

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-425

**ADMINISTRATIVE and
CORRESPONDENCE
DOCUMENTS**

**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
21-913

NAME OF APPLICANT/NDA HOLDER
Sanofi-aventis U.S. Inc

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)
MULTAQ

ACTIVE INGREDIENT(S)
dronedaron hydrochloride

STRENGTH(S)
400 mg (base)

DOSAGE FORM
Tablet

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

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

FDA will not list patent information if you 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 5,223,510	b. Issue Date of Patent June 29, 1993	c. Expiration Date of Patent July 26, 2011
---	--	---

d. Name of Patent Owner Sanofi-Aventis	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 sanofi-aventis U.S. Inc.	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)

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) 16 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.)
[Dronedarone hydrochloride] is indicated in patients with a history of, or current atrial fibrillation or atrial flutter, for the reduction of the risk of cardiovascular hospitalization or death.

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

Kelly L. Bender

May 27, 2008

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
Kelly L. Bender

Address
9 Great Valley Parkway

City/State
Malvern, Pennsylvania

ZIP Code
19355

Telephone Number
(610) 889-8995

FAX Number (if available)
(908) 231-2626

E-Mail Address (if available)
kelly.bender@sanofi-aventis.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**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
21-913

NAME OF APPLICANT/NDA HOLDER
Sanofi-aventis U.S. Inc

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)
MULTAQ

ACTIVE INGREDIENT(S)
dronedarone hydrochloride

STRENGTH(S)
400 mg (base)

DOSAGE FORM
Tablet

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

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

FDA will not list patent information if you 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 7,323,493	b. Issue Date of Patent January 29, 2008	c. Expiration Date of Patent June 19, 2018
---	---	---

d. Name of Patent Owner Sanofi-Aventis	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 sanofi-aventis U.S. Inc.	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)

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



May 15, 2008

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
Kelly L. Bender

Address
9 Great Valley Parkway

City/State
Malvern, Pennsylvania

ZIP Code
19355

Telephone Number
(610) 889-8995

FAX Number (if available)
(908) 231-2626

E-Mail Address (if available)
kelly.bender@sanofi-aventis.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 22-425

SUPPL #

HFD # 110

Trade Name Multaq

Generic Name dronedarone

Applicant Name sanofi-aventis

Approval Date, If Known

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

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: Russell Fortney
Title: Regulatory Project Manager
Date: 4/24/09

Name of Office/Division Director signing form: Norman Stockbridge
Title: Director, Division of Cardiovascular and Renal Products

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

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

/s/

Russell Fortney
4/24/2009 04:42:40 PM

Norman Stockbridge
4/24/2009 06:44:13 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-425 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Cardio-Renal PDUFA Goal Date: 4/30/09 Stamp Date: 7/31/2008

Proprietary Name: Multaq

Established/Generic Name: dronedarone hydrochloride

Dosage Form: Tablet

Applicant/Sponsor: sanofi-aventis

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Multaq is indicated in patients with either a recent history of, or current atrial fibrillation or flutter and with associated risk factors. Multaq has been shown to decrease the combined risk of cardiovascular hospitalization or death.

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

Russell Fortney
4/24/2009 04:46:27 PM

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.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹	
NDA # 22-425 BLA #	NDA Supplement # BLA STN #
If NDA, Efficacy Supplement Type:	
Proprietary Name: Multaq Established/Proper Name: dronedarone hydrochloride Dosage Form: Tablet	Applicant: sanofi-aventis, U.S., LLC Agent for Applicant (if applicable):
RPM: Russell Fortney	Division: Division of Cardiovascular and Renal Products
<p>NDA's: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>	<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)	April 30, 2009
❖ Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)	<input type="checkbox"/> None NA Ltt, 8/29/06
❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	<input type="checkbox"/> 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 ² Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 1 <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	4/8/09
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain 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	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> 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).

<p>(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?</p> <p>(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).</p> <p><i>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).</i></p> <p><i>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.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>CONTENTS OF ACTION PACKAGE</p>	
<p>❖ Copy of this Action Package Checklist³</p>	<p>Included</p>
<p>Officer/Employee List</p>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Action Letters</p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) 7/1/09, 8/29/06</p>
<p>Labeling</p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>N/A</p>
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	<p>N/A</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>6/27/08</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	<p>Cordarone Labeling</p>
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<p><input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None</p>

³ Fill in blanks with dates of reviews, letters, etc.
 Version: 9/5/08

<ul style="list-style-type: none"> Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	N/A
<ul style="list-style-type: none"> Original applicant-proposed labeling 	6/27/08
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	Cordarone
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent division proposal for (only if generated after latest applicant submission) 	N/A
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	5/18/09
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP 1/13/09 <input checked="" type="checkbox"/> DRISK 5/14/09 <input checked="" type="checkbox"/> DDMAC 4/23/09, 4/8/09 <input checked="" type="checkbox"/> Maternal Health Team 5/12/09 <input checked="" type="checkbox"/> SEALD 6/2/09
❖ Proprietary Name	
<ul style="list-style-type: none"> Review(s) (<i>indicate date(s)</i>) Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	1/13/09 N/A
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM review 7/1/09
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
<ul style="list-style-type: none"> Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	<input checked="" type="checkbox"/> 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 (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing communications (<i>if located elsewhere in package, state where located</i>) 	Detailed in approval letter
<ul style="list-style-type: none"> Incoming submissions/communications 	N/A
❖ Postmarketing Commitment (PMC) Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) 	

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.

