that 25% or more of elimination is renal, we recommend that a pharmacokinetic study in patients with renal impairment be performed. If the mass balance study shows that 25% or more of elimination is renal, do you plan to perform a pharmacokinetic study in patients with renal impairment? If yes, what will the design of the study be?

8. What is the design of the planned study in patients with hepatic impairment?

We recommend that you submit a summary that addresses the above questions and schedule a meeting to answer the question of the adequacy of the overall planned program.

Additional FDA comments:

1. Please provide information regarding the responses observed in patients with prostate cancer using this compound.

2. We remind you that you cannot claim efficacy based on the interim futility analysis. If you do conduct an efficacy overall survival interim analysis then you must adjust for alpha.

3. We recommend that you consider stratifying by measurable vs. non-measurable disease at randomization.

FINAL PROTOCOLS

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. A sample case report form (CRF) should be included. 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.

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 Investigational 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 Toigo at (301) 827-4460 or 113trials@oc.fda.gov.

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.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

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 encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. 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.

PEDIATRIC EXCLUSIVITY

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.

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					

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.

QT Evaluation

In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.

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/s/

John Johnson
6/29/2006 02:13:57 PM