<ul style="list-style-type: none"> Incoming submission documenting commitment 	
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
<ul style="list-style-type: none"> PeRC (<i>indicate date; approvals only</i>) 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	Included
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	3/18/09
<ul style="list-style-type: none"> 48-hour alert or minutes, if available 	Included
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/1/09
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/27/09
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/25/09, 2/19/09
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	N/A
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	2/18/09
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	4/27/09
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Page 10 of medical review
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management	<input type="checkbox"/> None
<ul style="list-style-type: none"> Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	5/15/09, 6/9/09
<ul style="list-style-type: none"> REMS Memo (<i>indicate date</i>) 	5/15/09
<ul style="list-style-type: none"> REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) 	6/9/09
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested Included
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 2/18/09
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1/30/09
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 4/30/09
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/10/08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 4/28/09, 7/7/08, 2/18/09
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<input checked="" type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	3/21/06 (under NDA 21-913)

<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i> 	Date completed: 4/27/09 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i> 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

Meeting Minutes

Date: May 15, 2009
Application: NDA 22,425
Drug: Dronedarone
Sponsor: sanofi-aventis
Purpose: Finalization of Dronedarone REMS

FDA Attendees:

Robert Temple, MD	Director, Office of Drug Evaluation I
Ellis Unger, MD	Acting Deputy Director, ODE I
Norman Stockbridge, MD, PhD	Director, Division of Cardiovascular and Renal Products
Abraham Karkowsky, MD, PhD	Medical Team Leader
Gail Moreschi, MD, MPH	Medical Officer
Mary Ross Southworth, PharmD	Deputy Director for Safety, DCRP
Gerald Dal Pan, MD, MHS	Director, Office of Surveillance and Epidemiology
Claudia Karwoski, PharmD	Acting Division Director, Division of Risk Management, OSE
Elizabeth Donohoe, MD	Drug Risk Management Analyst, OSE
Kendra Biddick	Office of Compliance
Sean Bradley, R.Ph.	Safety Project Manager, OSE
Russell Fortney	Regulatory Project Manager

sanofi-aventis Attendees:

Richard Gural, PhD	Head, Corporate Regulatory Affairs
Jon Villaume, PhD	Vice-President Cardio-thrombosis, Regulatory Development
Christopher Graham	Associate Vice President, US Regulatory Affairs Marketed Products
Marsha Miller, PhD	Assistant Director, Regulatory Development
Linda Scarazzini, MD	Associate Vice President, Risk Management
Barbara Rullo, MD	Vice President, Drug Safety
Laurent Auclert, MD	Head, Risk Management Evaluation Unit, Global Pharmacovigilance and Epidemiology

Background:

The action date for NDA 42,425 for dronedarone was April 30, 2009. The Agency did not provide a response to the Sponsor on the action date. Following the missed action date, the Sponsor submitted a Type A meeting request to meet with the Agency and discuss the Risk Evaluation and Mitigation Strategy (REMS). It was the Sponsor's understanding that this was the only major outstanding issue to be resolved prior to approval. A list of draft questions was provided in the May 1, 2009, meeting request, but these were revised and resent to the Agency on May 13, 2009, shortly after receiving additional comments from the Office of Surveillance and Epidemiology (OSE) regarding the REMS.

Meeting:

The following questions were submitted by the sponsor prior to the meeting and addressed during the meeting:

The Sponsor voluntarily submitted a proposed REMS on 22 January 2009. The Sponsor revised the REMS and submitted it to the Agency on 17 April and on 29 April 2009 following receipt of comments

from OSE on several occasions. These revised REMS have incorporated all comments and all changes requested by the Division and OSE. The Sponsor expects to submit the final REMS shortly following the 15 May 2009 meeting with the Division and OSE. It is the understanding of the Sponsor that labeling and all other approval issues, except finalization of the REMS, have been resolved to the satisfaction of the Agency. Therefore our questions concern only the path to approval of the REMS.

1. On 26 April 2009, the Sponsor received the following comment from OSE, "*This was stated in the previously, but the assessments (surveys and epi study analyzing prescribing patterns) will be required annually and will also be PMRs*". The Sponsor has updated the assessment table to reflect commitment for annual assessment of REMS performance. **Does the Agency concur with the updated assessment plan?**

Meeting Discussion:

The Agency agreed with the proposed plan to perform annual assessments for 5 years and at year 7. The Sponsor was asked to provide a brief summary of the information that would be included in the annual assessments. The Agency also noted that assessments must be received no later than the date specified and should have a data cut-off no earlier than 60 days prior to this date. After a short discussion, both the Sponsor and the Agency agreed that the due date will be calculated relative to the approval date. In other words, assessments are due 1 year, 2 years, 3 years, 4 years, 5 years and 7 years after the date the REMS is approved.

The Agency also noted that the Sponsor could expect to receive comments on the survey and the epidemiology study protocols, but that these would be advisory in nature and could be addressed post-approval. They would not impact the action date.

2. On 05 May 2009, the Sponsor received the following comment from the Agency, "*OSE comments on Medication Guide and Physician Information Sheet should be coming in the next 2 weeks.*" Once final labeling is agreed with the Division, any needed updates and revisions to the Medication Guide and Physician Information sheet will be incorporated. **Will OSE need to review the revised labeling again?**

Meeting Discussion:

The Agency noted that OSE will review final labeling including the Medication Guide, and the Physician Information Sheet. The Agency remarked that the Sponsor should be receiving comments on the Medication Guide very soon.

The Physician Information sheet had not been reviewed at the time of the meeting. Dr. Karwoski noted that comments on the Physician Information Sheet would be sent to the Division the following week and that the Sponsor would receive them shortly thereafter.

3. On 26 April, the Sponsor received the following comment from OSE, "*With regard to the collaboration with AHA, ACC: We cannot give specific guidance on how this type of outreach should be designed and want to see what the sponsor can create while working with these organizations. One example that has been proposed in other programs is scheduled "co-sponsored" advertisements in prominent medical journals which present risk information about dronedarone (in line with the goal of the REMS).*"

Additionally, on 05 May 2009, the Sponsor received the following comments from OSE, “*Add the following to the communication plan: Advertisements about the risk of dronedarone (and the importance of appropriate patient selection) should be placed regularly in prominent medical journals (for example, JACC, Circulation). Indicate the frequency of these ads (a suggestion: every month for the 1st two years; also consider the frequency with which marketing advertisements are run).*”

- A. It is the Sponsor’s understanding that professional societies do not partner with drug companies to co-sponsor advertisements in medical journals to avoid the appearance of endorsement of specific drugs. The Sponsor proposes placing advertisements in two professional society journals (JACC, and Circulation) once a month for 24 months. **Does OSE concur with the proposed plan?**

Meeting Discussion:

The Agency agreed that it would be acceptable to have advertisements placed in the *Journal of the American College of Cardiology* and *Circulation* once a month for 24 months.

The Sponsor asked whether the Agency had any comments on the advertisements and the Agency responded that they had not yet had time to review the proposed advertisement. Dr. Temple said that it was important to recognize that the purpose of the advertisement is to warn physicians appropriately regarding patients who should not receive dronedarone. He stated that the message about avoiding use of dronedarone in patients for whom the drug is contraindicated needs to be very prominent and appear at the top of the advertisement, and that the current version did not do this. He also remarked that the same comment applies to the Physician Information Sheet. The Sponsor offered to revise the advertisement and send new proposals to the Agency no later than May 19, 2009. The Agency agreed that this would be acceptable.

The Sponsor asked for clarification as to whether the advertisement would need to be approved prior to approval of the drug. The Agency responded that it needed to be approved prior to approval of the drug and that both OSE and DDMAC would be responsible for the review.

- B. In an effort to widely disseminate communication materials (Physician Information Sheet, combined with Simulated Case Studies via Virtual Cardiac Center [VCC]) to stakeholders, the Sponsor proposes:

(b) (4)

Does the agency concur with the Sponsors proposed communication plan?

Meeting Discussion:

The Agency commented that it is important that the REMS explains how materials are distributed. The Agency also noted that they felt this partnership with ACC was very positive

and encouraged the Sponsor to move forward with the partnership, (b) (4)

The Agency commented that the sponsor must distribute the Physician Information Sheet through U.S. mail; the sponsor may additionally use electronic communication.

4. The final process and the timings for the finalization and approval of the REMS are unclear to the Sponsor.
 - i. The Sponsor respectfully requests specific and detailed feedback from the Division and OSE with regard to any and all outstanding issues and concerns.

Meeting Discussion:

The Agency responded that the REMS, the REMS supporting documents, the Physician Information Sheet and the proposed advertisement and would be reviewed upon receipt and that the Sponsor could expect to receive marked up versions of all documents.

- ii. The Sponsor respectfully requests the Division and OSE clarify the process and timings for the final steps for approval of the REMS and the subsequent drug approval.

Meeting Discussion:

The Agency responded that the comments for the REMS, the REMS supporting documents, the Physician Information Sheet and the proposed advertisement will be sent to the Sponsor sometime during the week of May 18, 2009. They noted that the next step would be dictated by how quickly the Sponsor provided revised versions of these documents back to the Agency. The final step in the process would be the official REMS clearance process. When asked by the Sponsor if this group could review the documents in parallel with OSE, the Agency responded that the final clearance needed to be done with the final version and noted that it was possible that the Sponsor could receive additional comments as a result of this final clearance process.

The Sponsor asked whether it would be possible to initiate discussions with DDMAC regarding preclearance of launch materials, given that the professional part of the labeling was nearly final. Dr. Temple agreed that this would be acceptable. He also stressed that it is very important for the promotional advertisements to define clearly and prominently the patients who should not get this drug.

ACTIONS:

Agency actions from the meeting:

1. Provide final comments on the labeling, including the medication guide, incorporating comments from the Division and OSE.
2. During week of May 18, provide final comments on the REMS and the two REMS communication documents, the journal advertisement, and the Physician Information Sheet.

Sponsor actions from meeting:

1. On May 18, provide a brief summary of the information that would be included in the annual assessments.

2. On May 19, provide revised advertisement(s) (or more than one alternative) emphasizing the REMS goal of the patient who should not receive dronedarone. The revised text should also be applied to the Physician Information Sheet.

Minutes preparation: *{See appended electronic signature page}*
Russell Fortney

Concurrence, Chair: *{See appended electronic signature page}*
Robert Temple, M.D.

Drafted-6/16/09; Final-6/26/09

Reviewed: K.Biddick-6/18/09
S.Bradley-6/18/09
E.Donohoe-6/19/09
C.Karwoski-6/22/09
G.Dal Pan-6/22/09
M.Southworth-6/22/09
G.Moreschi-6/22/09
A.Karkowsky-6/22/09
N.Stockbridge-6/22/09
E.Unger-6/25/09
R.Temple-6/25/09

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

/s/

Russell Fortney
6/26/2009 01:13:56 PM

Robert Temple
6/26/2009 07:08:01 PM



NDA 22-425

INFORMATION REQUEST LETTER

sanofi-aventis U.S. Inc.
Attention: Marsha J. Miller, Ph.D.
Assistant Director, Regulatory Development
9 Great Valley Parkway
Malvern, PA 19355

Dear Dr. Miller:

Please refer to your July 31, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Multaq (dronedarone) Tablets, 400 mg.

Your NDA contains a risk management plan. This letter is the formal notification of the requirement for a Risk Evaluation and Mitigation Strategy (REMS) in lieu of a risk management plan. We acknowledge receipt of your proposed REMS, dated January 28, and April 29, 2009 which are currently under review.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if the FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Multaq (dronedarone) to ensure that the benefits of the drug outweigh the risks of fatal outcomes in patients taking Multaq (dronedarone) who have New York Heart Association (NYHA) Class IV heart failure or who have NYHA Class II and III heart failure and a recent hospitalization or referral to a specialized heart failure clinic for decompensated heart failure.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Multaq (dronedarone) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Multaq (dronedarone). FDA has determined that Multaq (dronedarone) is a product for which patient labeling could help prevent serious adverse events. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Multaq (dronedarone).

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Multaq (dronedarone) will support implementation of the elements of your REMS during the first five years after product launch. The communication plan must provide for the dissemination of information about the elements of the REMS, including the health care provider materials.

The communication plan must include, at minimum, the following:

- Information to potential and new prescribers of Multaq (dronedarone) about the risks of the drug, particularly the risks of fatal outcomes in patients taking Multaq (dronedarone) who have New York Heart Association (NYHA) Class IV heart failure or who have NYHA Class II and III heart failure and a recent hospitalization or referral to a specialized heart failure clinic for decompensated heart failure, including the appropriate patient population for the drug.
- A description of the audience for the communication plan, stating specifically the types and specialties of healthcare providers to whom the communication materials will be directed. Information must also be included on how often these materials will be distributed.
- A plan for dissemination of the risk and appropriate use information in conjunction with professional societies and/or their associated medical journals such as the American Heart Association (AHA) and American College of Cardiology (ACC).

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than annually after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Multaq (dronedarone). Additionally, all relevant proposed REMS materials, including educational and communication materials, should be appended to the proposed REMS. Once FDA finds the content acceptable, and if the drug is approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include but may not be limited to:

- a. An evaluation of patients’ understanding of the serious risks of Multaq (dronedarone)
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements of the Medication Guide, and corrective actions taken to address noncompliance
- d. An analysis of prescribers’ understanding (through surveys) of the contraindications to Multaq (dronedarone) therapy (i.e., NYHA Class IV patients, and NYHA Class II and III patients who have had a recent hospitalization for decompensated heart failure)
- e. An analysis of the prescribers’ compliance in observing the contraindications in epidemiologic databases

If you do not submit electronically, please send 5 copies of your proposed REMS as an amendment to your application. Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission.

PROPOSED REMS FOR NDA 22-425

On the first page of subsequent submissions related to the proposed REMS, prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-425 PROPOSED REMS-AMENDMENT

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures: Appendices A and B

Appendix A: REMS Template

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

- A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);
- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Appendix B: Supporting Document

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
 - a. Additional Potential Elements
 - i. Medication Guide
 - ii. Patient Package Insert
 - iii. Communication Plan
 - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
 - c. Implementation System
 - d. Timetable for Assessment of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

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

/s/

Robert Temple

5/15/2009 07:03:33 PM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: April 16, 2009

TO: Russell Fortney, Regulatory Project Manager
Gail Moreschi, Medical Officer
Division of Cardiovascular and Renal Drug Products

FROM: Sharon K. Gershon, Pharm.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA 22-425

APPLICANT: Sanofi-Aventis

DRUG: Multaq (dronedaronone hydrochloride) tablets

NME: Yes

THERAPEUTIC CLASSIFICATION: Antiarrhythmic/Priority Review

INDICATIONS: Reduction of the risk of cardiovascular hospitalization or death in patients with a history of, or current atrial fibrillation or atrial flutter (AF/AFL).

CONSULTATION REQUEST DATE: August 22, 2008

DIVISION ACTION GOAL DATE: April 30, 2009

PDUFA DATE: April 30, 2009

I. BACKGROUND:

The Review Division issued a not approvable letter for NDA 21-913 in 2006, and included a summary of questions raised by the (then) ANDROMEDA study, including a less-than

favorable risk-benefit relationship for either rate control or prevention of AF recurrence, along with lack of reassurance about the drug's possible adverse effect on increased mortality. The sponsor conducted another clinical study (ATHENA), with a primary composite endpoint of death from any cause or CV hospitalization, and submitted what they contended was a complete response to the NA letter. However, because the indication sought with the resubmission was different than the previous indication sought (prior submission was for rhythm and rate control), and the ATHENA study excluded very sick patients, and thus investigated a population which was also considered different than the prior ANDROMEDA study, the Division considered the submission a new NDA. As the new indication includes a mortality benefit, the Division granted priority review status for the new application.

Approximately 4300 patients, at 551 centers, in 37 countries were to be randomized in the ATHENA study. The Review Division recommended that DSI conduct inspections at 3 foreign sites. The Review Division did a funnel plot for relative risk by center, and these 3 sites were outliers, in that they had outstanding efficacy results. In addition a large majority of the centers in the trial were outside the U.S., and as such, there were insufficient domestic data in support of this application.

The protocol inspected included:

EFC5555 (ATHENA): “A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter (AF/AFL)”

II. RESULTS (by Site):

Name of CI/Sponsor	Site #/No. of Subjects:	Inspection Dates	Final Classification
Dr. Vratislav Dedek Czech Republic	Site #203002 56 subjects	November 10-13, 2008	NAI
Dr. Yuri Shubik St. Petersburg, Russia	Site #643010 23 subjects	October 27- 31, 2008	NAI
Dr. Vladimir Barbarich Novosibirsk, Russia	Site #643036 40 subjects	November 3- 7, 2008	NAI
Sanofi-aventis U.S. 11 Great Valley Parkway P.O. Box 3026 Malvern, PA 19355	Sponsor	February 18 – March 3, 2009	Preliminary NAI: EIR is pending

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Dr. Vratislav Dedek

Nemocnice Usti Nad Orlici

Interni Oddeeleni

Cs. Armady 1076

562 18 Usti Nad Orlici

Czech Republic

What was inspected: Dr. Dedek began this study in June 2006, and randomized 56 subjects into the ATHENA study. Using the Compliance Program, the inspection: reviewed inclusion and exclusion criteria for all 56 subjects; corroborated Case Report Forms with source records for all 56 subject; reviewed informed consent documents for all 56 subject; reviewed the primary efficacy assessments on the CRF, including the documented cause of hospitalization or death; reviewed the sponsor monitoring log; reviewed the drug accountability records for all 56 subjects; reviewed prior and concomitant medication therapy for all 56 subjects; performed a check of all patient ECGs within 6 months for all 56 subjects; performed a 100% check of each patient chart to verify the existence of a cardiac history.

General observations/commentary: In general, the inspection noted that all patient/subject records were maintained in good condition. The inspection noted that all subjects met inclusionary criteria, including 1 ECG within the last 6 months showing patient was or is in AF/AFL and 1 ECG within the last 6 months documenting the patient was or is in normal sinus rhythm prior to randomization. The inspection noted that the subject's past cardiovascular history and causes for all hospitalizations and deaths were properly documented and recorded to the CRF. A few discussion items at the end of the inspection included: the importance of recording accurate data and of following the protocol when making corrections; the importance of completing drug temperature monitoring logs as back-up in case of device failure. No FDA-483 was issued to Dr. Dedek.

Assessment of data integrity: The inspection concluded that Dr. Dedek adhered to the applicable FDA regulations and GCP guidelines during the conduct of the ATHENA trial. All subjects enrolled met inclusionary criteria. No major deficiencies were noted with regards to consistency between source medical records, CRFs and sponsor data listings. Required ECGs were present for each subject, and no deficiencies were noted with the permitted concomitant medication therapies. The discussion items concerning some minor recordkeeping errors and maintaining drug temperature logs are unlikely to affect data reliability. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Dr. Yuri Shubik

North-West Center for

Diagnostic and Treatment of Arrhythmias

8, Deputatskaya Str.

St. Petersburg 197110

Russia

a. **What was inspected:** Dr. Shubik enrolled 23 subjects into the ATHENA study. Following the Compliance Program, the inspection reviewed study records for all 23 subjects enrolled, including medical charts, informed consent documents, case report forms, ECGs and laboratory results. The inspection ensured that subjects met all inclusionary criteria; the inspection reviewed prior and concomitant medications for all 23 subjects; reviewed causes for all hospitalizations and deaths for all 23 subjects; reviewed adverse events; corroborated the efficacy endpoints with the sponsor's data listings; and evaluated test article accountability records for all subjects.

b. **General observations/commentary:** All patient/subject records were found in order and available. All subjects met inclusionary criteria, including 1 ECG within the last 6 months showing AF/AFL and 1 ECG within the last 6 months documenting normal sinus rhythm prior to randomization. Past cardiovascular history and causes for all hospitalizations and deaths were properly documented and recorded to the CRF. All adverse events, including SAES appeared as accurately documented for all 23 subjects. There was no evidence of underreporting of AEs. There was one cardiac related death (Subject #006, placebo) which was determined as unrelated to investigational product. Three minor discrepancies, considered as transcription errors, were found, in comparing source data with the CRF. For example, Subject #003 CRF (12/2/2005) documented potassium as 4.35, whereas the corresponding lab sheets documents potassium as 4.32. Subject #003 CRF (1/17/2008) documented the INR value as 0.90, whereas the corresponding lab sheet documented a value of 0.96. No FDA-483 was issued to Dr. Shubik. A Russian translator facilitated translation of documents and conversations between the field investigator and Dr. Shubik and the sub-investigators.

c. **Assessment of data integrity:** In general, Dr. Shubik adhered to the applicable FDA regulations and good clinical practice guidelines. The data transcription errors noted during the inspection are not considered significant, and do not affect data reliability. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. Dr. Vladimir Barbarich

City Clinical Hospital #1

6, Zaleskogo Str.

Novosibirsk 630047 Russia

a. **What was inspected:** Dr. Barbarich randomized 40 subjects into the ATHENA study. The inspection reviewed study records for all 40 subjects to ensure that all subjects met inclusionary criteria. The inspection reviewed informed consent documents for all 40 subjects; the inspection corroborated Case Report Forms with source records and with sponsor's data listings for all 40 subjects. The inspection reviewed ECGs, laboratory records, prior and current concomitant medications, reasons for hospitalizations and deaths, reviewed adverse events, confirmed efficacy endpoints, and looked at test article accountability records for all subjects.

b. **General observations/commentary:** All subjects met inclusionary criteria, including 1 ECG within the last 6 months showing AF/AFL and 1 ECG within the last 6 months documenting normal sinus rhythm prior to randomization. Past cardiovascular history and causes for all hospitalizations and deaths were properly documented and recorded to the CRF. All adverse events, including SAES were documented for all 23 subjects. There were three deaths (subject 20, 21 and 30) which appeared to be

documented as reported appropriately. No FDA-483 was issued to Dr. Barbarich. A Russian translator facilitated translation of documents and conversations between the field investigator and Dr. Barbarich and the sub-investigators.

c. **Assessment of data integrity:** In general, Dr. Barbarich adhered to the applicable FDA regulations and good clinical practice guidelines. There were a few minor transcription errors, but these errors were not significant, and are not considered to affect data reliability. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

4. Sanofi-aventis U.S.
11 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

a. **What was inspected:** The inspection reviewed SOPs, including the monitoring SOP, and conducted a data audit for at least half of the subjects for Dr. Dedek, Shubik and Barbarich. The inspection reviewed and compared case report forms with the data listings covering adverse event reporting, and confirmed their efficacy endpoints as well as any serious AEs. No deficiencies were observed and no FDA 483 was issued.

Observations noted above are based on communications with the field investigator, an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The final **sponsor** inspectional summary report is pending – a preliminary classification for the sponsor inspection is NAI. No deficiencies were observed with regard to NDA 22-425. **This observation is based on email communications with the field investigator. An inspection summary will be generated if conclusions change upon receipt and review of the EIR.**

The clinical investigator inspections (Dedek, Barbarich, and Shubik) were all classified as NAI. No major discrepancies were noted during the review of records for all subjects. There were a few minor transcription errors noted at several sites, but these observations are not significant and do not affect the reliability of the data.

The data is considered acceptable in support of this application.

{See appended electronic signature page}

Sharon K. Gershon, Pharm.D.
GCP Reviewer/
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

/s/

Sharon Gershon
4/16/2009 04:46:12 PM
CSO

Tejashri Purohit-Sheth
4/16/2009 04:51:13 PM
MEDICAL OFFICER

Internal Consult

******Pre-decisional Agency Information******

To: Russel Fortney
Division of Cardiovascular and Renal Products
Office of New Drugs

From: Lisa Hubbard, R.Ph., Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)
Office of Medical Policy (OMP)

Date: April 23, 2009

Re: NDA # 22-425
Multaq (dronedarone) Tablets
Comments on draft label

DDMAC has reviewed the proposed product labeling (PI) for Multaq (dronedarone) Tablets. The attached comments below are based on the attached draft label circulated on April 23, 2009.

23 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Administrative-1

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

/s/

Lisa Hubbard
4/23/2009 10:27:55 AM
DDMAC PROFESSIONAL REVIEWER

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: April 8, 2009

To: Russell Fortney
Senior Regulatory Manager
Division of Cardio and Renal Products

From: Zarna Patel, PharmD
Consumer Safety Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **Drug: Multaq (dronedarone) tablets**
NDA: 22-425

DDMAC has reviewed the draft patient package insert (PPI) for Multaq Tablets. DDMAC's comments are provided directly in the attached document (see below). DDMAC appreciates the opportunity to provide comments.

If you have any questions or concerns regarding my comments, please contact me.

8 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Administrative-2

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

/s/

Zarna Patel

4/8/2009 01:38:28 PM

DDMAC CONSUMER REVIEWER

Please refer to this document for DDMAC comments on the PPI.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-425

DISCIPLINE REVIEW LETTER

sanofi-aventis U.S., LLC
Attention: Marsha Miller, Ph.D.
Assistant Director, Regulatory Development
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Miller:

Please refer to your new drug application (NDA) dated June 27, 2008, received July 31, 2008, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Multaq (dronedarone hydrochloride) Tablets 400 mg.

Our review of the carton and container labels of your submission is complete, and we have identified the following deficiencies:

A. All Labels and Labeling

1. Although the font size of the established name appears $\frac{1}{2}$ the size of the proprietary name, it does not have a prominence commensurate with the prominence of the proprietary name. It does not take into account all pertinent factors, including typography, layout, contrast, and other printing features. Revise the labels and labeling to increase the prominence of the established name in accordance with 21 CFR 201.10(g)(2).
2. Revise the established name, dosage form, and strength so that it appears as follows:
"Multaq (Dronedarone) Tablets 400 mg"
3. Ensure that the unit-of-use bottles have a Child Resistant Closure (CRC) per the Poison Prevention Packaging Act (PPA) of 1970 to avoid accidental ingestion of Multaq.

B. Blister Labels and Blister Carton Labeling

1. Relocate the dosage form so that it appears immediately following the established name [i.e. (Dronedarone) Tablets 400 mg].
2. The blister carton labeling includes a (b) (4) statement. The use of abbreviations should be avoided when possible as it may not be readily understood. Please consider revising the current net quantity statement to "10 x 10 unit dose blisters" to be in alignment with standard label/labeling nomenclature.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user

fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Edward Fromm
1/21/2009 04:57:46 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-425

sanofi-aventis U.S., LLC
Attention: Marsha Miller, Ph.D.
Assistant Director, Regulatory Development
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Miller:

Please refer to your new drug application (NDA) dated June 27, 2008, received July 31, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Multaq (dronedarone hydrochloride) Tablets 400 mg.

On December 3, 2008, we received your major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 30, 2009.

If you have any questions, please call Russell Fortney, Regulatory Health Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Edward Fromm
12/18/2008 09:04:21 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-425

sanofi-aventis U.S., LLC
Attention: Jon Villaume, Ph.D.
Vice President, Regulatory Affairs
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Villaume:

Please refer to your new drug application (NDA) dated June 27, 2008, received July 31, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Multaq (dronedaronone hydrochloride) Tablets 400 mg.

We also refer to your submissions dated August 14 and 15, 2008.

Based on our filing review of your application, we have the following requests:

1. Regarding the 3 sites to be inspected, why are the patients censored at these sites as per the September 8 submission? Also, please compare these 3 sites to the overall submission.
2. Regarding Table 27 on page 80 of your application, please provide the following information regarding all patients but especially regarding the patients with atrial fibrillation and supraventricular arrhythmia, myocardial infarcts, and worsening of CHF:
 - a. What are the sites involved?
 - b. What drugs were the patients taking?
 - c. Were the patients anticoagulated?
 - d. Why were the patients hospitalized?
 - e. Did the patients spontaneously convert to sinus rhythm? If not, how were they treated and with what modalities or agents?
 - f. Were the patients symptomatic at the time of conversion??
 - g. What was the duration of their atrial fibrillation or arrhythmia?
 - h. What was their subsequent outcome after one month and after 6 months?
 - i. What other events occurred?
 - j. How many deaths occurred among these patients?
 - k. What was the creatinine of these patients?
 - l. How many patients were in failure?
 - m. How many patients on dronedaronone and placebo were taken off an ACE or ARB?
 - n. How many patients were on statins and/or fish oil?

3. Please identify a subset of patients in ATHENA who are similar to ANDROMEDA patients and do a primary and secondary analysis on this population. Include patients with the same inclusion criteria as ANDROMEDA. Provide the same tables as Tables 20 to 27 and the same figures as Figures 3 to 8 on this subpopulation.
4. Please provide the receptor binding profile of dronedarone and the metabolites SR35021A and SR90154. This should be a reasonably thorough investigation (e.g. a Nova screen) that includes the steroid hormone receptors and provides for side by side comparison of the 3 compounds.

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

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 2, 2009.

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Norman Stockbridge
10/9/2008 03:21:14 PM



DEPARTMENT OF HEALTH & HUMAN
SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-425

sanofi-aventis U.S., LLC
Attention: Jon Villaume, Ph.D.
Vice President, Regulatory Affairs
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Villaume:

We have received your new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Multaq (dronedaronone hydrochloride) Tablets 400 mg
Review Priority Classification:	Priority (P)
Date of Application:	June 27, 2008
Receipt Date of User Fees:	July 31, 2008
Our Reference Number:	NDA 22-425

This application was considered incomplete and was not accepted for filing because all fees owed for this application were not paid. Subsequently, we received on July 31, 2008 all fees due. The receipt date for fees due is considered the new receipt date for this application.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 29, 2008, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 31, 2009.

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

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

NDA 22-425
Page 2

5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Russell Fortney, Regulatory Health Project Manager, at (301) 796-1068.

Sincerely,

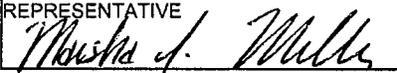
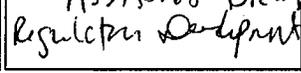
{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Edward Fromm
8/6/2008 12:09:28 PM

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.				
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET			
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm				
1. APPLICANT'S NAME AND ADDRESS SANOFI AVENTIS US LLC Diane Fisher 55 Corporate Drive, , NJ Bridgewater NJ 08807 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 22-425			
2. TELEPHONE NUMBER 610-8896363	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:			
3. PRODUCT NAME MULTAQ (Dronedrone)	6. USER FEE I.D. NUMBER PD3008557			
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY				
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO				
OMB Statement: Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: <table style="width:100%; border: none;"> <tr> <td style="width:33%; border: none;"> Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448 </td> <td style="width:33%; border: none;"> Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852 </td> <td style="width:33%; border: none;"> An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. </td> </tr> </table>		Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.		
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE <i>Assistant Director</i> DATE <i>31 July 2008</i> 			
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$1,178,000.00				
Form FDA 3397 (03/07)				

Close Print Cover sheet

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

/s/

David Jacobson-Kram
10/24/2005 10:49:00 AM

Meeting Minutes

Date: January 3, 2005
Application: IND 49,484
Drug: Dronedarone
Sponsor: Sanofi-Synthelabo Research
Purpose: Discuss New Protocol

FDA Attendees:

Robert Temple, M.D.	Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products
Femi Williams, M.D.	Medical Officer
Charles Le, Ph.D.	Statistician
Russell Fortney	Regulatory Health Project Manager

Sanofi-Synthelabo Research Attendees:

Jean Bouthier, M.D.	VP, Clinical Development
Alexander Gebauer, M.D.	VP, Project Direction
Sylvie Bozzi	Project Statistician, Biostatistics
Margaret Cros, Pharm.D.	Associate Director, Drug Regulatory Affairs
Christophe Gaudin M.D.	VP, Cardiovascular Clinical Development
Nacera Hamdani, Pharm.D.	Project Director
Ann Hards, Ph.D.	VP, Drug Regulatory Affairs
David Radzik, M.D.	Clinical Research Director

Background:

The sponsor is developing dronedarone for use in atrial fibrillation (AF). Two AF trials (EURIDIS and ADONIS) have been completed with positive results. However, ANDROMEDA, a long term morbidity/mortality trial in CHF patients, was stopped early due to an adverse mortality effect in the dronedarone treated group. At a July 13, 2004 meeting, the Agency agreed that while the ANDROMEDA data would not prevent the filing of an application, additional assurance that dronedarone will not lead to increased mortality in CHF patients will be needed. The sponsor has designed a protocol, entitled "Placebo-controlled parallel arm trial of the efficacy of dronedarone 400 mg BI for the prevention of cardiovascular hospitalization or death in patients with AF/AFL," to address the Agency's concerns. This meeting was scheduled to discuss the design of the protocol and reach agreement on whether the trial may be ongoing at the time of NDA submission.

Meeting:

After introductions, the sponsor provided a brief review of the July, 2004 meeting.

The sponsor then presented slides outlining the design of the new protocol.

Dr. Temple asked the sponsor to clarify the timing of AF/AFL episodes of patients to be enrolled in the trial. The sponsor said that patients will have been in AF/AFL at some point in the previous year, including patients currently in AF/AFL. Dr. Temple asked if those patients currently in AF/AFL will be converted prior to enrollment. The sponsor said that conversion is not required.

Dr. Temple asked if the sponsor is sure they have selected the correct dose. The sponsor explained that the dose they have chosen (400 mg BID) was the only effective dose in their dose-ranging trial, and that other (higher) doses showed increased adverse events.

Dr. Temple asked if patients would continue to use anticoagulants while in the trial. The sponsor said that decision would be left up to each investigator.

Dr. Temple recommended that resuscitated cardiac death should be included in the primary endpoint. The sponsor agreed to make this change.

Dr. Temple agreed that the statistical considerations seem acceptable. However, he added that the sample size should be based on the total number of events to be sure that the trial is adequately powered.

The sponsor asked if the new trial could be ongoing at the time the NDA is submitted. They said that based on their current timeline, they would expect the interim results to include approximately 80 deaths near the end of the NDA review period. Dr. Temple said that because dronedarone is not intended as a life-saving treatment, the Agency must be assured that it does not lead to increased mortality. The sponsor asked if there is any chance of approval prior to completion of the trial. Dr. Temple said that approval will depend on the available data, but at this point, approval without the final results seems very improbable.

The sponsor asked if a positive result from this trial would support an additional indication of reducing the risk of hospitalization and death in patients with AF/AFL? Dr. Temple agreed that it is possible depending on the results.

Minutes preparation: *See appended electronic signature page.*
Russell Fortney

Concurrence, Chair: *See appended electronic signature page.*
Robert Temple, M.D.

Drafted-1/21/05; Final-1/28/05

Reviewed: A.Williams-1/24/05
C.Le-1/24/05
N.Stockbridge-1/24/05
R.Temple-1/27/05

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

/s/

Russell Fortney
1/28/05 10:14:30 AM

Robert Temple
1/28/05 05:17:19 PM

Meeting Minutes

Date: July 13, 2004
Application: IND 49,484
Drug: Dronedarone
Sponsor: Sanofi-Synthelabo Research
Purpose: Discussion of ANDROMEDA Results and Their Impact on NDA Submission

FDA Attendees:

Robert Temple, M.D.	Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, Division of Cardio-Renal Drug Products
Tom Marciniak, M.D.	Medical Team Leader
Shari Targum, M.D.	Acting Medical Team Leader
Nhi Beasley, Pharm.D.	Pharmacokineticist
James Hung, Ph.D.	Team Leader, Statistics
Femi Williams, M.D.	Medical Officer
Russell Fortney	Regulatory Health Project Manager

Sanofi-Synthelabo Research Attendees:

Daniel Beaumont, M.D.	VP, Project Direction
Jean Bouthier, M.D.	VP, Clinical Development
Sylvie Bozzi	Project Statistician, Biostatistics
Sophie Claudel	Team Leader, Biostatistics
Margaret Cros, Pharm.D.	Associate Director, Drug Regulatory Affairs
Christophe Gaudin M.D.	VP, Cardiovascular Clinical Development
Douglas Greene, M.D.	VP, Regulatory Affairs
Nacera Hamdani	Project Director
Ann Hards, Ph.D.	VP, Drug Regulatory Affairs, Cardiovascular & Thrombosis
Catherine Marchese, M.D.	Cardiothrombosis Therapeutics Group Leader, Pharmacovigilance
David Radzik, M.D.	Clinical Research Director
Michael Spitz	Assistant Director, Drug Regulatory Affairs
Eric Sultan, Ph.D.	Team Leader, Clinical Metabolism and Pharmacokinetics

Background:

The sponsor is developing dronedarone for use in atrial fibrillation (AF). Two AF trials (EURIDIS and ADONIS) were completed and showed positive results. However, ANDROMEDA, a long term morbidity/mortality trial in CHF patients, was stopped early due to an adverse mortality effect in the

dronedarone treated group. The Sponsor requested this meeting to discuss these results and their impact on a potential NDA submission.

Meeting:

After introductions, the sponsor presented a series of slides outlining the results of their dronedarone development program.

The sponsor described the positive findings of EURIDIS and ADONIS trials in AF patients. Dr. Temple said that the overall effectiveness of dronedarone, while positive, is lower than three other treatments (dofetilide, sotalol and amiodarone). The sponsor said that it is difficult to compare such trials since they were of different designs. They noted that they saw no incidents of torsade de pointes, even at higher doses. Dr. Temple stressed that the effect size was extremely small.

The sponsor explained that dronedarone inhibits tubular secretion of creatinine, leading to elevated plasma creatinine levels. They theorized that in the ANDROMEDA trial, because of elevated creatinine levels, more dronedarone patients as compared to placebo patients had their ACE inhibitors discontinued. They attributed the increased mortality in the dronedarone group to ACE inhibitor management in a severe CHF population. Dr. Temple noted that an alternative hypothesis is that dronedarone has an adverse effect in CHF patients that is potentially corrected with ACE inhibitors.

Dr. Temple advised the sponsor that the Agency must be assured that dronedarone will not lead to adverse mortality in CHF patients. He said that potential strategies to follow might be another heart failure trial (difficult on ethical grounds), or a larger trial in AF patients, including some with heart failure.

(b) (4)

The sponsor asked if the Agency would be willing to participate in labeling discussions prior to submission of the NDA. Dr. Temple agreed to this.

The Sponsor asked if the application would be filed if submitted with no additional trials. Dr. Temple said that it would likely be filed.

Minutes preparation: _____
Russell Fortney

Concurrence, Chair: _____
Robert Temple, M.D.

Drafted-8/5/04; Final-8/12/04

Reviewed: N.Beasley-8/10/04
A.Williams-8/10/04

S.Targum-8/11/04
T.Marciniak-8/11/04
A.Karkowsky-8/11
N.Stockbridge-8/11/04
R.Temple-8/12/04

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

/s/

Russell Fortney
8/12/04 01:32:57 PM

Robert Temple
8/12/04 05:33:06 PM